Lecture Notes in Bioengineering

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Polymer Nanocomposites in Biomedical Engineering

Springer

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ISSN 2195-271X ISSN 2195-2728 (electronic)
Lecture Notes in Bioengineering
ISBN 978-3-030-04740-5 ISBN 978-3-030-04741-2 (eBook)
https://doi.org/10.1007/978-3-030-04741-2

Library of Congress Control Number: 2018964927

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Polymers are much significant in the advanced biomedical applications, especially in developing regenerative tissues, wound dressing, drug carriers and even the artificial skin. Polymer-based systems offer light weight, flexibility, environmental friendliness, ease of processability, etc., and provide the fabrication of artificial materials that mimic the biological tissues. Both natural and synthetic biopolymers are widely applied to most of those applications. However, the polymers have some drawbacks that negatively affect the device efficiencies and so composites and nanocomposites of them are widely reported. The current book deals with the biomedical applications of polymers, their composites and nanocomposites, focusing more on the design and development of such systems, their characteristic performances, and addresses the limitations in fabricating those materials. The whole book is divided into twelve chapters with the aim of making the reader more convenient in understanding the general concepts of biomedical requirements and how the polymers can be useful in solving the conventional issues.

The first chapter is written in such a way that the reader should get a basic and advanced idea about the whole book, and so the current advancement in the field of biomedical applications of polymers and its composites is discussed in detail. The widely explored properties such as porosity, mechanical strength, bioactivity, biocompatibility and biodegradability are addressed in detail, mainly targeting the tissue engineering, biosensing, drug delivery and imaging applications of both natural and synthetic polymers. The second chapter is arranged in line with the first chapter, in which the bio-based polymers are well explored emphasizing the fabrication methods and filler reinforcements. In fact, the field of polymers in biomedical applications is growing at super-speed from the conventional natural fiber-reinforced thermoplastics to advanced fully bio-based materials. It is also really important to characterize such materials more consistently so that the traditional difficulties can be fully eliminated by tuning the properties. The third chapter further differentiates the amorphous, semicrystalline thermoplastic polymer nanocomposites in biomedical engineering, on the basis of processing techniques and degree of crystallinity influences. Moreover, the direct impact of fillers such as

carbon nanotubes and graphene on the drug delivery and tissue culturing applications of polymers is also well investigated in this chapter.

Lipids, hydrogels and hydroxyapatites are three significant materials in biomedical engineering. These three pillars are included in the current book as three main chapters. Lipids are fundamental models to study the cell membranes as many living biological structures can be made based on lipid–polymer composites. Such composites find useful applications in diagnosis, cosmetics, imaging, vaccines, drug delivery, theranostics, tissue engineering and in protecting bioactive agents. In addition to investigating the significance of lipid-based materials, the chapter also addresses the challenges associated with controlled and stimuli-responsive drug delivery by lipid–polymer composites. It is rather necessary to develop sterile, well-characterized and stable products to validate its applicability, in vivo, in humans. While the hydroxyapatite nanocomposite-reinforced polymer nanocomposites are the subjects of study for one of the chapters, their superior physical, chemical, electrical and biological properties and porous molecular structure along with carbon-based, polymeric, ceramic and metallic nanomaterial-integrated apatite composites were also considered for the detailed investigation. The various synthesis methods such as expulsion, freeze drying and solvent casting were discussed in addition to the physicochemical properties, quality, long-haul stability, superior compressive and modulus properties, cytocompatibility and their applications as gene carriers and photodynamic therapy and tissue rejuvenation.

Hydrogels are one of the effective materials that offer an aqua environment with enriched oxygen and nutrition content that a biological cell needs. It is possible to replace natural tissues with some polymeric hydrogels whose mechanical behavior and biocompatibility resemble the natural tissues. The growing manufacturing technique of three-dimensional (3D) printing is adopted in this particular chapter to synthesize biomedical organs in the micron-scale resolution, to make the hydrogel applicable in skin bioprinting and tissue engineering. Such polymeric hydrogels repair and regenerate the organs and tissues, and sometimes help in whole organ transplantation.

Electrospinning is an inevitable technique when the polymer nanocomposites for biomedical applications are considered, and this vast topic is arranged as two significant chapters. While the biomedical applications of various electrospun polymer nanocomposites are explained in the beginning chapter, the fundamental concepts and the optimization techniques to make the fibers adaptable to biomedical engineering are discussed at last. The electrospun polymer fibers possess excellent mechanical strength, high surface areas, ultrafine diameter, lightweight, superior mechanical properties and good porosity and find applications mainly in tissue engineering, drug delivery, enzyme immobilization, infiltration and wound healing. The porous fibers also mimic the native extracellular matrix and bring advancements in smart medicine as well. In addition, various spinning processes such as emulsion spinning and coaxial spinning are also targeted for the discussions.

Cancer therapy is one of the increasing fields of attention in recent years. There is a specific chapter dealing with the polymers used in augmented stem cell osteogenesis, cancer therapy and diagnostics in the central nervous system. The whole

mechanism is explained on the basis of charge, size and surface modification on polymer surfaces and its nanocomposites. Another well-known concept applied to biomedical applications like tissue engineering, drug delivery and cell encapsulation is the photopolymerization. This method has effective applications in protein and gene delivery as well as other drug delivery systems in pharmaceutical field. The latest advancements in the utilization of photopolymerization technology based on the photoirradiation, common precursors and compatibility of photoinitiators are the topic of study of the chapter.

Shape-memory polymers and composites are very necessary in biomedical fields, and in the chapter by Muzaffar et al., different composites containing nickel, carbon nanotubes and electroactive fillers are explored for the shape-memory effect. Thrusts are given to various areas like mechanical properties, biocompatibility (cytotoxicity, mitochondrial activity, membrane damage and cytokine production), hemocompatibility, genotoxicity, histocompatibility, biodegradability and sterilizability of the developed composites. Finally, the much significant antibacterial and antimicrobial properties of silver nanoparticles, synthesized by microwave method, are also highlighted. Since Ag-based nanocomposites can reduce infections and hence provide faster healing and better health to the patients, an extensive study about such composites is rather necessary.

Thus, the current book on *Polymer Nanocomposites in Biomedical Engineering* mostly addresses the major issues in developing polymer nanocomposites in specific applications, by targeting main polymers and nanofillers that have particular roles in biomedical field. The book opens a new collection of information on polymers and targets a revolution in manufacturing artificial biomedical devices by applying polymer science and nanotechnology.

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The original version of the book was revised: Co-editors' names have been corrected. The correction to the book is available at https://doi.org/10.1007/978-3-030-04741-2_13

Contents

A Fundamental Approach Toward Polymers and Polymer Composites: Current Trends for Biomedical Applications

Rajan Choudhary, Mohit Saraswat and Senthil Kumar Venkatraman

Abstract Polymers and their composites are widely studied for various biomedical applications including hard tissue regeneration, wound healing, artificial skin, antibacterial oxygenators, and drug delivery carriers. Both natural and synthetic polymers are employed for clinical applications and possess numerous advantages and a few limitations. State-of-the-art microarray technique assists in rapid screening of most suitable polymeric materials for biomedical applications and 3D printing aids in fabricating scaffolds with desirable porosity to mimic the architecture of natural tissues. The insufficient mechanical strength and hydrophobic nature of polymers restrict their applications in the field of tissue engineering. The incorporation of inorganic bioactive ceramics as filler in the organic polymer matrix is expected to eliminate these limitations. The present chapter describes the current advancements made in using polymers and its composites for biological applications and predicts the future studies to make these materials as a promising alternative for traditional metallic implants. A brief discussion on the emerging techniques and significant research done is also presented.

Keywords Biomaterial · Polymer · Composites · Gas permeability · Additive manufacturing · Microarray · Tissue engineering applications

1 Introduction

Biomaterial science refers to detailed study of the characteristics of a material and its response toward biological systems. The term "biomaterials" has been defined through various explanations. A biomaterial can be defined as an ideal material (synthetic or natural) that can act/perform similarly to the natural host tissue (Williams 1999). The ultimate aim of biomaterials is to recover human health by

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K. K. Sadasivuni et al. (eds.), *Polymer Nanocomposites in Biomedical Engineering*, Lecture Notes in Bioengineering,
https://doi.org/10.1007/978-3-030-04741-2_1

repairing diseased organs and living tissues present in the body. This goal can be achieved by replacing the damaged tissues with artificial implants or prostheses. The biomaterials discipline involves the knowledge from multidisciplinary fields such as materials science, chemical science, biological science, mechanical, and medical science. Thus, it requires a synergetic interaction and comprehension from these areas to develop an implantable biomaterial that can perform effectively along with the normal functioning of the body (Dorozhkin 2010).

The requirements of a scaffold used for biomedical applications are extremely challenging as they are intended to face a complex and sensitive biological system of the human body. The material must be biocompatible and interact actively with the host tissues without immune rejection. The tissue scaffold must be mechanically stable to provide sufficient structural support and have an interconnected porous network to promote cell migration, vascularization, as well as tissue ingrowth. Moreover, the scaffold must be sterilizable and processed in the required shapes to match the defect sites (Rezwana et al. 2006).

Biomaterials are employed for various applications in different fields including orthopedics (joint replacements, bone plates, bone cement, artificial ligaments), cardiovascular (blood vessel prostheses, heart valves), dental fillers for tooth fixation, ophthalmic (contact lenses), wound healing and skin repair devices (Davis 2003).

During the last two decades, degradable scaffolds for biomedical application are preferred over bio-stable materials. This approach leads to the development of biodegradable medical devices as temporary scaffolds that assist body during healing and regeneration of damaged tissues. The long-term biocompatibility performance, stability issues, and the pain associated with multiple surgeries are eliminated by the utilization of biodegradable substrates (Naira and Laurencin 2007). The repairing and reconstruction of injured or aged tissues by degradable scaffolds have become the most investigated area in the twenty-first century (Parida et al. 2012). In the current scenario, polymers are the largest class of biomaterials employed in different fields of medicine such as dentistry, soft and hard tissue substituents, orthopedics, and cardiovascular (Dos Santos et al. 2017). Researchers, scientists, and doctors are exploring various biodegradable polymeric materials to predict their applications in biomedical engineering.

The composites assist in achieving superior biochemical and mechanical properties over its individual components. Natural bone is the best-known example of composite material in which apatite particles are embedded in collagen fibers. The concept of tissue inspired biocomposites has influenced several researchers for preparing various hybrids (Basile et al. 2012). The flexibility of polymers combined with bioactive materials in specific volume fraction helps in the development of composites with improved functionalities (Boccaccini and Maquet 2003). The composite architecture (orientation, distribution, and percentage reinforcements) and bonding between reinforcement and matrix also plays a key role. The effective control over these factors can assist in tailoring the mechanical and biological activity of the composites to meet the requirements of various biomedical applications (Antoniac 2016; Park and Lakes 2007; Bhat 2005; Narayan 2009).

2 Polymers

2.1 Classification of Polymers

The applications of polymers in biomedical engineering have been increased drastically due to its diverse properties (Piskin 1995). Polymers can be fabricated into different shapes and sizes with biodegradability and protein binding ability (Enderale et al. 2005). Researchers are employing different types of polymers to enhance human survival. Polymeric biomaterials for medical applications are mainly categorized into two groups as synthetic and natural polymers (Ratner et al. 2004; Stratton et al. 2016).

The natural polymers can be either an animal-derived material (collagen, hyaluronic acid) or a plant-based material (cellulose, sodium alginate) (Ratner et al. 2004). The natural polymers were the first degradable biomaterials used clinically, owing to their biological recognition and remarkable interactions with different cells to promote adhesion, proliferation, and lacking immune response. The insufficient mechanical stability, limited supply, and high cost are the few disadvantages of natural polymers (Stratton et al. 2016). Synthetic polymers include vast range of polymers starting from hydrophobic materials (polyethylene, polymethyl methacrylate, silicon rubber), polar materials (polyvinyl chloride, nylon) water absorbing materials (polyhydroxy methacrylate) to hydrophilic materials (polyvinyl alcohol, polyethylene glycol) (Ratner et al. 2004). Synthetic polymers possess good mechanical properties and the rate of degradation and molding ability can be altered (Armentano et al. 2010). The synthetic polymers are cheaper and possess improved functionality, despite few polymers have hydrophobic surface and lack cell attachment abilities (Dhandayuthapani et al. 2011).

2.2 Natural Polymer and Their Composites for Biomedical Applications

From an economic and environmental point of view, a vast array of naturally derived polymers has been explored as biomaterials for tissue engineering. Characteristics like low toxicity, superior biodegradability, low processing cost, renewability (Shogren and Bagley 1999), water solubility, pH stability, biological signaling, cell adhesion, and remodeling (Puppi et al. 2010) make natural polymers an excellent choice for scaffold materials.

2.2.1 Collagen

Collagen is a biological protein that can be extracted from every species including mammals. It occurs abundantly in the extracellular matrix of both hard (bone, teeth)

and soft tissues (skin, cartilage, blood vessels) that assist in providing structural support (Lee et al. 2001). Collagen exists in the form of 29 different types. The most widely studied collagen proteins for tissue repairing include I, II, III, V, XI type and among them type I collagen is reported as "Gold Standard" due to its poor immune reactivity (Parenteau-Bareil et al. 2010).

The biodegradation, cell attachment ability, and poor antigenicity indicate collagen as a promising polymer for biomedical applications. Studies indicate that collagen sponges stimulate adhesion and growth of cells and tissues (Freyman et al. 2001; O'Brien et al. 2005). Moreover, it promotes proliferation and differentiation of osteoblast cells leading to bone formation (Seol et al. 2004). The performance of mesenchymal stem cells seeded on collagen gel and implanted in osteochondral defects was studied. Formation of hyaline cartilage, as well as bone, was observed at the implant site, but the mechanical stability of regenerated tissue was significantly inferior to that of the natural tissues (Wakitani et al. 1994). It has been reported that the bioactivity of collagen is also dependent on the alignment of the collagen fibers. The biological behavior of aligned fibrous collagen scaffolds and random fibrous collagen scaffolds fabricated by electrospinning method was compared. It was found that the proliferation rate of rabbit conjunctiva fibroblast cells was faster on aligned fibrous collagen scaffolds (Zhong et al. 2006).

The low mechanical properties of collagen protein are associated with its rapid degradation rate. This limitation was overcome by preparing collagen composites with natural (glycosaminoglycans) and synthetic polymers (polyglycerol methacrylate) that lead to good mechanical strength, osteoconductivity as well as biocompatibility characteristics (Daamen et al. 2003; Woerly et al. 1991).

2.2.2 Silk

Silk fibroin falls into the category of naturally occurring polymeric proteins extracted from silkworms (Bombyx mori) and insects. The biocompatible properties of silk are due to the presence of protein component in it. The slow degradation, flexibility, permeable to water, oxygen, high strength, and tailorable composition of silk fibers make them as promising biomaterials for tissue engineering. The major disadvantage associated with silk is the presence of sericin protein which acts as a contaminant in the polymer by initiating adverse immune response at the site of application (Puppi et al. 2010). Studies show that the silk extracted from Bombyx mori has potential to promote the growth and development of bone-forming cells and silk sponges stimulated osteogenesis, chondrogenesis of mesenchymal stem cells extracted from bone marrow (Vepari and Kaplan 2007; Meinel et al. 2004). Fini et al. (2005) investigated the interactions involved in repairing of cancellous defects in rabbit using silk fibroin hydrogel. Results conclude that enhanced remodeling and maturation was observed in the presence of silk fibroin hydrogel when compared to commercial poly(lactide-co-glycolic acid) slurry (Fig. 1) (Fini et al. 2005).

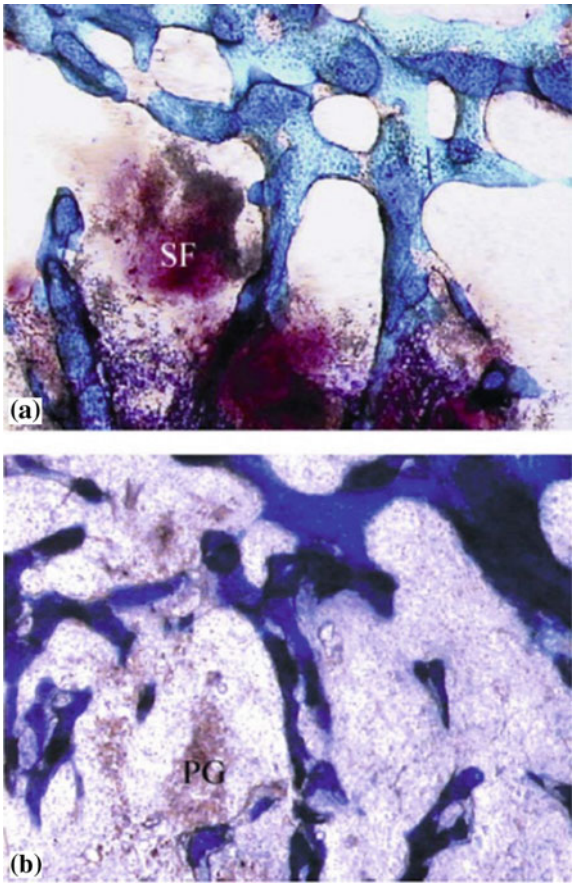

Fig. 1 Histological section of silk fibroin hydrogel treated defect (**a**) and synthetic polymeric gel-treated defect (**b**) after twelve weeks. Trabecular bone tissue having a microarchitecture similar to the normal healthy bone surrounding implant residues (PG) was noticed (Fini et al. 2005). Copyright 2005. Adopted with the permission from Elsevier

2.2.3 Hyaluronic Acid (HA)

Hyaluronic acid is a polysaccharide biodegradable material and known as hyaluronan. It is found in the extracellular matrix of connective tissues and plays a major role in structural support, regulating water balance, and lubricating medium for articular cartilage surface (Necas et al. 2008). Hyaluronic acid is extracted from synovial fluid, vitreous humor, and umbilical cord (Malafaya et al. 2007). The viscoelastic ability, biocompatibility, and swelling capability of hyaluronic acid indicate its applicability in encapsulation of cells and delivery systems (Kang et al. 2009; Wieland et al. 2007). The extensive availability, ease in manipulation of chain size, and non-immunogenic characteristics indicate HA as the most suitable material for tissue engineering applications (Allison and Grande-Allen 2006). Shu et al. (2003) reported that the polyanionic and hydrophilic surface of hyaluronic acid inhibits cellular attachment as well as tissue formation. These interactions were improved by coating the surface of HA by extracellular matrix proteins (Shu et al. 2003). Further, the

biomedical applications of HA have been widened by modifying its molecular characteristics by photo-crosslinking and covalent crosslinking (Allison and Grande-Allen 2006). The photo-crosslinked hyaluronic acid-based hydrogels retained the viability during the production of neocartilage under in vitro conditions. The human vascular endothelial cells seeded on hyaluronan-based Hyaff-11 biodegradable polymer reveal the formation of subendothelial matrix components within 24 h. This work indicates that the Hyaff-11-based polymers can be utilized as potential scaffolds to stimulate endothelialization in the vascular grafts (Turner et al. 2004).

2.2.4 Chitosan (CS)

Chitosan is a naturally occurring second most abundant polysaccharide biodegradable polymer known for its applications in food industry, cosmetics, drug delivery, tissue engineering, etc. (Perinelli et al. 2018). The partial deacetylation of chitin through chemical hydrolysis results in the production of chitosan (Chandy and Sharma 1990). The unique characteristics such as antibacterial activity, hydrophilicity, minimum immune response indicate the applicability of chitosan in the field of tissue engineering (Naira and Laurencin 2007). Recently, antibacterial and biocompatible chitosan derivative 1,3-diethyl-2-thiobarbituric acid (CS-DETBA) was developed. CS-DETBA derivative shows enhanced inhibition of *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*) *and Staphylococcus aureus* (*S. aureus*) bacteria and the non-toxic effect was observed on the growth of human gastric adenocarcinoma AGS cells (Rizwan et al. 2018). Xu et al. (2018) developed chitosan/tripolyphosphate scaffold and studied the cell proliferation ability of bone marrow mesenchymal stem cells and concluded it as a promising material for bone regenerative medicine (Xu et al. 2018). Although chitosan possesses osteoconductive ability to stimulate bone formation under in vitro and in vivo conditions, the poor mechanical stability restricts its capability to maintain precise shape which narrows its application areas.

2.2.5 Cellulose

Cellulose is a biologically derived polysaccharide biopolymer and an important structural component present in the cell walls of the plants. It also exists in other living microorganisms such as bacteria, algae, and fungi (Puppi et al. 2010). The hydrophilicity, bio-functionality, and biocompatibility of cellulose extended its applications in tissue engineering, drug delivery, biosensor, imaging, etc. (Klemm et al. 2005).

Porous cellulose hydrogel possessing good transparency and desirable mechanical stability can be produced by casting cellulose/1-butyl-3-methylimidazolium chloride. The hydrogel membrane prepared can be utilized as a drug carrier for the delivery of pharmaceutical agents, contact lenses, or wound

healing material (Peng et al. 2018). Earlier findings have shown that cellulose has ability to stimulate proliferation and growth of human chondrocytes indicating its applications in cartilage tissue engineering (Svensson et al. 2005). Recently, a cellulose-based composite material containing chitosan and silver nanoparticles was reported as a promising wound dressing agent. The scaffold showed good antibacterial activity against *E. coli* and *S. aureus* as well as support the adhesion, proliferation of NIH3T3 fibroblastic cells within three days of incubation (Fig. 2) (Haider et al. 2018).

An effective polysaccharide capsule for oral drug delivery was developed to carry hydrophobic drug (Ibuprofen) by physical crosslinking of carboxymethyl-cellulose (CMC) and hydroxymethyl cellulose (HMC). Results indicated that the release profile of samples varies under different environments. The complete release of drug in intestinal fluid from HMC was observed within 8 h whereas when CMC was mixed with HMC a prolonged (24 h) and sustained release profile of the drug from carrier was noticed (Chen et al. 2018). The performance of gelatin-based hydrogel with chitosan and hydroxyethyl cellulose was studied for tissue engineering scenarios. The gelatin/poly(ethylene glycol)/hydroxyethyl cellulose (G/PEG/HEC) hydrogel showed a reduction in stiffness, enhanced flexibility, and mechanical strength similar to soft tissues. The cellular study revealed non-toxic

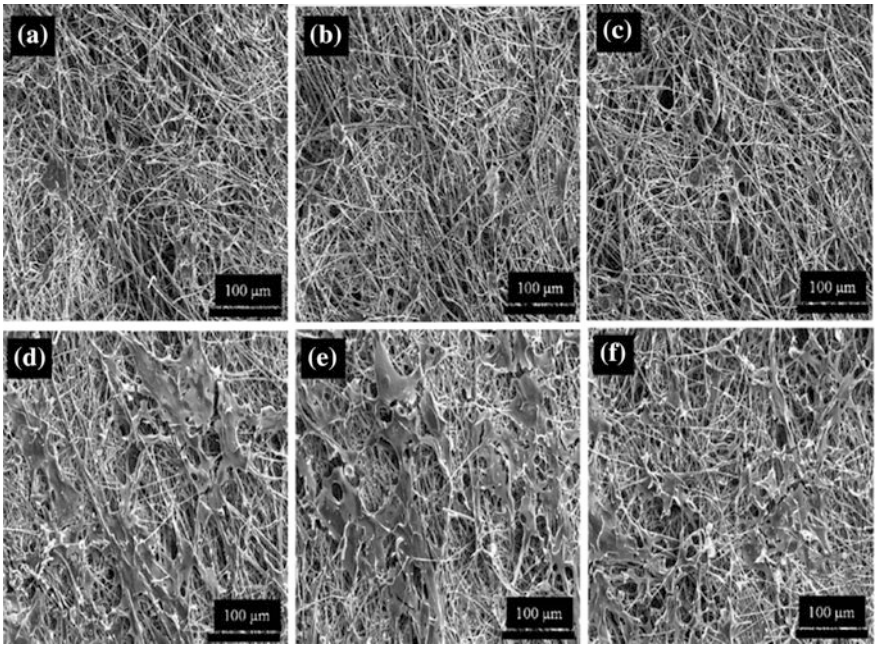

Fig. 2 FE-SEM images of the NIH3T3 fibroblastic cells on the surface of composites (pristine FP, CS-FP and Ag-CS-FP). **a–c** shows after 1 day and **d–f** shows after 3 days of incubation (Haider et al. 2018). Copyright 2018. Adopted with the permission from Elsevier

behavior of the hydrogel and supported adhesion and proliferation of human fibroblast and L6 rat myoblasts within four days (Dey et al. 2018).

2.2.6 Alginate

Alginate is a naturally derived polysaccharide polymer generally obtained from brown algae namely *Macrocystis pyrifera, Laminaria hyperborean,* and *Ascophyllum nodosum*. Alginate is widely studied for biomedical applications such as tissue engineering scaffolds, drug delivery, wound healing, cell transplantation, and anti-adhesion material (Puppi et al. 2010). The vast applications of alginate in biomedical engineering are due to its good biocompatibility, lower toxicity, and ability to form stable gelation in the presence of cations (Ca^{2+}, Sr^{2+}) (Lee and Mooney 2012).

In recent reports, polysaccharide template oxidized sodium alginate conjugated with acrylamide was prepared for biomedical applications. The tailored conductivity, stretch sensitivity, mechanically tough, and self-healing capability of hydrogel indicated it as a potential material for artificial skin and medical devices (Liu et al. 2015). Earlier, an injectable and self-healable alginate hydrogel was prepared for repairing the defects associated with the central nervous system (Tseng et al. 2015). The combination of alginate with guluronic acid promoted the proliferation and differentiation of murine marrow cells (Wang et al. 2003). Further, the in vitro study of chitosan/alginate gel showed the adhesion of bone-forming cells as well as deposition of apatite mineral on their surface (Li et al. 2005).

The antibacterial activity of bimetallic (copper/Zinc) alginate-based composite against biofilm forming bacteria (*E. coli*, *S. aureus*, *C. albicans*) was investigated for biomedical applications. The composites had a remarkable effect on the growth of the microorganisms and seem to possess bactericidal activity against these pathogens (Malagurski et al. 2018). Moreover, Safaei and Taran (2018) investigated the antibacterial behavior of alginate/copper oxide composites against *E. coli* and *S. aureus* by disk diffusion method. The alginate polymer showed no sign of antibacterial activity whereas the composite containing 2 mg/mL alginate and 8 mg/mL copper oxide revealed excellent antibacterial activity within 1 h. It was found that the composites produced a clear zone of inhibition (17.33 and 19.33 mL) against *E. coli* and *S. aureus*. This study indicated that these composites can be used as an effective antibacterial agent against human resistant bacterial strains (Safaei and Taran 2018).

Recently, chitosan/alginate interpenetrating polyelectrolyte-complex multilayer membrane was prepared to study their wound healing ability. The membrane exhibits effective antibacterial activity against *E. coli* whereas cellular attachment, growth, and development of L929 cells indicated non-cytotoxic nature (Sun et al. 2018). The poor mechanical strength of alginate in aqueous medium restricts its applications to a non-load bearing scenario. An improvement in the mechanical properties of alginate in wet conditions was observed by fabricating UV stimulus-responsive cellulose nanocrystals/alginate scaffolds (Smyth et al. 2018).

2.3 Synthetic Polymers and Their Composites for Biomedical Applications

The properties of synthetic polymers (physical, chemical) can be altered as per the requirements of the application. The flexibility of these polymers assists in molding them into different sizes and shapes. The risk of infection, toxicity, and immune rejection are found to be lower in case of synthetic polymers. The most commonly used synthetic polymers for biomedical applications are given below.

2.3.1 Polycaprolactone (PCL)

Polycaprolactone is a polyester material known for its elastic nature. It is composed of a semi-polar ester group and nonpolar methylene groups. Polycaprolactone is largely applied in biomedical applications and especially in tissue engineering due to its high elasticity and biocompatibility. Moreover, PCL is approved by Food and Drug Administration (FDA) as a drug delivery carrier, sutures and scaffold for repairing tissues, etc. (Woodruff and Hutmacher 2010). The degradation of PCL at a slower rate indicates that it can be used as an implantable material for long-term applications such as the drug carrier for controlled release of therapeutic agents (Cipitria et al. 2011). Polycaprolactone possesses slow adhesion and proliferation of cells when used as a bulk material. Several attempts have been made to enhance the bioactivity of PCL either by surface functionalization or by preparing its composites.

A chitosan-1,3-diethyl-2-thiobarbituric acid-polycaprolactone (CS-DETBA-PCL) blend was prepared for tissue engineering applications. The blend revealed negligible cytotoxicity response on AGS cells and remarkable inhibition on the growth of bacterial strains (*S. aureus*, *E. coli*, *P. aeruginosa*) (Xu et al. 2018). Recently, polycaprolactone/chitosan/magnesium oxide nanofiber was prepared by using electrospinning methodology. The PCL/MgO showed better mechanical stability (25 MPa) than PCL/chitosan (3 MPa). The cellular study showed attachment of 3T3 cells on the surface of the composites indicating their non-cytotoxic nature. This study suggested versatile applications in the field of drug delivery, bone regeneration, and wound healing (Rijal et al. 2018).

Polycaprolactone is widely used as a scaffold material for hard tissue regeneration either in pure form or in combination with bioactive ceramics. The degradation kinetics and biological interaction of pure PCL with bone marrow mesenchymal stem cells (BMSC's) show that the degradation by-products of PCL have negligible influence on the functioning of BMSC's and the viability of osteoblast cells was also well maintained in PCL extract (Sukanya and Mohanan 2017). The PCL/forsterite scaffold was fabricated by solvent casting and particle leaching method to study biodegradability, mechanical properties, bioactivity, and cytotoxicity of the scaffolds for bone regeneration applications. An improvement in mechanical properties was observed for the composites as compared to pure PCL.

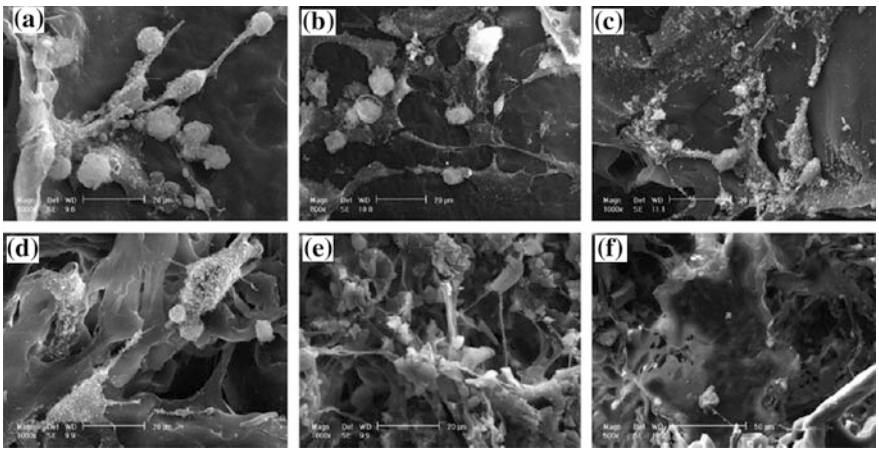

Fig. 3 Scanning electron microscopy images of the pure PCL (**a**) and nanocomposite scaffolds containing **b** 10 wt%, **c** 20 wt%, **d** 30 wt%, **e** 40 wt%, and **f** 50 wt% forsterite cultured with SaOS-2 cells for 2 days (Diba et al. 2012). Copyright 2012. Adopted with the permission from Elsevier

It was also observed that the cellular behavior of the composites was influenced by the forsterite content (Fig. 3) (Diba et al. 2012). Thin membrane patch of polycaprolactone/β-tricalcium phosphate was prepared by using 3D printing for repairing orbital fractures in white rabbits. Results showed that about 40% reduction in the fracture volume was observed after two months, whereas new bone formation at the mesh implant was noticed within four months. This report proposed that the 3D printed membrane patch could be a promising approach for filling defected spaces in bone as well as preventing inflammatory response at the site of application (Han et al. 2018).

2.3.2 Poly(Methyl Methacrylate) (PMMA)

The self-hardening ability and superior mechanical properties of Poly(methyl methacrylate) (PMMA), when compared to other synthetic polymers, make it as a promising material for fixing implants with bone (Lee and Rhee 2009). PMMA provides immediate structural support to the metallic implant but due to its bioinert nature, it shows negligible chemical and biological interactions with bone. PMMA is considered as a weak link between an implant and bone (Renteria-Zamarron et al. 2009). Moreover, the inert behavior of PMMA results in osteolysis and loosening of the implant under the influence of repeated interfacial movements (wear debris) (Goodman 2005). These challenges can be overcome by introducing the bioactive ceramics as a filler in the polymer matrix (Shinzato et al. 2000). This provides adequate osteoconductivity and sufficient mechanical stability to the resultant composite.

PMMA-reinforced hydroxyapatite shows good anchorage of human osteoblast cells (HOB), enhanced proliferation as well as ALP activity (Dalby et al. 1999). The PMMA containing 39% of wollastonite exhibits good apatite formation ability and optimum compressive strength (Renteria-Zamarron et al. 2009). Lee and Rhee suggested PMMA/SiO_2-CaO nanocomposites as a filler material in dental composite and bone cement (Lee and Rhee 2009).

2.3.3 Poly(L-Lactic Acid) (PLLA)

PLLA is a form of a polyester degradable polymer. It can be either obtained from natural renewable source (starch) or by the polymerization of L-lactide. PLLA has been significantly investigated for various biomedical applications such as drug delivery carrier, scaffolds for tissue regeneration, screws, and pins for fixing bone implants and sutures. Sculptra™ is an FDA-approved injectable PLLA material used commercially for the treatment of facial atrophy (Stratton et al. 2016). It has been reported that the high crystallinity of PLLA undergoes rapid degradation resulting into an inflammatory response at the site of application (Lasprilla et al. 2012). This drawback can be overcome by fabricating it as a composite with other polymers.

Novel PLLA/Rg3 scaffolds were prepared to reduce the inflammation-related with PLLA and study their response to skin regeneration (Cui et al. 2013). The uniform surface morphology and interconnected porosity of scaffolds inhibit the proliferation of fibroblast cells. This indicates that the fabricated composites have the ability to restore the structural and functional properties of damaged skin due to severe burn or surgical incision. Further, PLLA/PGS (polyglycerol sebacate) defect-free fiber was prepared by utilizing electrospinning technique. The incorporation of PGS in the fibers enhanced the wettability and super hydrophilicity was achieved. It was found that as the concentration of PGS (polyglycerol sebacate) in the fibers was increased to 25%, a sudden decrease in Young's modulus was observed from 35.9 to 7.4 MPa. This results in twofold improvement in the stretching ability of the samples. The cellular study showed adhesion and proliferation of A59 nerve cell lines suggesting PLLA/PGS fibers as the promising biomaterial for nerve regeneration (Yan et al. 2017). The corrosion resistance of Mg alloy (WE43) under deformation was improved by a dual coating of hydroxyapatite and PLLA. The stability of coating under the influence of deformation was improved by applying PLLA on the surface by dip coating. The hydroxyapatite forms an intermediate layer to enhance the adhesion of PLLA. The dual-coated Mg alloys show improved mechanical stability and biological response when compared to single-coated or non-coated samples. This approach might accelerate the development of Mg-based alloys for biomedical applications (Diez et al. 2016).

2.3.4 Poly(Lactic-Co-Glycolic) Acid (PLGA)

Poly(lactic-co-glycolic) acid is a biodegradable polyester polymer prepared by combining poly(L-lactic acid) and poly(glycolic acid). Poly(lactic-co-glycolic) acid

has attracted the attention of researchers for tissue engineering applications owing to biocompatibility, tailorable degradation rate, and ease of modifying the surface properties to promote better interaction with biological materials (Gentile et al. 2014).

OsteofoamTM is a FDA-approved poly(lactic-co-glycolic) acid scaffold for hard tissue regeneration (Shen et al. 2008). A uniform blend of poly(lactic-co-glycolic) acid and polyisoprene was studied for treating craniosynostosis and the scaffolds possess interconnected porous structure having the optimum pore size which acts as a template for supporting the growth of C2C12 cell lines and formation of extracellular matrix. The mechanical strength of these scaffolds was found to be similar to that of soft tissues. Authors suggested that these scaffolds can be a suitable material for soft tissue engineering (Marques et al. 2017). The poly (lactic-co-glycolic) acid/silk scaffolds have been explored for tendon regeneration. Results showed that the scaffolds exhibit good mechanical stability as well as have potential to stimulate mesenchymal progenitor cell to undergo adhesion and differentiation (Sahoo et al. 2010). Hydroxyapatite supported poly(lactic-co-glycolic) acid/silk composites were fabricated to study their application for hard tissue engineering. MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) indicates that the prepared scaffold supports adhesion and proliferation of osteoblasts (Sheikh et al. 2015). Further, chitosan/poly(lactic-co-glycolic) acid microspheres were found to stimulate the growth and development of MC3T3-E1 cell line over their surface (Jiang et al. 2006).

The highly acidic nature of by-products produced during the degradation of PLGA limits its drug delivery applications. Scientists are attempting different strategies to overcome this drawback by varying the content of poly(glycolic acid). An increase in the ratio of poly(glycolic acid) to that of poly(L-lactic acid) leads to slower degradation rate and less acidic by-products (Houchin and Topp 2008).

2.3.5 Poly(Ethylene Glycol) (PEG)

Poly(ethylene glycol) is a biocompatible polyester polymer existing in several molecular weights which is soluble in water as well as in organic solvents. PEG possesses the ability to interact with cell membranes without influencing the activity of active proteins of cells. The unique ability of PEG for maintaining chemical reactivity and solubility even after surface functionalization and chemical modifications indicate its versatile applications in the biomedical field (Harris 1992).

PEG supported multi-walled carbon nanotubes in the form of nano-cocoons were prepared and loaded with curcumin to study their efficiency as a drug delivery carrier for the treatment of cancer. These nano-systems were non-toxic to blood and promoted the proliferation of L929 fibroblast cell lines. It was also found that the curcumin-loaded nano-cocoon effectively dispersed in the saline medium and interacted with C6 glioma brain cancer cells, whereas alone curcumin was unable to enter brain cancer cells (Fig. 4) (Hindumathi et al. 2018). The utilization of hydrogels as a wound dressing material has drawn attention of several research

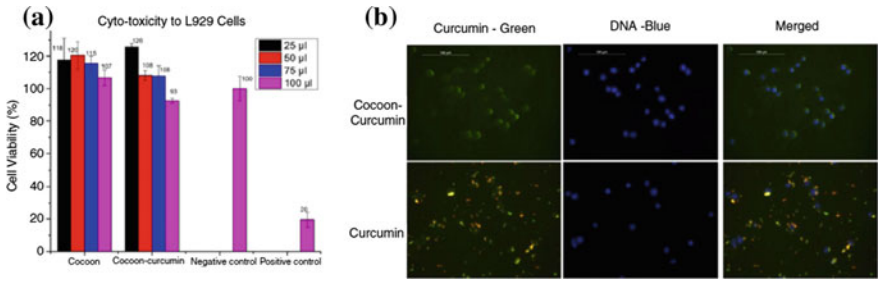

Fig. 4 Cytotoxicity of cocoon and curcumin samples at various concentration (**a**) and Uptake of cocoon–curcumin (**b**). Images revealed that the uptake of curcumin with cocoon and no uptake without cocoon (Hindumathi et al. 2018). Copyright 2018. Adopted with the permission from Elsevier

groups. Haryanto and Mahardian (2017) prepared hydrogel film composed of polyethylene oxide and poly(ethylene glycol) dimethacrylate. It was found that the addition of poly(ethylene glycol) dimethacrylate in hydrogel played a major role in improving mechanical strength, vapor transmission, and percentage elongation. Thus, the tensile strength of hydrogel was increased from 5 to 20% with the steady improvement in the elongation behavior. The water vapor transmission rate of polyethylene oxide-poly(ethylene glycol) dimethacrylate hydrogel was noticed to be near to the ideal value favorable for wound healing (Haryanto and Mahardian 2017).

An environment friendly, non-toxic, porous and biocompatible poly(ethylene glycol)/cellulose scaffolds were fabricated. The close-grained sheet like network was observed due to the addition of crosslinked PEG in regenerated cellulose. This modification resulted in an increase in the compressive strength of scaffolds by 33 times as compared to that of regenerated cellulose (0.007 MPa). Moreover, the water absorption capacity of scaffolds was found to be nearly 83% higher than that of regenerated cellulose. These scaffolds can be employed for biomedical devices and packaging applications (Teng et al. 2018).

2.3.6 Polystyrene (PS)

Polystyrene is a biocompatible, non-degradable polymer exhibiting insignificant cytotoxicity. Polystyrene nanoparticles can be prepared in different sizes with various surface functionalizations that are being investigated to look for its pertinence in biomedical therapies (Loos et al. 2014a).

Loos et al. (2014b) prepared amino (PS-NH_2) and carboxyl (PS-COOH) functionalized polystyrene nanoparticles to contemplate their interaction with THP-1 cell lines for targeting acute myeloid leukemia (Loos et al. 2014b). It was observed that carboxyl functionalized polystyrene nanoparticles induced an insignificant effect on the proliferation rate of THP-1 cell lines and exhibited negligible toxicity

on THP-1, differentiated THP-1 or macrophages even after exposure for longer durations. Proliferations of THP-1 cells were immediately inhibited by amino-functionalized polystyrene nanoparticles which lead to decrease in their cell size and finally cell death. This study proves that the functionalization of biocompatible polystyrene can be a viable strategy to design new drug delivery systems for the treatment of malignant cells.

Earlier, *N*-hydrosuccinimide functionalized polypyrrole coated polystyrene latex particles (NHS-functionalized PPy–PS) were fabricated to investigate their biomedical application as bioadsorbents of human serum albumin (HSA) (Bousalem et al. 2003). The concentration of initial comonomer was 50/50 and 25/75 for pyrrole and pyrrole-NHS. The mechanism of attachment of HAS protein on the surface of NHS-functionalized PPy–PS particles was due to the formation of covalent bond between them. The immobilization isotherms for HAS showed maximum adsorption of 0.2 mg/m^2 for 50/50 ratio, whereas about 0.02 mg/m^2 was detected in case of 25/75 ratio. The presence of surface-reactive groups in higher concentration was found to restrict the covalent attachment of HSA protein on the surface of NHS-functionalized PPy–PS latex particles. Hence, a lower concentration of *N*-hydrosuccinimide groups can assist in better attachment of proteins on their surface.

Later, Miroslawa El (Fray et al. 2006) compared the biocompatibility and fatigue properties of therapeutic grade silicone rubber with Food and Drug Administration approved SIBS30 biomaterial (polystyrene-*b*-polyisobutylene-*b*-polystyrene thermoplastic elastomer with 30 wt% polystyrene) (Fray et al. 2006). The non-toxic nature of SIBS30 disks was confirmed by immersing in human as well as sheep red blood cells. The outcomes showed no sign of hemolytic responses and the hemolytic indices were observed to be zero.

The in vivo biocompatibility of sterilized silicone rubber and SIBS30 disk was examined by implanting in the muscle tissue of male white mice. Following 30 days of implantation lower tissue reactions and a negligible inflammatory response was detected in SIBS30 samples. This behavior was found to be similar to that of silicone rubber (control). The histological investigation confirmed the formation of fibrous connective tissue covering both the samples. The long-term implantation (180 days) resulted in the formation of a compact capsule having a thickness of 21 μm (silicone rubber) and 47 μm (SIBS30), respectively. This data indicates good biocompatibility of the tested polymeric samples. The dynamic modulus of SIBS30 biomaterial was found to be nearly 10 times higher than the medical-grade silicone rubber utilized for tendon prosthesis. Moreover, better fatigue properties and creep resistance were noticed for SIBS30 when analyzed under different environments (air and simulated in vitro conditions). The remarkable biocompatibility of SIBS30 inferred that it as a potential biomaterial having close resembles with medical-grade silicone rubber and does not require synthetic cross-linkers or reinforcing fillers.

2.3.7 Polyvinylidene Fluoride (PVDF)

The remarkable chemical resistance, biocompatibility, thermal stability, and stimulus-responsive characteristics made fluorinated polymers as potential biomaterials for biomedical applications. PVDF is the most common fluorinated polymer. It is semi-crystalline, non-reactive polymer and synthesized by polymerization of vinylidene fluoride monomer (Cardoso et al. 2018).

Ribeiro et al. (2017) studied the potential of piezoelectric PVDF biomaterial for hard tissue regeneration (Ribeiro et al. 2017). The osteogenic properties of PVDF films were investigated by implanting it in Wistar rats (Fig. 5). After 28 days, no sign of inflammatory response and infections was noticed around the implanted films. Moreover, significant bone regeneration was observed at the defected site that led to the formation of trabecular bone.

The extensive utilization of PVDF for biomedical, pharmaceutical applications and hygienic products cause their exposure to microorganisms leading to biofilm formation. In order to prevent bacterial infections, a flexible PVDF composite containing three different nanofillers was fabricated to study their antibacterial properties against *Pseudomonas aeruginosa* (Bregnocchi et al. 2016). The PVDF composites contain graphene nanoplatelets (GNPs), zinc oxide nanorods (ZnO-NRs), and ZnO-NR-decorated GNPs (ZNGs) as nanofillers. The PVDF composites containing GNPs and ZNGs have shown superior antimicrobial activity than ZnO-NRs. The GNPs and ZNGs nanostructures grown on the surface of PVDF film are bigger and occupied major portions. This offers a larger interacting surface with the bacteria leading to good antibacterial activity. The current report concludes low-cost methodology for the preparation of biofilm resistant biocompatible polymers.

Earlier solvent casting method was utilized for the fabrication of PVDF/HAp film to study their mechanical as well as cytotoxicity properties for repairing bone defects (BragaI et al. 2007). It was observed that the incorporation of hydroxyapatite (HAp) in PVDF matrix caused reduction in mechanical stability of the

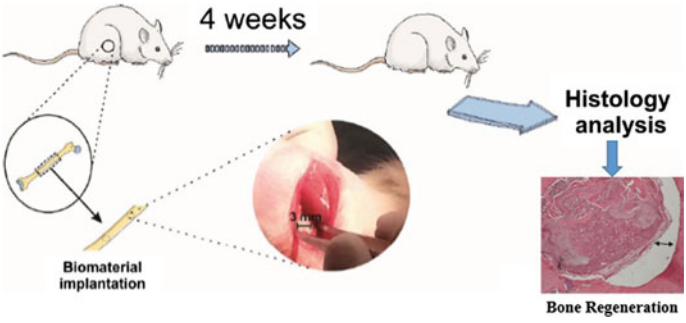

Fig. 5 Bone regeneration at the defected site in Wistar rats (Ribeiro et al. 2017). Copyright 2017. Adopted with the permission from Elsevier

composites. The cell viability results showed no toxicity. Thus, the samples were found to be biocompatible and can be promising candidates for bone and dental restoration.

It has been reported that hydrophobic nature of fluorinated membranes restricts their cell attachment and proliferation ability. Pei et al. (2015) attempted to enhance the cytocompatibility of PVDF by preparing its composites with reduced graphene oxide (RGO) (Pei et al. 2015). The reduced graphene oxide/PVDF composite membranes were cultured with human umbilical vein endothelial cells (HUVECs) to evaluate their cellular adhesion and proliferation response. It was found that the addition of RGO facilitated in the transformation of alpha phase PVDF to beta phase PVDF. The beta phase PVDF has the ability to promote endothelial cell secretion of prostacyclin, which has anti-thrombotic functions. The adhesion and proliferation of HUVECs on the surface of composites were found to be superior to the pure PVDF.

2.4 *Gas Permeable Polymeric Membranes for Biomedical Applications*

Polymeric membranes for hemodialysis or as oxygenators are widely studied for the treatment of infants with insufficiently developed lungs, chronic problems, and cardiac surgery. These membranes have tendency to deposit blood components (proteins, platelets) over their surface which reduces the gas exchange efficiency (Kolobow et al. 1986). In order to overcome these problems, 2-methacryloyloxyethyl phosphorylcholine (MPC) copolymers were been prepared and studied for surface modification of conventional polymers. When MPC copolymers and alkyl methacrylate were coated on substrate polymer, a constant decrease in the protein adsorption as well as inhibition of cell adhesion was observed even when the polymer was placed in direct contact with the blood without anticoagulants (Ishihara et al. 1992). Later, Iwasaki et al. synthesized novel oxygenator membrane composed of poly[(2-methacryloyloxyethyl phosphoryl-choline) (MPC)-co-dodecyl methacrylate] (PMD) skin film adhered to polyethylene (PE). The oxygen gas permeation analysis through PMD/PE membrane was found to be similar to that of polyethylene membrane even when the unit mole fraction of MPC in PMD was higher than 0.2. This observation suggested that MPC content in the polymer film effectively improved the gas permeability. Moreover, the protein adsorption on the surface of PMD was found to be significantly decreased when compared to polyethylene surface (Iwasakia et al. 2002). The mechanism for reduced protein adsorption on membrane surface was also proposed. The hydrophobic interactions assisted in the adsorption of protein molecules on the surface. Thus, the membrane surface which inhibits hydrogen bonding with water prevents protein adsorption (Lu et al. 1991). This report suggested simple and

cost-effective method for the preparation of PMD/PE porous membrane having good hemocompatibility and gas permeability.

The polysulfone (PSF) membranes containing polyethylene glycol (PEG) and heparin (Hep) were prepared by plasma-induced surface modification to predict their applicability as an artificial lung (Wang et al. 2016). The improvement in the surface hydrophilicity and steric hindrance of polysulfone-polyethylene glycol-heparin membrane resulted in decrease in adsorption rate of bovine serum albumin and fibrinogen when compared to pristine PSF. The pure PSF membrane exhibited greater platelet adhesion over its surface whereas polysulfone-polyethylene glycol-heparin membranes revealed steep decline as the molecular weight of PEG was increased. Hence, PSF-PEG10,000-Hep and PSF-PEG6000-Hep showed good platelet adhesion resistance. Moreover, polysulfone-polyethylene glycol-heparin membrane revealed excellent gas exchange performance in the presence of porcine blood. The gas exchange rate of oxygen and carbon dioxide in PSF-PEG6000-Hep membrane was noticed to achieve 100–200 and 50–300 mL/min at blood flow rate of 5 L/min. Later, PSF chloromethylation, PEGylation, and heparin immobilization process was employed to synthesize polysulfone (PSF) membranes embedded in polyethylene glycol (PEG) and heparin (Hep) to study their performance for use in membrane oxygenators (Zheng et al. 2016). Blood oxygenate results of PSF-PEG10,000-Hep membrane showed the carbon dioxide and oxygen exchange rates of about 102 and 110 mL/min at a flow rate of 1.5 L/min. These values were found to satisfy the gas exchange potential of commercially used membrane oxygenators. These findings indicated polysulfone-polyethylene glycol-heparin as potential oxygenator membrane for the treatment of various lung diseases.

Recently, Zheng et al. employed low-temperature plasma treatment for surface modification of polysulfone for extracorporeal membrane oxygenators (Zheng et al. 2018). In this work, three different additives such as Acrylic acid (AA) with heparin (Hep), 2-methacryloyloxyethyl phosphorylcholine (MPC) and collagen (Col) were grafted over the surface of PSF to prepare PSF-AA-Hep, PSF-MPC and PSF-Col membranes. The protein adsorption trend on the surface of membranes was found to be least for PSF-AA-Hep followed by PSF-MPC, PSF-Col, and pristine PSF. These membranes exhibited similar behavior when studied for platelet adhesion. The potential reason for such activity was due to charged groups from heparin, biomimetic structures from collagen or MPC, and hydrophilic groups from acrylic acid. These factors might exhibit steric hindrance in preventing protein adsorption on the surface of membranes. The gas permeation results revealed that the surface-modified PSF membranes have lower activity than pristine PSF membranes. This was due to thin layer formation of grafted molecules on the surface of modified PSF membranes. This might have hindered in gas permeation of oxygen and carbon dioxide. Hence, the modified polysulfone (PSF) membranes demonstrated an acceptable gas transmission performance that might meet the needs for artificial respiratory devices or membrane oxygenators.

2.5 Other Polymeric Composites for Biomedical Applications

Polymers and ceramics are the most abundantly used materials in clinical practice. Holzapfel et al. (2013) emphasized them as key players of biomaterials market. The basic requirements to meet the clinical demands such as biocompatibility, controlled degradability, optimum porosity, and mechanical stability cannot be satisfied by a single component material. Hence, scientists have attempted to develop multicomponent materials in the form of composites to tackle these challenges. The advancements made in the field of polymer/ceramic composites to study their biomedical applications are given below. The major reason for designing polymer/ceramic composites is to introduce bioactive characteristic in the polymer matrix (Dziadek et al. 2017).

Gil-Albarova et al. (2012) investigated the in vivo behavior of glutaraldehyde crosslinked, gelatin-coated hydroxyapatite scaffold implanted in defected femur bone of New Zealand rabbits. After four months of implantation, the histopathological studies revealed that macroporous hydroxyapatite foam assisted in healing the critical-sized bone defect followed by bone conduction over its surface. This study showed that the gelatin-coated hydroxyapatite scaffold can provide optimum conditions for promoting bone ingrowth at the defected site. These results indicated the biocompatibility of the scaffold and offer a potential material for biomedical applications such as orthopedics and dentistry.

Additive manufacturing technique was utilized to prepare 3D biomimetic collagen/hydroxyapatite scaffolds for hard tissue regeneration (Lin et al. 2016). The scaffolds having dimensions of 600 μm exhibit better mechanical stability and possess good adhesion, proliferation, and differentiation of bone marrow stromal cells seeded on the surface of scaffolds. The in vivo study conducted in femoral condyle defect in rabbit showed growth and development of new bone within the scaffolds. It was concluded that 3D printed collagen/hydroxyapatite scaffolds having interconnected pores can be utilized for tissue engineering applications.

The biomimetic inorganic/organic composites were developed by using 3D X-ray micro-tomography (Alonso-Sierra et al. 2017). Gel-casting method was employed for the preparation of hydroxyapatite and molded into required shape by adding PMMA microspheres. The hydroxyapatite scaffold with controllable porosity was achieved by burning the organic matrix during sintering. Finally, bovine tail-derived gelatin and collagen were used to fabricate biomimetic inorganic/organic composites. The compressive strength of gelatin-based composite was 18 MPa, whereas 13.2 MPa was noticed for collagen. Hence, the mechanical stability of the composites was found superior to cancellous bone. The pore structure and their distribution observed in this work suggested that these composites could be a promising material to support cell proliferation, tissue ingrowth, nutrient supply, and removal of waste products during hard tissue regeneration. A recent article reviewed the in-depth progress involved in starch/hydroxyapatite-based composites for various biomedical applications such as

bone cement, adhesives, bone waxes, drug delivery applications, and delivery of antibiotics (Miculescu et al. 2017).

Recently, polycaprolactone/hydroxyapatite/gelatin scaffolds loaded with doxycycline were fabricated to evaluate their antibacterial activity, drug release behavior, and cytotoxicity. The antibacterial study revealed effective inhibition on the growth of *Staphylococcus aureus* and *Porphyromonas gingivalis* bacteria. The release profile of doxycycline in phosphate buffer solution took place in two steps. Initially, the scaffolds exhibited burst release of nearly 60% of the drug within an hour and later the remaining drug was continued to release for 55 h. The anticancer activity of scaffolds was studied against three different cancer lines (A-431, 4T1, CACO-2) by using MTT assay. The A-431 and 4T1 cells showed a high level of toxicity than CACO-2 when treated with polycaprolactone/hydroxyapatite/gelatin scaffolds. This report indicated that the doxycycline loaded polycaprolactone/hydroxyapatite/gelatin composites can be suitable biomaterial for drug delivery, antibacterial and anticancer applications (Ramirez-Agudelo et al. 2018).

The influence of compositional ratio and chemical constituents on biomineralization activity of chitin/larnite composites was investigated (Choudhary et al. 2016). The apatite deposition ability of chitin/larnite composites (30:70, 20:80) and pure larnite was studied by immersion in SBF (simulated body fluid) for five days. The apatite precipitation on the surface of composites increased with the increase in polymer content in the composite. Thus, the bioactivity of chitin/larnite (30:70) ratio was found to be superior to chitin/larnite (20:80) and pure larnite. A similar finding was reported in which the chitosan/larnite composite ratio mimicking natural bone [eggshell derived chitosan/larnite (30:70)] exhibited better apatite deposition (Choudhary et al. 2015).

Multicomponent poly(lactic acid)/poly(caprolactone)/wollastonite composite system was prepared to predict their applicability as a biomedical scaffold (Goswami et al. 2013). The compressive test of porous foams under dry and wet conditions was carried out in order to analyze the performance of composites under physiological conditions. It was observed that the mechanical stability of composites increased with the increase in the wollastonite content. The hydrophobic nature of polymers restricts their interaction with the cells and decelerates tissue regeneration process. The contact angle measurement of the composites was done to study their wettability. It was found that the presence of wollastonite lowered the contact angle as well as enhanced the wettability of the composites. The MTT assay of the composites shows enhanced proliferation of osteoblast cells on the surface of the composite having maximum filler content (PLCLW8) within 7 days. It can be concluded that the scaffolds containing bioactive silicate as filler promoted the adhesion and proliferation of osteoblast cells at a faster rate than the pure polymer (PLCL15).

Recently, cell viability and mechanical properties of Poly(butylene adipate-co-terephthalate)/wollastonite biocomposites were studied (Bheemaneni et al. 2018). The surface of composites after immersion in simulated body fluid shows good apatite deposition within five days. The tensile strength of composites was found to increase with the increase in filler (wollastonite) content. The

composites showed better proliferation of MG63 cells within short incubation period. Thus, bioactive silicate (wollastonite) was noticed to play a vital role during biomineralization as well as cell proliferation on the surface of composites when compared to pure poly(butylene adipate-co-terephthalate).

Santos et al. (2017) reported simple and scalable processing method for the preparation of hydroxyapatite/poly(L-lactic acid) electrospun membranes for bone regeneration (Santos et al. 2017). The interaction of poly(L-lactic acid) and hydroxyapatite/poly(L-lactic acid) membranes with MG63 osteoblastic-like cells was evaluated to confirm their biocompatibility. The cell proliferation on the surface of hydroxyapatite/poly(L-lactic acid) membranes was found to be higher than neat poly(L-lactic acid). The metabolic activity of hydroxyapatite/PLLA membranes (582 ± 182%) was highest when compared to PLLA (321 ± 36%) and control (117 ± 16%). These values indicated that the rate of cell growth was faster on the surface of membranes. This study further strengthens the fact that the presence of ceramic particles in polymer matrix improved the biological properties of the composites with the cells.

Macha et al. (2017) developed polylactic acid (PLA) thin film composed of coralline hydroxyapatite. Presence of coralline hydroxyapatite in the composite supported the proliferation and cell attachment of human adipose-derived stem cells whereas no sign of cellular activity was observed on the surface of polylactic acid. Therefore, the combination of flexibility and biodegradability of polymer with bioactivity and osteoconductivity of ceramic can assist in designing an effective scaffold for biomedical applications. The biological performance of hydroxyapatite/ultrahigh molecular weight polyethylene composites was studied (Mirsalehi et al. 2015). The composites were fabricated in different ratios by varying the amount of hydroxyapatite to analyze the effect of ceramic content on biocompatibility. The adhesion and proliferation of MG-63 cell were found to be higher for all the samples than positive control. Moreover, the composite containing the higher weight percentage of hydroxyapatite showed better proliferation and differentiation of bone-forming cells. This study suggested that bioactive ceramic as fillers reinforced in polymer matrix assists in the development of non-toxic materials having the potential to stimulate the ingrowth of new bone on their surface.

2.6 Polymer Microarrays for Biomedical Applications

Researchers across the globe are attempting different fabrication techniques to explore polymeric materials for clinical applications. Microarrays have evolved as an effective method to screen hundreds of polymers on a single microscope slide. This process facilitates the identification of a range of suitable polymers for different applications in the field of medicine and biotechnology (Zhang et al. 2009).

A microarray of 381 polymers was prepared for selection of promising materials having the ability to inhibit growth of clinical bacteria (Venkateswaran et al. 2016). The microarrays were prepared by placing different polymers on agarose-coated

glass slides by using contact printing. The polymer microarrays were dried, sterilized, and incubated in clinical pathogen cultures. The polymers having ability to prevent bacterial growth were studied by coating on coverslips for hit validation and characterized by scanning electron microscopy. The polymers having bacteria repelling activity were coated on commercially available catheters. Among all samples (poly(methylmethacrylate-co-dimethylacrylamide) have shown about 100 fold reduction in the growth of clinical bacterial on the surface of central venous catheters.

Three-dimensional microarray platform was developed for the fabrication of about eighty single and double network hydrogel on a single microscope slide (Duffy et al. 2016). The single network hydrogel was prepared by printing acrylate-based monomers on a slide which was immersed in the components of second network followed by photopolymerization leading to the development of three-dimensional double network hydrogel arrays. The mechanical test indicated that wide range of compressive and tensile strength can be achieved by preparing double network hydrogel microarrays. The cellular study revealed that both microarrays (single and double network) have potential to bind to HeLa cells and these cells were found to cover major portions of their surface. This generation of 3D microarrays can be a promising platform for the discovery of new biomaterials.

Khan et al. (2013) utilized microarray technique for rapid screening of most promising polymeric composites having the potential to support growth and development of skeletal progenitor cells (Khan et al. 2013). Ternary composites of natural (chitosan) and synthetic (Polycaprolactone, Polyethyleneimine, Poly(L-Lactide), Polyethylene oxide, Poly(vinyl acetate), Poly(2-hydroxyethyl methacrylate) polymers were prepared by solvent blending. The microarray screening approach assisted in the identification of Chitosan/Poly(vinyl acetate)/Poly(L-Lactide) as the most effective composite for hard tissue regeneration applications. The in vitro cellular studies showed that chitosan/poly(vinyl acetate)/poly(L-Lactide) composite has the ability to stimulate the proliferation and differentiation of human bone marrow-derived STRO-1 + skeletal cells and also possess osteogenic potential when trialed for in vivo studies. Thus, present work concluded that microarray could be utilized as an effective identification of potential biomaterials for repairing bone defects.

Earlier, microarray technique was utilized to study 135 binary polymer blends for screening cell-compatible materials for hard tissue regeneration (Khan et al. 2010). The cytocompatibility of these polymer blends was investigated for various cell populations such as fetal femur-derived skeletal cells, osteoblast-like SaOs cell line, bone marrow-derived STRO-1+ skeletal stem cells and osteoblast-like MG63 cell line bone. Results show that poly(L-lactic acid)/polycaprolactone was noticed as the most promising blend for providing an excellent platform for stimulating adhesion and proliferation of skeletal stem cells as well as enhanced bone formation. This report suggested that microarray technique can be considered as a unique strategy to identify biologically active materials for exploring their biomedical applications.

2.7 Challenges and Future Prospective

The requirements of an ideal scaffold for biomedical applications are its biodegradability, bioactivity, mechanical stability, precise shape to fit at the defective site and suitable internal structure to facilitate cell proliferation and vascularization (Chung et al. 2007). Despite remarkable advancements in medical technology, few limitations such as controllable porosity, adequate mechanical strength, and good bioactivity are found to be associated with polymers. In order to tackle these challenges, it is necessary to modify the properties of polymers by fabricating their composites with suitable materials. To achieve controllable porous network, 3D printing has evolved as a potential fabrication technique which involves layer-by-layer fabrication of scaffolds without special tools, molds or dies. 3D printing is the state-of-the-art manufacturing technique that provides fabrication of patient-specific scaffolds having complex structures mimicking native tissues (Guvendiren et al. 2016).

Polymers possess controllable degradability and flexibility, the mechanical stability as well as bioactivity should be improved to achieve desired biological performance. It is known that calcium and magnesium-based silicate ceramics have reasonable bioactivity and promising mechanical stability (Diba et al. 2014; Lin et al. 2016). Hence, polymer composites with silicate ceramics can assist in designing and development of biomaterials to overcome the present issues related to tissue engineering applications. From all the above discussions, it can be concluded that polymer-based scaffolds can be emerging biomaterials for versatile biomedical applications in near future.

2.8 Conclusion

The recent trend toward designing polymeric composites for biomedical applications is expected to possess porous structure, biodegradability, bio-functionality, and sufficient mechanical stability. Polymers and their composites are versatile in nature that allows the flexibility for altering their properties as per the requirements. A wide range of polymeric materials, reinforcements, and fabrication routes are extensively studied to explore their applicability in tissue engineering. In this chapter, a detailed literature of current developments in the field of polymer matrix composites has been reviewed. The experimental studies (both in vitro and in vivo) and their results indicated the excellent performance of composites with good biocompatibility that might open the new perspectives for their applications in tissue engineering, drug delivery, biosensor, imaging, etc.

Acknowledgements Authors thank Vellore Institute of Technology (VIT) for financial support. With immense pleasure and deep sense of gratitude, authors wish to express sincere thanks to Dr. S. Sasikumar, Associate Professor, School of Advanced Sciences (SAS), VIT, without his motivation and continuous encouragement, this book chapter would not have been successfully completed.

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Synthesis of Bio-based Polymer Composites: Fabrication, Fillers, Properties, and Challenges

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Abstract The bio-based polymer composite industry is growing dramatically following economic and environmental concerns over constant use and dependence on non-renewable feedstock, such as crude oil. It is notorious that there has been a continuous increase in the research activity related to the development of novel bio-based materials over the past couple of decades. The focus has slowly shifted from simpler systems, consisting primarily of traditional thermoplastics reinforced with natural fibers, to more advanced composites with carefully engineered bio-based matrices, or fully bio-based materials in which both matrix and reinforcement are of bio-based origins. In the realm of bio-based biomedical applications, the efforts are vastly dominated by investigation of PLA and PLA-based composites. The existing challenges for the fabrication and the use of bio-based composites are mainly associated with the lack of consistency in materials' characterization among the various proposed systems, which makes a direct comparison of different materials exceedingly hard. This manuscript contemplates the fabrication of bio-based composites through a processing perspective, and by also covering the literature of the many resin/reinforcement systems investigated to date, before concluding with brief remarks on the desired properties and challenges related to the use of bio-based composites in biomedical applications.

Keywords Polymer composites · Bio-based materials · Natural fibers · Reinforcement · Bio-based resins

1 Introduction

The bio-based polymer composite industry is growing dramatically within the field of biomedical engineering which fosters many practical applications. Economic and environmental issues surrounding the world of oil-based polymers call for increased

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K. K. Sadasivuni et al. (eds.), *Polymer Nanocomposites in Biomedical Engineering*, Lecture Notes in Bioengineering,
https://doi.org/10.1007/978-3-030-04741-2_2

innovation and application of bio-based materials as an alternative. From an environmental standpoint, petroleum products lack sustainability (Alghazali et al. 2015). The realm of bio-based materials is expanding because the development of bio-based products is more environmentally friendly and often safer for human use/intake than petroleum-based materials. Economic factors, such as oil price and supply, are driving forces in this new era for the transition from crude oil-based materials to bio-based materials of both natural and synthetic origin (Alghazali et al. 2015). The economy and research industry surrounding the biomedical field spans from topics of drug delivery to joint replacement materials. An example of bio-based biomedical advancements includes bio-based topicals that enhance salicylic acid delivery (Langasco et al. 2016). This advancement in the drug delivery of salicylic acid explores gel formulas containing natural polymers with the goal of permeating the skin to treat acne vulgaris, while still being safe enough to use as a topical on human skin. Another medical application of bio-based materials is the use of calcium carbonate nanoparticles to enhance drug delivery of anticancer drugs (Render et al. 2014). Porous structures of biomaterials are also grounds for the practical medicinal application. These porous polymer structures have been used in synthetic tissue engineering for osteoblasts, hepatocytes, and even synthesized bone tissue (Alghazali et al. 2015). Drug delivery applications for porous structures have also been implemented to control timely drug delivery by diffusion through a matrix of the drug (Alghazali et al. 2015). Osteopathic medicine specifically contemplates polyethylene becoming a substitute for platinum in joint replacements in recent years. Problems such as debris from the components of polyethylene causing infection are a current topic of debate.

1.1 Polymer Composites

By definition, a polymer is a large molecule comprised of repeating chemical units (Isabelle and Lan 2009). The large class of chemical polymers can be broken down into natural polymers and synthetic polymers. Natural polymers include proteins (such as albumin and collagen) and polysaccharides (such as chitosan and dextran). Common biomedical applications of these natural polymers include reactive sites for drug delivery systems (Isabelle and Lan 2009). There is a multitude of synthetic polymers. They are usually classified based on their repeating chemical functionality. Examples of synthetic polymers include polyethers, polyesters, polyoxamers, and RP polymers. Biomedical research surrounding synthetic polymers spans many topics including circulation rates of pharmaceuticals in the body and adapting chemical release to fit optimal times (Isabelle and Lan 2009). These synthetic and natural polymers vary most obviously in source, but also notably in chemical structure. Both natural and synthetic polymer composite materials are used in the biomedical industry for various applications such as implants, bone plates, vascular grafts, and artificial hearts. The functionally of these applications is ultimately to restore or replace damaged or nonexistent human tissues.

1.2 Bio-based Materials

Bio-based materials are materials that contain components of bio-renewable origins. With time, crude oil-based polymers are being replaced with these novel bio-based materials (Alghazali et al. 2015). Common examples of these bio-renewable resources include biomass feedstock, biofibers, and biopolymers (Mohanty et al. 2002). Biomass feedstock is commonly used as a more environmentally safe alternative to otherwise used petroleum resources. Biofibers, such as hemp and flax, are commonly used as reinforcement in the fabrication of bio-based composites. Another common example of a biopolymer is cellulosic plastics (Mohanty et al. 2002). For bio-based composites, the bio-renewable portion does not have to be specifically in one realm. It can be the filler, the matrix, or both.

The following sections will give insight into further applications of bio-based polymer composites in the biomedical realm. In covering these applications, this chapter will focus on the fabrication and the different kinds of processing applied to thermoplastic and thermosetting bio-based polymer composites. These various composites require different processing methods. The preparation of these bio-based composites for biomedical applications stems from the use of different fillers and reinforcements, as unveiled in Sect. 3. Indeed, various bio-based and non-bio-based fillers/reinforcements with either bio-based or non-bio-based polymers used in biomedical practical applications are also discussed in this chapter. Also explored, are properties of bio-based polymer composites as intended for biomedical applications. The chapter concludes with a brief discussion of challenges encountered for the application of bio-based polymer composites in the biomedical field. Bio-based composites are an ever-expanding topic in biomedicine which, through the continuation of research, will keep on positively impacting the industry both environmentally and economically.

2 Fabrication/Processing of Bio-based Polymer Composites

Polymers have become fundamentally incorporated into almost every aspect of life, from medical applications to cosmetics. Biodegradable polymers have become the central focus over the last few decades because of their ability to break down and degrade without environmental harm (Gunatillake et al. 2006). Some applications for such polymers include pharmaceuticals (Chiellini et al. 2008), mechanical support (Ju et al. 2009), artificial tissue and organs (Piskin 2002), medical implants, surgical glues, and sutures (Kiick 2007). For some biomedical applications, it is more advantageous to have the polymer degrade naturally, after serving its purpose (Dash and Cudworth 1998).

Polymers can be divided up into multiple categories based on their mechanism of polymerization or origin. This section focuses on the processing conditions and

contemplates polymers based on their classification as thermoplastics or thermosets. In thermoplastic polymers, the polymer chains interact with each other through non-covalent interactions, whereas in thermosets, these interactions are of a covalent nature, constituting cross-links and resulting in an overall rigid, interconnected structure. The non-covalent interactions in thermoplastics allow the polymers to melt and make recycling possible at the end of the polymer's life cycle. On the other hand, thermosets do not melt and cannot be dissolved in a solvent due to their highly cross-linked structure. Consequently, thermosets must undergo harsher conditions in order to be recycled due to their enhanced mechanical properties compared to thermoplastics.

Currently, the majority of thermosetting polymeric materials are derived from crude oil and are non-biodegradable (Bisio and Xanathos 1995; Mustafa 1993). Often times, thermosets and thermoplastics derived from bio-renewable resources exhibit flexible, long-chain polymer characteristics such as high elongation at break, low glass transition temperatures, and relatively low stiffness (Frederick et al. 2004). Therefore, the preparation of copolymers from a combination of synthetic and renewable co-monomers is a common practice in order to improve structural properties. In the following sections, some of the latest and most popular techniques of polymer processing will be discussed.

2.1 Thermoplastic-Based Composites

Thermoplastic polymers are generally formed by condensation or free radical polymerizations, creating linear polymer chains with weak intermolecular interactions. These intermolecular forces can be easily overcome through heat, making these polymers moldable at high temperatures. Under the umbrella of thermoplastics are hydrogels, which exhibit swelling properties that make them ideal candidates for applications such as disposable diapers and feminine products (Shen et al. 2015).

Most common and conventional ways to process thermoplastics are through injection molding, extrusion, and blow molding. Injection molding involves melting the polymer, followed by pressure to force the polymer into a pre-formed mold. The mold is held under pressure until the polymer solidifies and then the newly formed part is removed. Extrusion and blow molding are similar techniques in which the polymer is melted, manipulated based on application, and then cooled to the desired shape. In the extrusion method, after melting, any desired additives are added and the materials are extruded through a dye to produce a continuous material, such as cables, lines, wires, films, sheets, and beams. In blow molding, pressurized air is used to keep the polymer in contact with the mold's walls while maintaining an empty core, creating hollow objects, such as bottles. The succeeding sections will discuss these techniques as they are applied in current research related to biomaterials.

2.1.1 Injection Molding

Injection molding (Fig. 1) is one of the oldest and simplest forms of polymer processing. Several studies have shown its successfully implementation in the development of scaffolds for drug delivery (Gomes et al. 2001), orthopedic implants (Kobayashi and Suong 2010; Karande et al. 2004), and tissue engineering (Mi et al. 2013; Wu et al. 2006; Haugen et al. 2006; Miller et al. 2017; Hooreweder et al. 2013; Yang et al. 2001). In a recent comparison study, polycarbonate/urethane composites were fabricated by injection molding and 3D printing for applications in orthopedics and soft tissue replacement (Miller et al. 2017). It was found that the 3D printing processing method produced equal or better results in monotonic tension, compression, shear, and tensile fatigue tests than the injection molding controls (Miller et al. 2017). However, in comparison to selective laser sintering, injection molding was found to have equivalent fatigue properties (Hooreweder et al. 2013). Differences between samples produced by the two methods only became apparent when their geometry was altered (Hooreweder et al. 2013).

Highly porous, biodegradable scaffolds are essential to accommodate the regeneration of tissue and guide cells' growth in three dimensions, while degrading in a neutral manner to avoid inflammation or tissue rejection (Yang et al. 2001; Quirk et al. 2004). Therefore, other studies have used a combination of processing methods in addition to injection molding, due to its simplicity, to produce repeatable and precise parts (Kramschuster and Turng 2010). Due to the necessity of pore size and structure precision, conventional techniques have been abandoned in favor of more advanced techniques, such as particulate leaching (Mikos et al. 1993), temperature-induced phase separation (TIPS) (Nam and Park 1999), emulsion freeze drying (Whang et al. 1995), electrospinning (Bognitzki et al. 2001), and rapid prototyping (Ma 2004). These advanced techniques will be further discussed in Sect. 2.3.

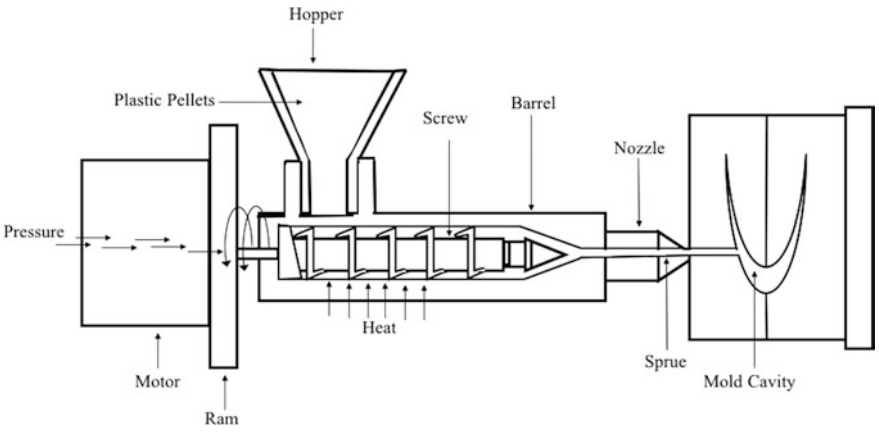

Fig. 1 Schematic of a typical injection molding system

2.1.2 Extrusion

Reactive extrusion is a more efficient form of extrusion in which a chemical reaction occurs during the blend–melt process. One of the pivotal aspects of reactive extrusion is the introduction of modification, polymerization, and in situ processing (reactive phase) through chemical reactions. This process has been most recently used in bio-based polymer bends and composites research (Formela et al. 2018). The practicality of this processing technique is demonstrated by its continuous successful use in the preparation of biodegradable polymers (Bonnet et al. 2015; Spinella et al. 2015), functionalization of natural fibers/fillers (Gibril et al. 2013), and the compatibilization of bio-based polymer blends and composites (Korol et al. 2015). A simplified extrusion system is illustrated in Fig. 2.

As an example, the in situ reactive extrusion of grafted poly(3-hydroxybutyrate) (PHB) onto cellulose with dicumyl peroxide (DCP) as a radical initiator was studied in recent years (Wei et al. 2015). The highest yield of cellulose-*g*-PHB copolymer was obtained through a reaction time of 5 min and 2 wt% of initiator (Wei et al. 2015). The thermomechanical properties of the copolymer were enhanced and could be easily tailored by altering the weight percentages of the monomers, therefore creating a wide range of applications for the biocomposites under study (Wei et al. 2015).

Cellulosic fibers from natural resources are one of the most common fillers used in bio-based polymer composites to enhance the thermomechanical properties. In these cases, the performance of the bio-based composite is directly related to the fiber–matrix interface compatibility. Several approaches have been developed over the years to enhance fiber–matrix interactions, including the manipulation of the matrix to create a more polar matrix that will inherently bind better with the polar fiber/filler. For example, maleated polyolefins were blended with wood particles by a reactive extrusion technique (Carlborn and Matuana 2006). It was found that the

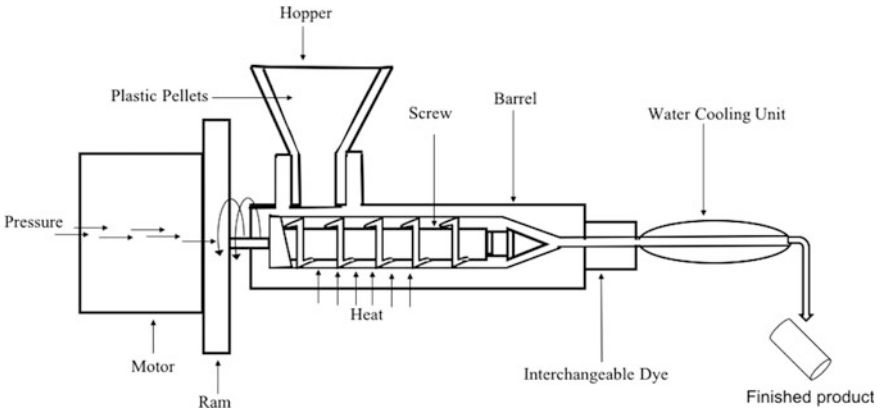

Fig. 2 Schematic of a simplified extrusion system

degree of maleated polyolefin grafting onto the hydroxyl groups of the wood particles was directly related to the maleated polyolefin feed ratio (Carlborn and Matuana 2006). Interestingly enough, there were no significant discrepancies reported in the grafting efficiency under variable extrusion parameters (Carlborn and Matuana 2006).

2.2 Thermoset-Based Composites

Thermosetting polymers have some advantages over thermoplastics, such as extended life span, and chemical and corrosion resistance, but due to their highly cross-linked networks, recycling/reprocessing is virtually impossible. Two of the most popular thermosetting polymers employed in biomedical applications are polyurethanes (PU) and polytetrafluoroethylene (PTFE). These materials cannot be melted and are insoluble. At the end of the polymer's life cycle, harsh and potentially environmentally hazardous procedures must be employed to break down the thermoset. Therefore limitting its application in drug delivery. In the following subsections, three of the more common fabrication methods of polymer processing: injection, compression, and transfer molding, will be discussed in regard to their application in the biomedical field.

2.2.1 Injection Molding

Several cure factors can play a role in the quality of a thermosetting polymer, such as cure temperature, time, injection rate, and pressure. Careful monitoring of these parameters has led to optimized molding conditions (Scheffler et al. 2015). In order to circumvent problems associated with the extrusion of thermosets, three different materials have recently been investigated as melt mixers to enhance the homogeneity of the final polymers (Rochman and Zahra 2016). Nitrile butadiene rubber, ethylene propylene diene monomer, and fluorocarbon were added to thermosetting polymers during extrusion, resulting in increased homogeneity and better mechanical properties (Rochman and Zahra 2016).

2.2.2 Compression Molding

Compression molding is a quick and simple processing method in which a partially cured thermoset, an impregnated filler, or a preheated thermoplastic is placed into an oven, heated, and pressure is applied as the polymer flows and cures into the shape of the mold (Fig. 3). This processing method is suitable for complex and high production rate products. Additionally, in comparison to injection molding, it contains less knit lines, which usually act as a weak point in the final part. Nevertheless, in comparison to resin transfer molding and vacuum bagging

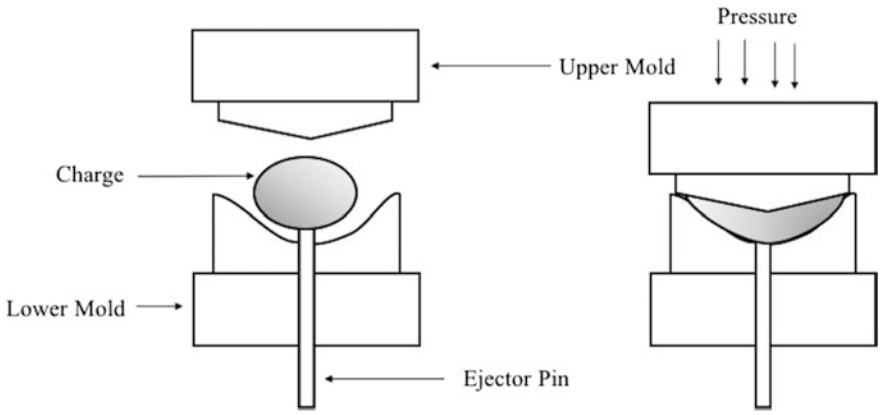

Fig. 3 Representation of a typical compression molding system

molding, this technique negatively affects the mechanical properties, being more suited for uses where the mechanical properties must not supersede normal working conditions (Gascons et al. 2012). Common biomedical devices prepared through compression molding of thermosetting polymers include diaphragms for respiratory appliances, lip seals or O-rings, and isolation bumpers used to dampen vibrations (Rogers 2017).

The investigation of composite processing has revealed that compression molding reduces the changes in the physical properties of the final parts because the fiber orientation is not significantly disturbed during fabrication (Aji et al. 2009). Additionally, fiber distribution was found to be superior than in other techniques (Aji et al. 2009). Enhanced mechanical properties were also observed in comparison to injection molded samples (Liu et al. 2007). Many combinations of compression molding and other advanced techniques have been utilized over the years, including a sequence of compression, extrusion, and sheet molding (Faruk et al. 2012). Overall, in combination with one another, these techniques reduced the production cost by decreasing the cycle time (Faruk et al. 2012). The combination of compression molding with particle leaching was successfully used in the fabrication of a biocomposite scaffold with hydroxyapatite whisker-reinforced poly(L-lactide) to serve as a viable orthopedic implant (Xie et al. 2016).

2.2.3 Transfer Molding

In transfer molding, a pre-measured amount of thermosetting crude resin is loaded into a chamber, closed, and a transfer plunger forces the crude resin from the chamber into preheated mold cavities, where the cure is completed. There are several variations of transfer molding methods, including resin transfer molding (RTM), vacuum-assisted resin transfer molding, and micro-transfer molding. In RTM, reinforcement fibers are commonly placed on the mold prior to resin

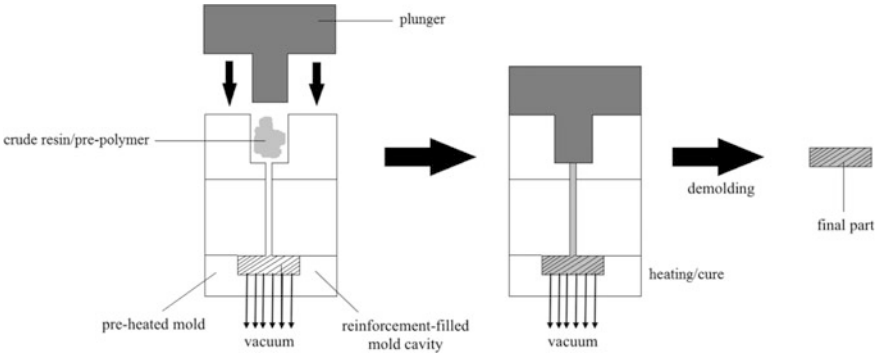

Fig. 4 Simplified schematic of vacuum-assisted resin transfer molding (VARTM)

transfer. Vacuum can be applied to remove any residual air, while the oriented fibers and resin are compressed and heated to complete the cure. One advantage of this method is the flexibility to orient the fibers' geometry as needed, potentially saving material cost and maximizing desired properties (Mallick 2007). Figure 4 depicts the schematics of vacuum-assisted resin transfer molding.

2.3 Bio-based Composites

Often times, natural polymers are reinforced with fibers, such as cellulose, or polymerized in combination with synthetic polymers to enhance the overall thermomechanical properties. Normally, bio-based polymers offer unique advantages with respect to biodegradability and biocompatibility, especially in the biomedical field, and more specifically in tissue engineering. The scaffolds engineered must degrade in a non-toxic manner, as well as mimic the body's own extracellular matrix to allow for cell proliferation and avoid an immune response. Additionally, the scaffold must be degraded at the proper rate; therefore, some bio-based polymers cannot be synthesized alone. Hybridization of synthetic and natural materials can be achieved at the nanoscale by incorporating nanoparticles such as hydroxyapatite (HA) (Xie et al. 2016) or carbon nanotubes (Li et al. 2013). Some of the more popular methods of biocomposite fabrication include solvent casting and particulate leaching (SCPL), emulsion freeze drying, electrospinning, blow film extrusion, and 3D printing as discussed below.

2.3.1 Solvent Casting and Particulate Leaching (SCPL)

During SCPL, soluble particles are initially incorporated within the polymer matrix (Lu et al. 2000). Once the material is consolidated, the particles are dissolved and washed off by an appropriate solvent, leading to a porous material (Lu et al. 2000).

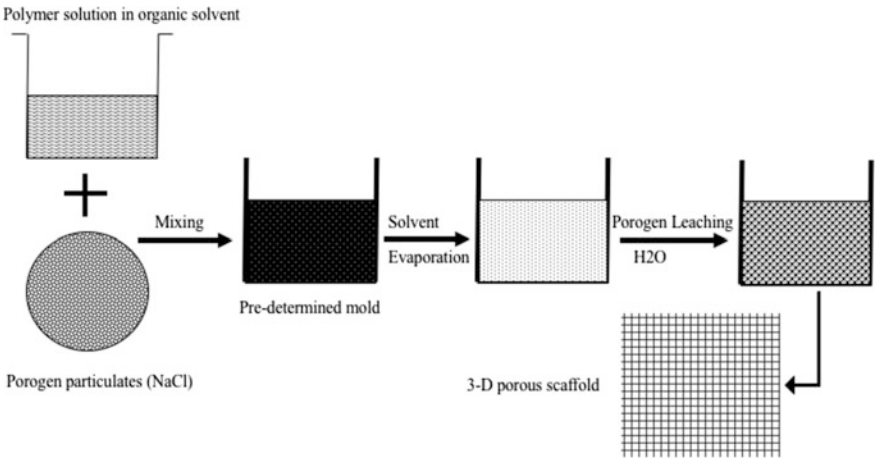

Fig. 5 Generic schematic of the steps involved in solvent casting and particulate leaching

For thicker parts, evaporation of the solvent and removal of the soluble particulates become difficult (Chen and Badylak 2001). In such cases, residual amounts of solvent or particulate may be removed with the aid of vacuum drying (Rogers et al. 2013). Scaffolds fabricated by SCPL methods have been utilized as orthopedic scaffolds for bone tissue replacement or repair (Prasad et al. 2017). Additionally, to avoid toxicity issues of the solvents with the host tissues, gas foaming via carbon dioxide in addition to particulate leaching can be used to create a highly porous biopolymer foam (Okamoto 2006; Kim et al. 2007). Figure 5 depicts the steps involved in solvent casting and particulate leaching. The polymer solution is created with an organic solvent and mixed together with the porogen particulate (i.e., NaCl), creating a homogeneous mixture. The mixture is poured into a mold and the solvent is evaporated. Water, or another particulate dissolving solution, is added to the mold to remove the particulates, leaving behind a porous structure. The newly formed scaffold is dried under vacuum to remove any residual solvent or particulate.

2.3.2 Emulsion Freeze Drying

Freeze-drying emulsion is a commonly used method for collagen-based scaffolds, due to collagen's sensitivity to chemical and heat denaturation. It has been used to create porous collagen scaffolds for the growth of aortic heart valve cells (Taylor et al. 2006). In that instance, collagen type 1 fibers were frozen at −30 °C, entrapping ice crystals. Lyophilization of the sample removed the crystals, resulting in the desired porous material (Taylor et al. 2006). The pore size was highly dependent on the temperature, pH, and solution concentration (Taylor et al. 2006). Scaffolds with porosity greater than 90%, pore sizes ranging from 20 to 200 μm,

and with heat-sensitive bioactive molecules have also been fabricated by the emulsion/freeze-drying method (Aranaz et al. 2014; Hottot et al. 2004).

2.3.3 Electrospinning

Electrospinning is often used in the fabrication of cardiovascular scaffolds (Das et al. 2003). In this technique, an electric field is applied while a solution containing a conductive polymer is ejected from a needle and collected on a target, as represented in Fig. 6. The solvent dries as a fibrous network with a structure very similar to the body's natural extracellular matrix (ECM) is formed (Xie et al. 2008). The fiber diameter and structure can be altered by simply adjusting the polymer solution conditions (conductivity, viscosity, concentration) or the processing parameters (voltage, working distance, flow rate, temperature) (Xu and Zhou 2008).

There have been recent efforts toward the hybridization of synthetic and natural polymers, taking advantage of synthetic polymers' mechanical strength and natural polymers' biocompatibility. Interesting advancements have been made in the realm of heart valve tissue engineering (Hong et al. 2009). In that context, the fabrication of a bio-hybrid scaffold, using non-cross-linked decellularized bovine pericardium extracellular matrix coated with an adhesive layer of polycaprolactone (PCL)-chitosan nanofibers, has been reported making use of electrospinning (Jahnavi et al. 2015). It was also reported that due to the hydrophobic nature of PCL, a blending technique with dextran, cellulose acetate, polyhydroxybutyrate, and chitosan nanofibers was utilized to enhance fiber–polymer interactions (Malheiro et al. 2010). Dip coating has also been used to increase the mechanical properties of the decellularized scaffolds without the use of cross-linkers (Nirmal and Nair 2013). Although the dip-coated scaffolds resulted in better mechanical properties than electrospinning, the use of organic solvents disrupted the structural integrity of the

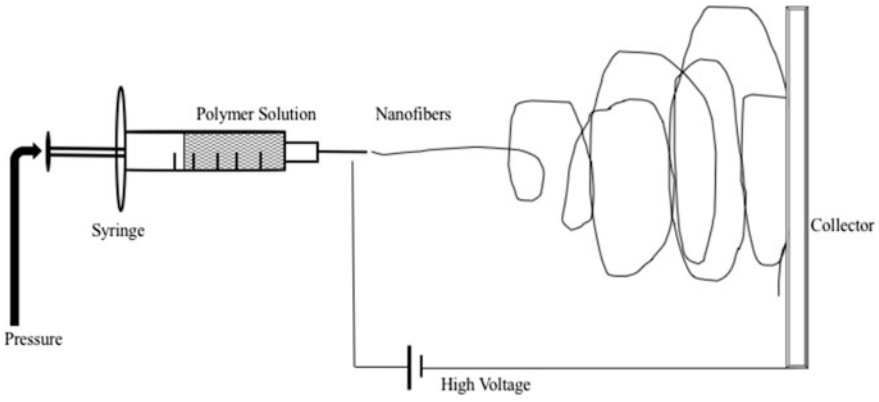

Fig. 6 General scheme for the fabrication of electrospun nanofibers under high voltage

ECM nanofibers, making electrospinning a more appropriate choice for processing (Nirmal and Nair 2013).

2.3.4 Blow Film Extrusion

Blow film extrusion is most commonly used in the manufacturing of polymeric films. The process involves extrusion of molten polymer through a die while air inflates the thermoplastic to form a thin film. Blown films have become increasingly popular in the pharmaceutical industry due to their biodegradability, lack of toxicity, and low cost of processability. Common bio-based polymers used in the film industry are polysaccharides (Al-Hassan and Norziah 2012), chitosan (Dutta et al. 2009), cellulose (Yu et al. 2017), and their derivatives. More recently, the preparation of blown films from starch-based materials has gained increasing attention (Dang and Yoksan 2015). Starch- and chitosan-based thermoplastic films have found to be suitable for applications in the food and pharmaceutical industries (Dang and Yoksan 2016). It has been noted that water vapor and oxygen barrier properties increase with the percentage of chitosan in the film, while the surface hydrophilicity is reduced (Dang and Yoksan 2016). Therefore, the degradation rate of the film, and consequently, its shelf life can be tuned by controlling the concentration of chitosan in the film (Dang and Yoksan 2016).

2.3.5 3D Printing

In one of the currently known setups for three-dimensional (3D) printing, a movable printer head casts the molten polymer on a target following a pre-programmed design. The deposition of polymer is done on a layer-by-layer fashion to create the final desired three-dimensional part. This process can also be referred to as rapid prototyping and has been used in various applications in the biomedical field, including dental implants (Wu et al. 2017), hearing aids, 3D surgical and medical models, and orthopedic prosthetics (Gross et al. 2014; Zopf et al. 2013). 3D bio-printing is a variation of traditional 3D printing that uses living cells deposited onto a gel medium to engineer bio-functional structures (Schubert et al. 2014). Recent studies have explored using nanomaterials in conjunction with bio-hybrid scaffolds, creating additional functions (Roh et al. 2017). For example, the addition of magnesia nanoparticles to PCL promoted new bone growth through the modulation of signal transduction and cell proliferation (Roh et al. 2017), while other studies have found that the addition of magnetic nanoparticles to PCL creates a material able to stimulate cell proliferation through magnetic heating (Meng et al. 2013).

Ultimately, polymer processing is highly dependent on polymer properties and intended application of the material sought. Thermoplastics tend to be more commonly found in drug delivery than thermosetting polymers, due to their easier degradability, while thermosetting polymers may be more appropriate for structural

applications that require thermal and chemical resistance. In the context of tissue engineering, scaffolds are most often fabricated by electrospinning or 3D printing, although common biomedical supplies are typically prepared by more conventional methods like injection or compression molding. In some special applications, a combination of conventional and more advanced methods can be used to reduce the overall cost and processing time, as, for example, solvent casting and particulate leaching (Okamoto and John 2013).

As commonly seen in processing-based applications, the manufacturing properties of 3-D scaffolds for heart valve tissue replacements are greatly impacted by the choice of the advanced fabrication technique. For example, solvent casting is ideal for the fabrication of scaffolds with pore sizes of 50–1000 μm, and with 30–90% porosity, whereas freeze drying is more suitable for samples with desired pore size <200 μm and porosity of 70–95% (Fallahiarezoudar et al. 2015). Both of these methods require the polymer to be soluble in a solvent, which can cause solvent toxicity in the scaffold. Alternative techniques, such as solid-free form (a layer-by-layer 3D deposition/printing), allow for unique geometries while avoiding the toxicity issue, but exhibit other problems, such as the high cost of production and varying accuracy of the computer-based design (Fallahiarezoudar et al. 2015). Overall, based on production cost, flexibility of design, and ease of processibility, electrospinning was deemed the most suitable choice of fabrication for heart valve scaffolds (Fallahiarezoudar et al. 2015).

3 Fillers and Reinforcements Used in the Preparation of Bio-based Composites

By definition, a bio-based composite is a reinforced polymeric material in which either one or both components (polymer matrix and reinforcement) are from bio-based origins. In this section, the three different possibilities for obtaining a bio-based composite will be contemplated, namely (a) the reinforcement of non-bio-based polymers with bio-based fillers/fibers, (b) the reinforcement of bio-based polymers with non-bio-based fillers/fibers, and (c) the reinforcement of bio-based polymers with bio-based fillers/fibers.

3.1 Bio-based Fillers/Reinforcements with Non-bio-based Polymers

Due to environmental concerns (Hamzeh et al. 2011), the earliest efforts in the preparation of bio-based composites consisted in the reinforcement of regular petroleum-based thermoplastic polymers with natural fibers (Stark 1999). Such approach showed promise due to the low cost, abundance, and low weight of the

fibers typically employed. It is notorious that with the growth of global population over the years, increasing urbanization and rising standards of living due to technological innovations have contributed to increase both the quantity and variety of solid wastes generated by industrial, domestic, and agricultural activities (Hamzeh et al. 2011). In that context, wood-waste products are among the most abundant bio-based materials that can be easily used as reinforcement in bio-based composites, having shown a trend of increasing industrial use over the past 15 years, in a market traditionally dominated by the use of inorganic fillers (Stark and Matuana 2004). Wood flour (Hamzeh et al. 2011; Stark and Matuana 2004) and wood fiber (Stark 1999) are waste products from the wood industry that are highly abundant and readily available for experimentation and use in the preparation of bio-based composites.

In the search for more environmentally friendly materials, waste paper sludge (WPS) and ink-eliminated sludge (IES) have been used as fillers/additives in high-density polyethylene (HDPE)/wood flour composites (Hamzeh et al. 2011). It has been shown that the addition of WPS to HDPE/wood flour composites resulted in an increase of flexural properties, which could be further enhanced with the incorporation of maleated anhydride grafted polyethylene (MAPE) as a compatibilizer between matrix and reinforcement (Hamzeh et al. 2011). Addition of WPS and IES also resulted in a decrease of swelling and water absorption properties (Hamzeh et al. 2011). Overall, IES-added composites resulted in better physico-mechanical properties in comparison to WPS-added composites, with an optimum loading of 60 wt%, showing good promise for their use in the preparation of bio-based composites (Hamzeh et al. 2011).

Due to their growing demand for exterior applications in the Construction Industry, the investigation of sunlight and weathering damage on HDPE/wood flour composites has been used as a means to indicate the material's durability (Stark and Matuana 2004). These properties can be inferred by assessing chemical changes on the surface of the composites after artificial weathering experiments (Stark and Matuana 2004). It has been shown, by use of XPS and FT-IR, that wood flour-reinforced HDPE is 16-fold more susceptible to weathering than the unreinforced plastic (Stark and Matuana 2004). The results corroborate the degradation mechanism that suggests that polymer chain scission is triggered by the presence of carbonyl groups, generated after surface oxidation (Stark and Matuana 2004). Chain scission culminates in an overall decrease in crystallinity over time (Stark and Matuana 2004).

In terms of mechanical properties, a direct comparison of polypropylene (PP) reinforced with wood flour and wood fibers has revealed the latter to impart better tensile and flexural strength, as well as less molding shrinkage (Stark 1999). It has also been shown that the use of maleated PP as a compatibilizer results in improved mechanical properties (Stark 1999). Very similar trends have been observed later on with bio-based thermosetting composites (Quirino et al. 2012).

3.2 Non-bio-based Fillers/Reinforcements with Bio-based Polymers

Research efforts on the development of bio-based composites in which a bio-based polymer is reinforced with non-bio-based materials are mostly restricted to the addition of reinforcements to poly(lactic) acid (PLA) (Kasuga et al. 2001; Chiu et al. 2008). In this context, significant improvement in Young's modulus has been obtained when reinforcing PLA with up to 60 wt% of hydroxyapatite fibers (HAF) under compression molding at 180 °C (Kasuga et al. 2001). Indeed, a maximum value of 10 GPa was obtained for PLA/HAF composites (Kasuga et al. 2001). For heavily loaded composites, brittle behavior was observed and a covalent fiber–matrix interaction was revealed (Kasuga et al. 2001). Similarly, when PLA is reinforced with carbon nanotubes (CNTs), significant increases in Young's modulus and hardness are observed (Chiu et al. 2008). A comparison between the effects of purified versus non-purified CNTs indicated that purified CNTs are able to better disperse in the PLA matrix, resulting in better thermomechanical properties (Chiu et al. 2008).

3.3 Bio-based Filler/Reinforcement and Bio-based Polymer

Bio-based composites with natural fibers have several advantages over synthetic polymers and have become an increasingly popular research topic. Natural polymers deriving from renewable resources are relatively inexpensive to produce and are more environmentally friendly. Composites with high flexibility and good dampening properties have been developed from flax, keratin, hemp, and pure cellulose fibers (John and Thomas 2008; Sydenstricker et al. 2003). Most of the current research efforts have been centered around enhancing fiber–resin interactions, while neglecting fiber orientation. The lack of uniformity in fiber length and orientation in bio-based composites results in significant variations in mechanical properties between similar samples and represents one of the major limitations for their commercial use. Overall, physical and chemical surface treatments are currently employed to produce competitive alternatives to materials present in the market.

Lignocellulosic reinforcements derived from natural wood fibers are heterogeneous polymers composed of cellulose, hemicellulose, and lignin. Cellulose is the most abundant polysaccharide consisting of repeating linear D-glucose units, while hemicellulose and lignin are composed of a multitude of branching monomer subunits. These components tend to be hydrophilic, while the typical matrix is generally hydrophobic, creating an inherent incompatibility between the two. In order to fully understand the physical properties of natural fibers, and how to appropriately optimize fiber–matrix interactions, each component has been isolated and studied individually. Some the optimization modifications include physical

methods such as fiber stretching (Zeronian et al. 1990), calendaring (Semsarzadeh 1986), thermo-treatment (Ray et al. 1976), and electric discharge (Paiva and Frollini 2006). These methods do not change the chemical makeup of the fibers, and they simply change the fiber's surface physically, on a macroscale, sometimes helping with fiber orientation and improving adhesion with the polymer matrix. Solvent extraction can be used to filter plant particulates and short fibers from high-cellulose content fibers. Although due to the use of potentially hazardous and non-environmentally friendly solvents, as well as the potential for fiber degradation during extraction (Le Guen and Newman 2007), electric discharge processes have been preferred. This method separates the fibers by electric discharge and modifies the lignocellulosic fibers' hydrophobic surface through corona, plasma, or ionized air treatments (Paiva and Frollini 2006).

Additionally, fibers can be treated chemically to enhance the fiber–matrix interactions. Alkaline treatments are commonly used and can even be used as a pre-treatment in combination with other chemical modifications. Sodium hydroxide is used in such treatments, converting cellulose lattices into more stable conformations (Agrawal et al. 2000). As an example, flax/epoxy polymers were found to have significantly increased mechanical properties after alkaline treatments in comparison to non-treated samples (Vandeweyenberg et al. 2006). Alkaline treatment, however, results in shrinkage whenever the fibers are not stretched during the NaOH/water treatment (Baley et al. 2006). In order to mitigate this effect, water can be substituted by ethanol (Baley et al. 2006). The use of coupling agents, such as organosilanes, is another common chemical modification method that helps improving the interfacial adhesion between the polymer matrix and reinforcement (Lee et al. 2008). Indeed, silane treatment of wood flour resulted in an overall increase of the tensile properties of PLA/wood flour composites, despite an observed decrease of the reinforcement's crystallinity (Lee et al. 2008). Evidence of stronger interfacial bonding was also found upon morphological analysis of the composites (Lee et al. 2008). Figure 7 presents a reaction scheme showing the change in surface chemistry upon silane treatment of a bio-based reinforcement.

Alternatively, natural fibers, such as flax, can be treated with a combination of alkali and anhydrides, to improve fiber–resin interactions in bio-based composites (Taylor et al. 2017). Indeed, when epoxidized sucrose soyate resins are cross-linked in the presence of treated flax fibers, composites with superior properties than their regular epoxy/flax composite equivalents are obtained (Taylor et al. 2017).

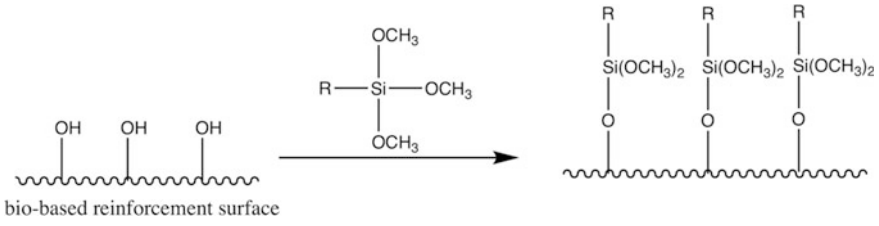

Fig. 7 Silane treatment of a bio-based reinforcement

Over the past few years, a strong focus has been put in the development of biocomposites from cellulose nanoparticles. In such efforts, the cellulose nanoparticles are typically obtained after chemical treatment of lignocellulosic biomass for removal of lignin and hemicellulose, as shown in Fig. 8. For instance, biodegradable composite films have been obtained from the reinforcement of κ-carrageenan with cellulose nanocrystals isolated from kenaf fibers through alkali, bleaching, and sulfuric acid treatments (Zarina and Ahmad 2015). Similarly, commercial grade microcrystalline cellulose (MCC) was converted into cellulose nanowhiskers through ultrasonication followed by acid hydrolysis and has been used as a reinforcement in castor oil-based polyurethane composites, imparting significant enhancement of tensile properties (Park et al. 2013). Acid hydrolysis was also employed to obtain MCC from oil palm empty fruit bunch for use as reinforcement in PLA composites (Haafiz et al. 2013). The addition of MCC resulted in an increase of Young's modulus and a decrease in tensile strength that was attributed to aggregation and uneven distribution of MCC in the PLA matrix, as observed after morphological analysis (Haafiz et al. 2013).

More complex systems, such as hybrid nano-composites, have been proposed and studied. The reinforcement of a blend of commercial polyester and soybean oil-based epoxy with a combination of nano-clay and hemp fibers resulted in composites exhibiting synergistic properties, including high stiffness, elongation at break, hygro-thermal properties, and toughness (Haq et al. 2008). In a very application-oriented effort, a double-layer composite material has been developed from the coating of a corn stover-based polyurethane with a water-absorbent acrylic acid layer, reinforced with chicken feather protein (Yang et al. 2013). The material had intended application as a nitrogen release medium for polymer-coated urea fertilizers, with more efficient nitrogen release and lower loss through leaching than conventional methods (Yang et al. 2013).

The intended application dictates whether a fully bio-based composite or a synthetic hybrid material is more suitable in polymer manufacturing. Fully synthetic polymers have ruled the polymer industry with increasing progress since the early 1940s, mostly due to their inherent versatility in mechanical and physical

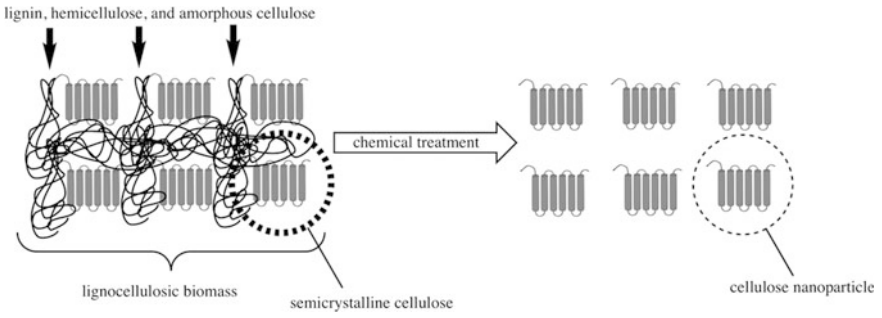

Fig. 8 Isolation of cellulose nanoparticles (nanocrystals/nanowhiskers) from lignocellulosic biomass

properties, easily modified by adjustments made at the monomer unit level. Synthetic polymers have mostly been used for their structural and mechanical capabilities, while bio-based polymers offer a different set of benefits. For example, bio-based polymers are often utilized in drug delivery due to their carbon-based chemistry, biocompatibility potential, and biodegradability. As discussed in Sect. 3.1, wood-waste reinforcement fibers used in conjunction with synthetic polymers have shown comparable thermomechanical properties to non-bio-based competitors. Additionally, bio-based resins filled with synthetic reinforcements have been investigated. One of the most popular instances is carbon nanotubes, which can confer many interesting properties to otherwise structurally uninteresting bio-based resins. Fully bio-based polymers are theoretically ideal for alleviating petroleum demands. Although there has been a significant increase in scientific interest over the past several years, more research needs to be done to make them as cost and manufacturing friendly as their synthetic counterparts.

4 Properties of Bio-based Polymer Composites Used for Biomedical Applications

The increasing production of bio-based polymers, stimulated by dwindling global crude oil resources (Babu et al. 2013), can be noticed in the biomedical field, where novel biomaterials find a wide array of applications. Despite the many interpretations and definitions found in the literature, in this chapter, a biomaterial is considered to be a material of natural origin that has been engineered or modified to interact with biological systems in order to direct medical treatment (Ulery et al. 2011). It is questionably assumed, in many cases, that due to their natural origin, biopolymers exhibit an intrinsic compatibility with living systems.

Among the different kinds of bio-based polymers currently under study, the ones most commonly associated with biomedical applications include chitosan (Croisier and Jérôme 2013; Dash et al. 2011), alginate (Lee and Mooney 2012), and collagen (Scholz et al. 2017). By definition, biodegradable polymers are polymers whose physical and chemical properties undergo deterioration and completely degrade when exposed to microorganisms under appropriate conditions (Babu et al. 2013). The most common biomedical applications for both biodegradable and non-biodegradable, bio-based polymer materials include tissue engineering, drug delivery, bone grafting, and wound healing.

The three main desirable characteristics for bio-based polymers used in biomedical applications are biocompatibility, biodegradability, and low toxicity. These three features need to be present in any biomedical material regardless of its specific application, which is determined based on the material's other physical, chemical, and mechanical properties. For example, biocompatible sponges impregnated with alginate and chitosan have been tested as a biomaterial for chondrogenic human cell differentiation because of their porosity, wettability, and

swelling properties (Zimoch-Korzycka et al. 2016). In another instance, the chiral selectivity between oligopeptides and polysaccharides was used to tune the mechanical and structural properties of bio-based hydrogels, leading to an overall control of mechanical durability and a better understanding of how these properties affect stem cell behavior (Hyland 2012). Due to the lack of consistency on the characterization of the different bio-based polymers reported in the literature, the comparison of different biopolymers' properties is exceedingly challenging. The suitability of novel materials for a specific application is done almost exclusively on a case-by-case basis.

In the case of shape-memory applications, thermomechanical properties determine the suitability of a material for a specific use (Sokolowski et al. 2007). In evaluating the thermomechanical behavior of prospective materials, certain key points are often considered. One of these points is known as the glass transition temperature (T_g), which is the temperature when a polymer transitions from a glassy state to a rubbery or viscous state. This transition is regulated by the structure and chemistry of the polymer. Another key point considered is the pre-deformation temperature (T_d), defined as the temperature beyond which a polymer can deform into a temporary new shape (Gall et al. 2005). The T_d usually happens immediately before or after the T_g (Gall et al. 2005). The temperature beyond which a shape-memory material undergoes irreversible deformation is defined as the storage temperature (T_s) and is usually lower than the T_d (Gall et al. 2005). Finally, the temperature required to return a shape-memory material to its original shape is known as the recovery temperature (T_r) and, like the T_d, is very close to the T_g (Gall et al. 2005).

A great variety of bio-based polymer composites can be prepared by the use of various natural polymers as reinforcement/filler, such as chitosan (Croisier and Jérôme 2013; Dash et al. 2011; Zimoch-Korzycka et al. 2016), alginate (Lee and Mooney 2012; Zimoch-Korzycka et al. 2016), collagen (Scholz et al. 2017; Lu et al. 2003), pectin (Noreen et al. 2017), and keratin (Rouse and Dyke 2010). Additionally, composites formed from a bio-based polymer matrix, such as poly (lactic acid), have found a wide array of applications in the biomedical field (Nampoothiri et al. 2010). It is worth noting that in order to guarantee that bio-based polymers will uphold under physiological conditions, biocompatibility tests need to be the first run. Singular applications within the biomedical field where these bio-based polymers have already started being used include tissue engineering, drug design and delivery methods, and scaffolds for tissue regeneration (Lu et al. 2003).

Despite their low toxicity and immunogenic response, these polymers are highly susceptible to water absorption, which can have a negative impact on their thermomechanical properties, making them inappropriate for long-term structural applications. Ultimately, more research needs to be done to improve the thermomechanical properties and shelf life before the current market's synthetic polymers can be fully replaced.

5 Challenges Encountered in the Design of Novel Bio-based Polymer Composites for Biomedical Applications

5.1 Desired Properties for Biomedical Materials

A biomedical material can be described as any manmade product that is designed to serve a certain biological function. For instance, when a person has an amputated leg, the individual is able to still walk by using a prosthetic leg. A prosthetic leg is a biomedical material because it is engineered to serve the same function as a real leg. Although a prosthetic leg is a common biomedical material, it is certainly not the only one. Other biomaterials include dental implants, heart valves, pacemakers, and spinal cages (Williams 2008).

In order for biomaterials to mirror their intended function, their properties must be similar to the original material. For example, dental implants are commonly made of titanium alloys because of the similarity of strength compared to regular teeth (Williams 2008). Likewise, heart valves are usually composed of cobalt or chromium alloys since chromium is known to improve heart function (Williams 2008). There has also been an increased use in polyether ether ketone (PEEK) for spinal cages due to its persistence in extremely acidic conditions. Materials composed of PEEK are also known to be effective at temperatures as high as 250 °C (Williams 2008). Finally, calcium phosphate is a common material for prosthetics because of its similarity in performance to actual bones (Williams 2008).

Before implementing a biomedical material, biocompatibility must first be considered. It is often preferred that a new material mirrors the natural process of the part it replaces, rather than create a new biological function. Other factors that must be considered include age, sex, lifestyle, and medical history (Williams 2008). An individual's background is crucial to ensuring that the correct composition of the material is made. Detection of microorganisms is also crucial because of the possibility of infections (Williams 2008).

If the biomaterial is incorrect in its composition, or the background of the host is unknown, then it could cause a variety of adverse effects. For instance, if the host is allergic to calcium phosphate, an acute hypersensitivity could occur. Acute hypersensitivity is an over-exaggerated immune response to an allergy which can result in headaches, abdominal pain, nausea, or even loss of consciousness (Shleton and Shivnan 2014). Cytotoxic effects can also arise if the environment where the biomaterial is placed is extremely acidic. If a cytotoxic effect is induced, then irreversible tissue destruction can occur (Williams 2008).

In 1987, the ESB consensus conference of 1987 defined a bioactive material as "one which has been designed to induce specific biological activity". Since then, nanomaterials have been implemented into most biomaterials (Li et al. 2013). Most biomaterials contain either carbon nanotubes, carbon nanofibers, or boron nitride nanotubes because they promote protein absorption, cellular adhesion, and tissue growth (Li et al. 2013).

5.2 Challenges Faced by Bio-based Materials

Although bio-based materials solve an abundance of environmental problems associated with fossil fuels, they do have their challenges. Crude oil and gas are cheaper to produce at this point than biomaterials (National Research Council 2000). This is because biomaterials require a much larger workforce, which adds to the overall cost of production (National Research Council 2000). In addition, the process of making biomaterials requires a more educated workforce because of its complex process of production.

There are three main ways to produce a biomaterial. The most common method preserves a polymer backbone through the chemical modification of natural polymers, such as starch and cellulose (Storz and Vorlop 2013). This process usually requires prior modification of the polymer so that it can survive extreme heat (Storz and Vorlop 2013). This prior modification adds to the cost of production, rendering a final product that is more expensive than its petroleum counterpart. Another production method involves converting biomass, such as starch, into monomers that can be subsequently polymerized. One limitation of this method is that starch is extremely hydrophilic, which makes it unusable in humid environments and significantly limits applications of this method (Storz and Vorlop 2013). The third method involves taking advantage of photosynthesis in plants to directly produce the desired biomaterial. This method, however, is not fully understood and needs further study.

An important challenge to consider is that bio-based monomers, like starch, usually produce a significantly lower overall yield compared to their crude oil-based competition, which represents a major con from an economic standpoint (Storz and Vorlop 2013). Another challenge associated with biomaterials is that the supply chain for production is often a lot longer than that of the currently established industry, contributing to an increased cost of production. In addition, the technology required for production has not been fully tested. Therefore, many companies are hesitant to implement a new process because of the uncertainty that the process is truly better than the current technology. Finally, the majority of the bio-based monomers currently considered for the production of biomaterials derive from food, so if bio-based materials are used widely, the offer for food production would decrease, increasing food prices (National Research Council 2000).

6 Conclusion

It is notorious that there has been a continuous increase in the research activity related to the development of novel bio-based materials over the past couple of decades. The focus has slowly shifted from simpler systems, consisting primarily of traditional thermoplastics reinforced with natural fibers, to more advanced composites with carefully engineered bio-based matrices, or fully bio-based materials in

which both matrix and reinforcement are of bio-based origins. Research efforts in bio-based composites over the years have also focused on the improvement of matrix–reinforcement interactions with the purpose of increasing physico-mechanical properties. The progress in the development of novel bio-based composites is naturally accompanied by advances in polymer and composites processing, especially in cases of commercial and industrial applications. In the realm of bio-based biomedical materials, current applications are vastly dominated by PLA and PLA-based composites, with limited work done on other systems, such as hydrogels, for use as scaffolds in cell growth and tissue regeneration. The existing challenges for the fabrication and the use of bio-based composites are mainly associated with the lack of consistency in materials characterization among the various proposed systems, which makes a direct comparison of different materials exceedingly hard. It is expected that the trends in the development of novel bio-based materials will continue in the future with some materials finding suitable applications across many different areas, including in the biomedical field, especially for drug delivery and cell scaffolding, as reported in this manuscript.

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Amorphous and Semicrystalline Thermoplastic Polymer Nanocomposites Applied in Biomedical Engineering

S. S. M. Abdul Majeed, Aqib Muzaffar, Kalim Deshmukh and M. Basheer Ahamed

Abstract This chapter is intended to provide an insight into the biomedically engineered polymer nanocomposites (PNCs). It provides an introductory review about the amorphous, semicrystalline thermoplastic PNCs. The processing techniques pertaining to the amorphous, semicrystalline thermoplastic PNCs along with their consequences on the nanocomposite formation are mentioned. The impact on the addition of various fillers such as carbon nanotubes (CNTs) and graphene on the overall characteristics of the PNCs is elaborated. The examples of different amorphous and semicrystalline PNCs and their applications in biomedical engineering are discussed.

Keywords Amorphous polymer · Thermoplastics · Polymer nanocomposites · Graphene · Carbon nanotubes · Nanoclay · Biomedical engineering

1 Introduction

Polymer nanocomposites (PNCs) form a field of material research with great and prospering future due to the credibility of their performance optimization. The increasing trend in developing PNCs predicts an uphill in their demand with hitherto unnoticed properties. In response to the rise of globalization, there is a constant focal shift toward the development of new techniques to meet the demand (Ponnamma et al. 2018a). In recent times, PNCs of all categories have provoked a lot of research interest pertaining to the enrichment of nanocomposite properties especially at lower

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K. K. Sadasivuni et al. (eds.), *Polymer Nanocomposites in Biomedical Engineering*, Lecture Notes in Bioengineering,
https://doi.org/10.1007/978-3-030-04741-2_3

fractions of volume (Fadiran et al. 2018). The synergistic improvements in the nanocomposite properties are achieved on the basis of compact optimization leading to the superiority of the overall nanocomposite with respect to the components (Nagaraj et al. 2018). This formulates an enviable objective in the area of material science research for the production of multifunctional materials which are defined on the basis of composition causing particular property improvement desired for some specific application (Popelka et al. 2018). Therefore, the development of such multifunctional materials allows replacement of one material in an otherwise engineered object or a particular set of materials whose combination serves the same functionality (Janson et al. 2018; Abdullah et al. 2018).

PNCs are an innovative group of materials possessing improved properties and can be exploited for a variety of applications. Mainly the research in the area of PNCs is purposeful on the applications in emerging fields (Muzaffar et al. 2018). PNCs are promising materials to be utilized for biomedical applications and are developed by integration of nanoscale materials into the polymer matrix (Sankaran et al. 2018). Common types of nanofillers used are layered silicates, metal oxides, carbon nanotubes (CNTs), graphene, etc. The major challenges in the synthesis of PNCs are achieving a consistent allocation of nanofillers in the polymer matrix and the filler–matrix interaction (Joseph et al. 2018).

The advent of PNCs in the biomedical industry holds its roots in the first half of the twentieth century. The field of polymer nanoscience saw development prior to World War II and polymer revolution began post-World War II due to their usage for common applications apart from military applications (Osborne 2005). The reason behind the growth of PNCs was a shortage of metals and consideration of alternatives. The polymers like nylon, polytetrafluoroethylene (PTFE), and poly (methyl methacrylate) (PMMA) were extensively used in the rope industry, metallic coating, and biomedical applications respectively. In the biomedical field, PMMA was used widely in orthopedics as bone cement, prosthetic joint replacement, as bone fillers and in dentistry as cavity filling. For the polymer used in orthopedics, the essential requirement is the matching of the elastic modulus of the polymer in the proximity to that of the bone (Kurtz and Devine 2007). The PNCs offer cheap and disposable medical devices owing to their flexible production at high scale. These devices include syringes (plastic), blood storage units (polyvinyl chloride), drug delivery (polyglycolic acid), sutures, and stents (polylactic acid) (Smith et al. 2010; Puppi et al. 2010).

Currently, the PNCs form an interesting class of productive engineering materials. The engineering mechanism comprising of designing and fabrication is based on the empirical extrapolation of certain parameters related to the selection of components and processing technique. This is to attain certain properties on the selection of particular nanocomposite component on employment of specific processing techniques. Since in present times the designing aspect of the nanocomposites forms an essential criterion, there arises a paradigm shift from fabrication-oriented construction to design and construction oriented fabrication. The engineering aspects as such provide an insight into the investment costs for processing of complex tools.

However, this imposes a restriction on the designing and functionality of the product. To overcome such restrictions, new techniques like additive processing covering the complexity and pricing require proper establishment. It is, however, worth mentioning that physical characteristics of the PNCs are based on the type of monomers constituting it and stereochemistry of the linkage (Parambath et al. 2017). The stereochemistry of the polymer explains the chain length, distribution, structure and its propensity to crystallize or stay amorphous under different conditions. In addition to that, the stereochemistry determines the shape and distribution of the chain shapes in both amorphous and crystalline states.

The advances in polymer chemistry have worked wonders in designing the PNCs with specific properties. The polymer chemistry provides much-needed control over the nanostructure of the composite comprising of the molecular weight distribution of the polymers and the tacticity (Morozowich et al. 2011). Generally, the PNCs after being designed must retain stability, structure, and morphology under different environmental conditions during its activity. Contrary to that, in recent times there has been keen interest in changing the morphology without accompanying any hysteresis or memory effects on providing stimulus in the form of electric, optical, or mechanical nature leading to the formation of smart materials (Liu et al. 2012). These smart materials are designed for applications including memory storage and recovery, and molecular identification of the biological structure. The smart polymeric materials are intended to attain the knack to manage the material at the nanoscale (Thangamani et al. 2018).

The amorphous PNCs form a group of materials having glassy, brittle, and ductile nature without exhibiting any crystalline features. The structure of such polymers is globular and only accessible after pre-treatment of the polymer using staining causing contrast enhancement in transmission electron microscopy (TEM) (Thostenson et al. 2005). The mechanical behavior of such polymers is as a consequence of localized deformation zones (crazes), deformation bands or shear bands. The amorphous polymers lack long-range molecular arrangement. The examples of such polymers include polycarbonate, acrylic, polyethylene terephthalate glycol (PETG), polysulfone, acrylonitrile butadiene styrene (ABS), polyesters and epoxies. Semicrystalline polymers, on the other hand, are composed of the highly ordered molecular structure along with sharp melting points. The semicrystalline polymers possess the tendency to retain solid state until the particular quantity of heat is absorbed, changing it into a liquid with low viscosity. In addition to that, these polymers are anisotropic in flow, exhibit greater shrinkage transverse to the direction of flow. The properties of these polymers include excellent chemical resistance and retention of strength and stiffness beyond glass transition temperature. These polymers display hierarchical morphology like crystalline blocks, lamellae, spherulites, and fibrils. The examples of semicrystalline polymers are polyethylene (PE), polyphenylene sulfide (PPS), polypropylene (PP), polyether ether ketone (PEEK), polyetherketone (PEK), polyphthalamide (PPA), polyetherketoneketone (PEKK), polyamides, fluoropolymers, and polyurethanes (Thostenson et al. 2005).

Unsurprisingly, the consequences on the characteristics of PNCs are based on the size of the nanomaterial and the eminence of the interface linking the filler material with the polymer matrix (Thangamani et al. 2017). The interactions exhibiting between the nanomaterial and the polymer matrix can be either physical or chemical leading to the formation of PNCs with enhanced properties in contrast to the virgin polymer (Pasha et al. 2017; Deshmukh et al. 2017b). Hence, the enhancements pertaining to the properties like the mechanical properties, thermal stability, heat distortion temperature, chemical resistance, electrical conductivity, and optical clarity of the parent polymer systems significantly can be attributed to the low filler loading. This makes the PNCs ideal for many applications like aerospace, automobile industry, biomedical field, metal coatings, and sensors (Deshmukh et al. 2017a; Sumathra et al. 2018; Ponnamma et al. 2018b). This chapter deals with the amorphous and semicrystalline thermoplastic PNCs for biomedical applications.

2 Processing of the Amorphous and the Semicrystalline Thermoplastic Nanocomposites

For the processing of the PNCs, numerous approaches can be followed; however, in general, four processing methods—in situ template synthesis (sol–gel), solution intercalation, in situ intercalative polymerization, and melt intercalation—are widely applied (Abraham et al. 2010). The outcome and applicability of PNCs are based to a greater extent on the processing procedure. Therefore, processing method requires proper consideration prior to nanocomposite formation. The above mentioned processing methods are illustrated briefly in the following sections.

2.1 Template Synthesis (Sol–Gel Technology)

In this technique, nanocomposites like clay minerals consisting of the aqueous solution of polymer material and silicate are synthesized inside the polymer matrix (Kim et al. 2007). Sol–gel method has been comprehensively used in the synthesis of silica, glass, and ceramic materials owing to the credibility of the method to yield pure and homogenous products under serene conditions. The sol–gel process is initiated by hydrolysis and followed by condensation reactions (Neena et al. 2016). The structure-related properties of organic–inorganic sol–gel composites aided by either hydrogen bonding or weaker interactions have been studied (Rahman and Padavettan 2012). A typical sol–gel synthesis procedure follows a conversion scheme engrossing the use of metal-inorganic precursors and converting them into inorganic materials using organic solvent or simply by use of water (Boccaccini

et al. 2010). In the synthesis of the bioactive silicate-based nanocomposites, a sol–gel method of processing is widely used.

In the sol-gel synthesis procedure for bioactive silicate glasses, the precursors exploited are tetraethyl orthosilicate, calcium nitrate and triethylphosphate (Veerapandian and Yuna 2009). The precursors undergo hydrolysis and polycondensation reactions to yield a gel which is afterward calcinated at 600−700 °C to form the glass. The nanocomposites synthesized by sol–gel method exhibit high porosity and specific surface area (Hong et al. 2009). However, it is essential to direct the morphology of the nanocomposites to get the intended biological properties. The bioactive nanocomposites synthesized by the sol–gel method have been applied as coatings on different materials to improve mechanical and biological properties (Esfahani et al. 2008; Fathi and Doostmohammadi 2009). For example, the bioactive glass synthesized by a sol-gel method was applied as a coating on the struts of porous hydroxyapatite to improve the mechanical characteristics of the scaffold with an increase in sintering temperature (Esfahani et al. 2008). The enhancement in mechanical properties can be accustomed to the crystallization occurring in the bioactive nanocomposites. However, in some applications like tissue engineering of scaffolds, anisotropic structures (elongated and fibrous structures) are more convenient. To achieve more features from nanocomposites, the combinations of the sol–gel method with electrospinning have been developed (Kim et al. 2006). In such scenarios, it is obligatory to use additives like polyvinyl butyral for adjustment of rheological characteristics of the sol for electrospinning. It is worth mentioning here that in sol–gel and sol–gel derived techniques, the product must undergo heat treatment to evacuate the organic additives. The two combined processes can be used in the synthesis of nanosize bioactive glass fibers for tissue engineering scaffolds.

The sol–gel method despite being versatile is used to synthesize a wide range of nanoscale bioactive glasses, although being inadequate with respect to the compositions, which can be produced. The residual water or solvent used sometimes can produce complications especially in the field of biomedical applications. Therefore, it is essential to eliminate the organic residue by calcination.

2.2 Intercalation Methods

This technique is applicable to the nanocomposites consisting of layered hosts like silicates. The intercalation technique provides a successful synthesis approach for polymer–layered silicate nanocomposites. The intercalation technique is categorized into three main types namely intercalation of polymer or pre-polymer from solution (solution intercalation), in situ intercalative polymerization method and melt intercalation method based on the precursors and processing techniques. These methods are separately mentioned for convenience in the upcoming section.

2.2.1 Solution Intercalation Method

This method is based on the solvent related to the solubility and swellability of the polymer/pre-polymer and layered silicate, respectively (Ray and Bousmina 2005). The silicate is initially inflated in the desired solvent like water, chloroform, or toluene. This is followed by addition of polymer leading to intercalation of layered silicates between the chains of polymer matrix causing solvent displacement within silicate layers. When the solvent is completely drained out, a polymer–layered silicate nanocomposite is produced.

The schematic diagram of the solution intercalation process is shown in Fig. 1. In this technique, the layered substance and polymer are first solvated on the usage of a solvent wherein the polymer and silicate are soluble. After the exfoliation of the organoclay, the polymer solution is added to the organoclay solution. At this step, intercalation of organoclay takes place among the organoclay layers. Finally, the solvent is evaporated by vaporization, under vacuum or by precipitation. Once, the solvent is completely removed, the layers reassemble holding the polymer to form the nanocomposite structure. This technique is also applicable to the nanocomposites which are obtained by emulsion polymerization in which the layered silicate is dispersed in the aqueous phase (Beyer 2002). The plus point of this method is the non-dependency of intercalated nanocomposites on polarity. However, the solvent dependency marks difficulty in the utilization of this approach.

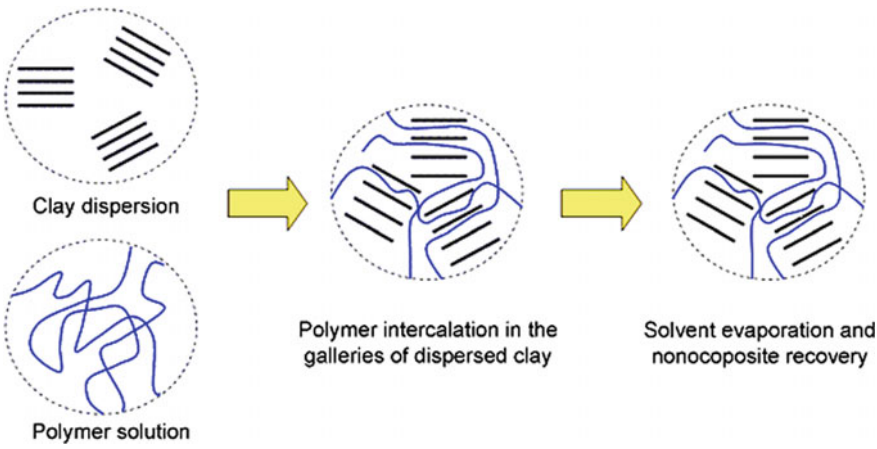

Fig. 1 Schematic illustration of the solution intercalation process of polymer–layered silicate nanocomposite (Pavlidou and Papaspyrides 2008). Copyright 2008. Reproduced with Permission from Elsevier

2.2.2 In Situ Intercalative Polymerization Method

In this method, monomers are polymerized in presence of the layered silicate minerals. Polymerization of monomer occurs between the silicate layers (Avella et al. 2001). This method is schematically shown in Fig. 2. The layered silicate is exfoliated inside the liquid monomer, and the polymer takes sites between the intercalated sheets to form the polymer nanocomposite. This method requires stimulus for polymerization, which is provided in the form of heat or radiations or by the diffusion of initiator (catalytic or organic) or by cation exchange taking place in the interlayers of layered silicate prior to exfoliation (Mittal 2009).

2.2.3 Melt Intercalation Method

In this method, the mixture of polymer and organically modified layered silicate undergoes either static or shear annealing above the softening point of the polymer (Hasegawa et al. 2005). It leads to other intercalation methods due to its benign impact on the environment. This method does not aid any organic solvent in addition to its compatibility. The polymers which are not suitable for other intercalation methods can be used in melt intercalation. The purpose of annealing is to diffuse the polymer chains amid the silicate layers from the bulk polymer melt as shown in Fig. 3. The melt intercalation method forms an appealing and promising approach for nanocomposite preparation. This method is simple, compatible, and cost effective and has prospering future in the field of commercial nanocomposite technology (Wang et al. 2005). It allows direct formulation of nanocomposites aiding to conventional compounding devices like mixers and extruders, thereby providing an edge with respect to final product characteristics.

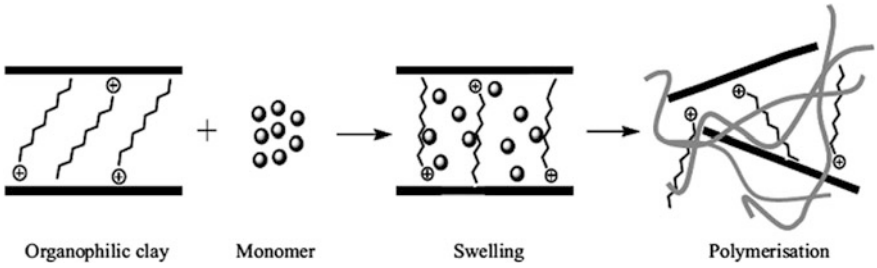

Fig. 2 Schematic representation of in situ polymerization

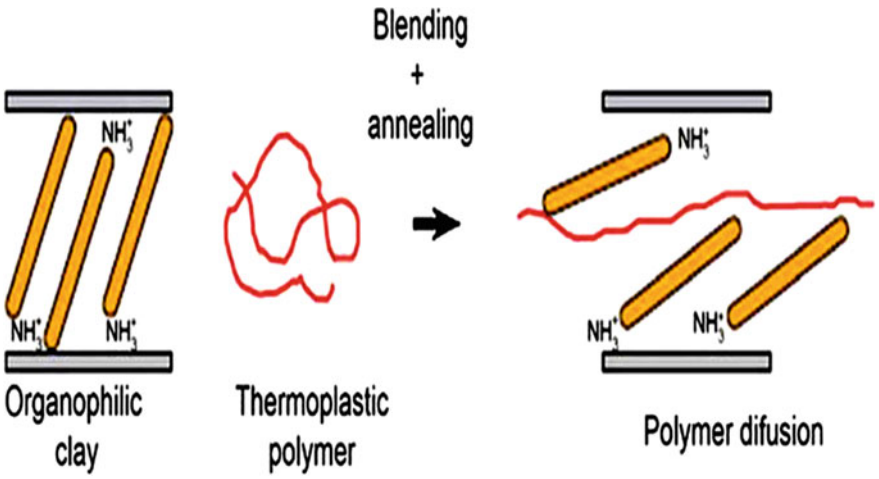

Fig. 3 Schematic representation of melt intercalation (Beyer 2002). Copyright 2002. Reproduced with Permission from Elsevier

3 Examples of the Polymers Used in Biomedical Engineering

3.1 Amorphous Polymers

In amorphous polymers, the anisotropy of thermal properties exists as a consequence of the partial orientation of polymer chains with thermal conductivity along the chain direction greater than that of perpendicular to chain orientation. The addition of nanoparticles to an amorphous polymer leads to an increase in the strain as a consequence of the increase in strain failure coinciding with a decline in particle size (Jordan et al. 2005). The examples of amorphous polymers include the following:

3.1.1 Polycarbonate (PC)

PC is a transparent and hard engineering thermoplastic offering immense strength and high elasticity modulus. It also has higher heat deflection temperature and does not absorb a lot of moisture. It also exhibits low-frequency and high voltage-based characteristics and hence is ideal for electrical and electronic components (Mohanapriya et al. 2015). The thermal properties of PC, however, are enhanced by the accumulation of inorganic fillers (Possner and Kolbesen 2007). The addition of filler causes scratch resistance and surface gloss without causing any impact on transparency and hardness of PC. The addition of conventional fillers in PC is avoided in order to retain its optical property and increases in heat distortion

temperature and glass transition temperature. PC is biomedically engineered with organophilic clay using in situ polycondensation reaction to obtain an exfoliated structure (Rama and Swaminathan 2010). The intercalation occurs between the polymer chains and clay layers accompanied by electrostatic forces. The nanocomposite displayed excellent thermal, mechanical, and barrier properties.

3.1.2 Rubber Nanocomposites

Rubber nanocomposites especially polydimethylsiloxane (PDMS) has been used as a substituting material for soft tissue (Abbasi et al. 2002). However, the incorporation of silicon with rubber, when implanted in place of soft tissue, lacked long-term stability due to their high exposure to the peril of infection. The risk of infection arises due to the presence of dead space between the implanted device and the tissue and lack of the bond formation between the implant to adhere itself to the skin tissue. The risk can be avoided by using silicone rubber implants with controllable swellings to be more efficient in biomedical applications (Ai et al. 2003). The control on the swelling of the implant can be achieved by means of surface and bulk modifications like copolymerization, functionalization, interpenetrating polymer networks, laser-induced sequential method, surface grafting and blending (Rajan et al. 2012). After modifications, the nanocomposite composed of PDMS with surface-grafted poly(2-hydroxyethyl methacrylate) by using laser shows the potential application of the nanocomposite in platelet adhesion thereby providing procoagulant sites.

3.2 Thermoplastic Polyurethane (TPU)

TPU is the material ideal for biomedical applications owing to its simplicity in device fabrication, flexibility, biocompatibility, bio-stability and electrically insulating nature (Simmons et al. 2008; Ward et al. 2006). The combination of TPU with multiwalled carbon nanotubes (MWCNTs) has also been reported for biomedical use (McClory et al. 2007). The nanocomposite comprised of MWCNTs at 1% loading by means of an addition polymerization reaction. The addition of MWCNTs leads to considerable enhancement in stiffness, strength, and Young's modulus. The reports about tailoring TPU and organically modified nanosilicates suggest its bio-stability and benefitting mechanical characteristics, thereby explaining its credibility for fabrication of a variety of medical devices (Styan et al. 2012).

3.2.1 Polystyrene (PS)

PS is among the versatile thermoplastics having commercial and medical applicability due to its hard and solid plastic appearance (Neuberger et al. 2005). It is an

aromatic polymer formulated on the combination of styrene monomers. Based on its appearance, PS is mostly used in medical products requiring clarity and ease of sterilization (Gil and Hudson 2004). In the medical field, PS is used in applications like manufacturing of tissue culture and disposable trays, Petri dishes or plates, test tubes, diagnostic components, as housings in testing kits and other medical devices (Stuart et al. 2010; Roy et al. 2010). These devices are based on the biodegradability and biocompatibility feature of the PS. The medical devices made of PS are sterilized by using ethylene oxide and UV light without any impact on cell growth. PS is not prone to degradation in the cellular environment and does not cause any restraint to cells, even for the longer duration of investigations (Kumar et al. 2007).

3.2.2 Polyvinylidene Difluoride (PVDF)

PVDF is an important thermoplastic polymer inherited with advantages like stability, toughness, low thermal conductivity, low heat chemical corrosion resistance, high abrasion resistance, and distinctive engineering features (Sathapathy et al. 2017). PVDF withstands severe chemical, thermal, and ultraviolet circumstances. PVDF exhibits enviable insolubility and electrical properties as an outcome of the polarity arising between alternating CH_2 and CF_2 groups on the polymer chain. The applicability of PVDF, especially in the field of health care, utilizes the properties like pyro and piezoelectricity, ferroelectric characteristics, admirable biocompatibility, and chemical resistance (Pawde and Deshmukh 2009). Based on piezoelectricity, PVDF finds its application in biomedical ultrasound exposimetry using spot poled membrane hydrophone design in its a variety of embodiments, thereby exemplifying biomedical ultrasound fields (Harris 2009). The progress in such devices has made quantification of ultrasound exposure levels possible according to the established standards for device safety (Agarwal et al. 2011). PVDF is also used in pressure sensing equipments based on its ferroelectric behavior (Braga et al. 2007). PVDF sensor displays the great response in the measurement of mechanical pressures of both low and high magnitudes. However, the measurements greatly depend on the material used to construct the sensor. Likewise in ophthalmology, PVDF-based pressure sensor possesses the capability to measure the low magnitude intraocular pressure within a specific pathology named glaucoma (Aronov et al. 2010). In addition to that, PVDF finds its application in bone regeneration due to antibacterial property of PVDF membrane when incorporated with other materials (Samanta et al. 2009).

3.3 Semicrystalline Polymers

The crystallinity of polymers produces noteworthy optimizations subsequent to optical, thermal, chemical, and mechanical properties. The crystallinity in polymers is attained due to cooling the polymer from the molten state, stretching due to

mechanical stress or simply by evaporation of the solvent. The estimation of the extent of crystallinity is done by means of various analytical methods. For semicrystalline polymers, the extent of crystallinity is between 10 and 80%. The characteristics of semicrystalline polymers are based on the extent of crystallinity in addition to orientation and size of polymer chains. The examples of semicrystalline polymers are listed in the following section.

3.3.1 Polyethylene (PE)

PE is a thermoplastic semicrystalline polymer exhibiting variable crystalline structure. As a consequence of that, the applications are enormous and it is mostly used in the production of plastics. It lies in the class of polyolefinic plastics, and PE is the most preferred material for the development of PNCs. For biomedical engineering, PE is generally grafted with fillers to achieve the desired applicability.

3.3.2 Polypropylene (PP)

PP is another thermoplastic semicrystalline polymer formed due to the combination of propylene monomers. PP is widely used in packaging, as plastic parts for automobile and textile industry. For medical applications, PP is grafted with fillers and other organic materials. For example, the nanocomposite composed of grafted PP/Cloisite 30B maleic anhydride prepared by water-based extrusion and by simple extrusion (Zheng et al. 2010). By using water, the nanocomposite exhibited enhancements in clay delamination dispersion and in rheological, thermal, and mechanical assets also observed. The other example is that of CO_2-assisted extrusion of polymer/clay nanocomposites enabling elevation in the separation among the clay layers. CO_2 helps in the expansion of the layer spacing between the clay particles, thereby encouraging exfoliation of the nanocomposite during the foaming process. The strength optimizations are achieved due to the addition of clay particles in small amounts during the foaming process hindering cell coalescence of the linear PP matrix. The modification in morphology presents PP/Cloisite 20A nanocomposites for applicability in the medical field.

3.3.3 Polyamide (PA)

PA is a synthetic thermoplastic linear semicrystalline polymer. It is widely used in clothing, rubber reinforcement, rope and thread making, injection molding. PA comprises characteristics like exceptional strength, resistant to abrasions, chemicals and moisture, long durability, and highly elastic. Among all engineering plastics, PA present the premier quantity of research work. For example, PA 66/Hectorite nanocomposites synthesized by melt compounding displayed a decrease in the rate of moisture absorption and the addition of organoclay enhanced the barrier property

of the nanocomposite (Timmaraju et al. 2011). The nanocomposite showed amplification in tensile modulus and hardness. The enhancements are, however, directed by the nanostructure of the organoclay in PA matrix.

3.4 Polymer–Clay Nanocomposites Types

The layered silicates generally exhibit exceptionally higher aspect ratios. For the development of PNCs, a small percentage of layered silicates are dispersed onto the polymer matrix (Ray and Bousmina 2005). Based on the nature of the materials in consideration, and the means of synthesis, mainly three kinds of composites can be produced (Alexandre and Dubois 2000). The polymer-layered silicates (PLS) prepared by these three methods are shown in Fig. 4.

(a) Phase-Separated Structure The structure formation initiates with the dispersion of layered silicates in a polymer matrix. The polymer may be incapable of interaction between clay layers, and the clay attributes to the aggregation or clustering inside the polymer matrix. The nanocomposite structure obtained by this kind of dispersion of silicates is considered "phase separated" (Wu and Yang 2006).

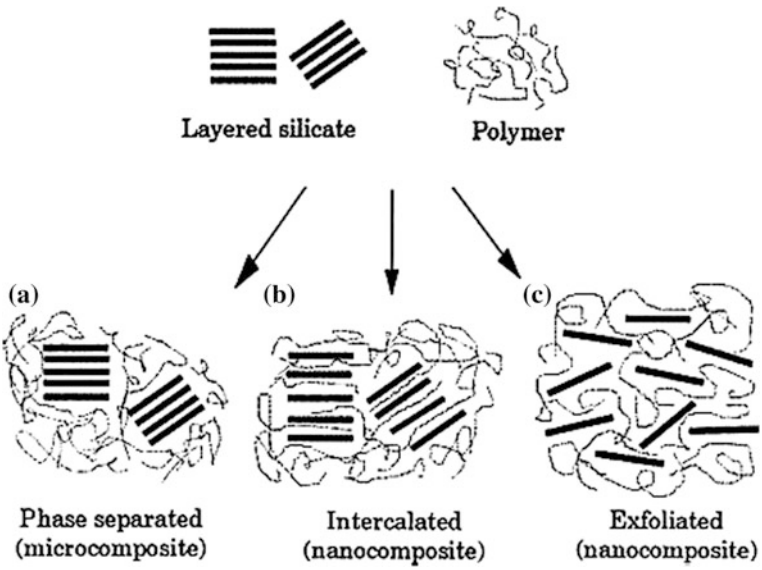

Fig. 4 Schematic illustration of three different types of thermodynamically achievable PLS nanocomposites (Alexandre and Dubois 2000). Copyright 2000. Reprinted with permission from Elsevier

(b) Intercalated Nanocomposites When the better interaction between the polymers and the layered silicates is achieved, intercalated structures are formed as a result of a regular stacking of alternative layering of polymeric and inorganic material accompanied with increasing interlayer separation (Pavlidou and Papaspyrides 2008).

(c) Exfoliated Nanocomposites This type of structure formulation occurs between well-separated clay and polymer layers when individually dispersed in an incessant polymer matrix to obtain exfoliated structure (Pavlidou and Papaspyrides 2008).

Some of the polymer–clay nanocomposites used in biomedical engineering are listed in the next section.

3.4.1 Polyurethane–Urea (PUU)

PUU is a segmented block copolymer in the class of reactive polymers. PUU used in biomedical field like in total artificial hearts and blood sacs in ventricular assist devices consists of ca. 80 wt% poly(tetramethylene oxide) (PTMO) soft segments and polyether (Xu et al. 2001). However, when PUU is used in completely implantable devices, it suffers consequences due to relatively high permeability to air and water vapors. The presence of soft phase polyether leads to high permeability as a result of penetrant diffusion. To reduce the permeability of PUU without altering its properties pertaining to mechanical strength and biocompatibility, several chemical methods have been developed. One of such methods includes replacement of PMTO with soft segments of aliphatic polycarbonate (Kwak and Sei 2003). The modified PUU with a biocompatible layered filler of alkylammonium is used in medicines for reduction of stomach acid. The other poly–clay nanocomposites include poly(vinyl alcohol) (PVA)–clay and poly(ethylene oxide) (PEO)-clay nanocomposites which are used in medical field.

4 Nanoscale Reinforcements in the Polymer Nanocomposites

CNTs, graphene, and nanoclays are widely explored nanofillers in the processing of polymer-based nanocomposites (Liff et al. 2007). These fillers impart different characteristics like thermal, chemical, electrical and mechanical. The functional and mechanical characteristics among nanofillers and polymer matrix are governed by their interaction (Ahmad et al. 2013). Desired properties combinations can be achieved by the alterations and of various parameters and by the restraining nanostructures and polymers interactions.

4.1 Carbon Nanotubes (CNTs)

CNTs comprises of a monolayered sheet of graphene, i.e., single-walled carbon nanotubes (SWCNTs), or several concentric layers graphene through the multi-walled structure, i.e., MWCNTs (Serrano et al. 2014). CNTs have attractive mechanical, electrical, and thermal characteristics. They exhibit outstanding mechanical characteristics like high Young's modulus and tensile strengths up to 63 GPa (Wang et al. 2012). CNTs find many applications including their combination with polymers forming nanocomposites.

CNTs have been explored as a better reinforcing material for PNCs attributing exceptional mechanical, electrical, and surface characteristics (Cooper et al. 2002). The amalgamation of a small quantity of CNT considerably increases the mechanical strength of polymer matrix. The mechanical properties of PNCs are based on the nature of the polymer. The polymer matrix and the CNTs interactions in addition to the homogeneous dispersion of nanotubes in the polymer matrix provide improved properties in the nanocomposites (Wong et al. 2003).

The characteristics of nanocomposites are prejudiced by the processing method also. The incorporation of CNTs as nanofiller in the polymer matrix improve the physicochemical properties like flexibility and strength of the polymer matrix and adds to their functionalities for different applications (Spitalsky et al. 2010). CNTs are functionalized by chemical treatment to improve their interaction with the polymer matrix (Macossay et al. 2012).

4.2 Graphene

Graphene is composed of hexagonal-packed lattice forming a two-dimensional single layer material inhibited with unique characteristics like elevated mobility even at room temperature, high Young's modulus, and outstanding conductivity (Deshmukh et al. 2015; Lee et al. 2008; Fayyad et al. 2016). Graphene is produced by mechanical exfoliation of graphite, chemical vapor deposition (CVD) growth or exfoliation of graphite oxide (Deshmukh et al. 2016b).

Graphene has been reported as superior nanofiller in contrast to the other carbon-based nanomaterials, because of its high electrical and thermal conductivity. The physical and chemical properties of nanocomposites are governed mostly on the basis of allocation of graphene layers in the polymer matrix and interfacial bonding involving graphene layers and polymer matrix (Deshmukh et al. 2016a). Development of graphene-reinforced PNCs is an interesting area of research. Graphene-based PNCs have been reported for numerous biomedical applications.

4.3 Nanoclays

Nanoclays consisting of layered silicates are regarded as very efficient reinforcing materials when incorporated with polymers. They exhibit interesting characteristics like high aspect ratio, high strength, and stiffness. Clay minerals comprise of both natural clays (e.g., hectorite, montmorillonite, and saponite) and synthetic clays. The conventional composites are formed by filling layered clays into a polymer matrix. The layered clays are based on the nature of the components and processing conditions. In case of conventional composite or nanocomposite, the polymer is prohibited to intercalate between the spacing of clay minerals. Based on the spacing of clay minerals, the nanoclay-based nanocomposites are classified as intercalated and delaminated or exfoliated nanocomposite.

The intercalated nanoclay-based nanocomposites are composed of monolayer extensions of polymer chains which are infused into the vicinity of clay minerals leading to a well-organized multilayer structure. The multilayer structure consists of alternative clay platelets and polymer layering. Contrary to that, exfoliated nanocomposites are composed of consistent and homogeneous diffusion of nanoclay platelets in the continuous polymer matrix that leads to enhanced interactions between polymer and clay (Kiliaris and Papaspyrides 2010). The nanocomposites containing nanoclay exhibit better interactions among the diffused clay and the polymer interfaces. The interactions lead to improvements in thermal, mechanical, and barrier properties of the nanocomposite as compared to the nascent polymer (Lecouvet et al. 2013). However, there exists an incompatibility among hydrophobic polymer and clay. This incompatibility is among the shortcomings of such nanocomposites during insemination of nanoclay particles in the polymer matrix. Hence, a significant role is played by surface modification of clay minerals to form PNCs. The exclusive encrusted configuration and elevated intercalation potential of clay minerals avail their chemical modification for compatibility with polymers which is crucial for the development of such nanocomposites. Based on the targeted application, a particular nanoclay is selected for the formation of particular PNCs.

The promising applications of these nanocomposites are in the biotechnological and biomedical field. Clay-based PNCs have been investigated in biosensors, tissue engineering, drug delivery, and biomedical devices (Paul and Robeson 2008). However, major challenges arise while developing nanocomposites for biomedical relevance having characteristics like biodegradability and long-term biocompatibility.

5 Polymer Nanocomposites in Biomedical Applications

The polymer-based nanocomposites enclose greater credibility in many biomedical and biotechnological applications (Goenka et al. 2014). The combination of chemical, physical, and biological properties of nanocomposites provides new

avenues for designing and developing materials with improved properties for biomedical applications (Satarkar et al. 2010). PNCs possess improved mechanical properties, and they can be used to replace bones (Tripathy 2017). PNCs find applications in the latest technologies like tissue engineering, biomedical imaging, sutures, surgical implants and drug delivery. The schematic representation of biomedical applications of polymer–silicate nanocomposites is given in Fig. 5.

The scaffold used in tissue engineering, serve as an outline and support for cell adhesion, proliferation, and the creation of extracellular matrix (Lee et al. 2008). Polymer-based nanocomposites are extensively considered for tissue engineering applications (Serrano et al. 2014). PNCs can be used for hard and soft tissue engineering due to their enhanced mechanical and electrical properties. PNCs could be used as a credible material for drug delivery because they can deliver huge and directed doses of therapeutic objects prospering toward the specific site. The applications of PNCs in the medical field are listed below.

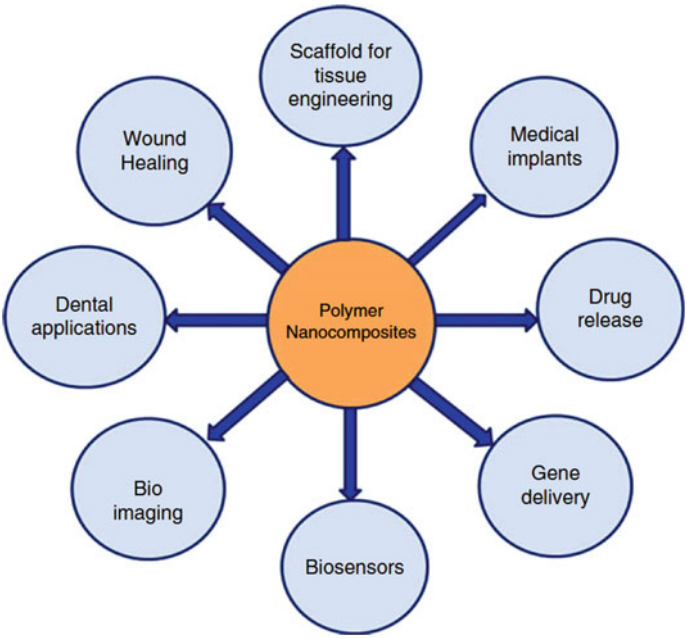

Fig. 5 Schematic representation of biomedical applications of PNCs (Tripathy 2017). Copyright 2017. Reproduced with permission from Springer Nature

5.1 Scaffold Tissue Engineering

The methods utilizing the material, engineering and biological sciences to formulate synthetic constructs for new tissue regeneration form the basis of tissue engineering. The field of tissue engineering provides substitution alternatives in repairing or replacing a failing tissue or organ. The growth of cells on scaffolds acting as temporary support for cells especially during target tissue regeneration without incorporating any changes to the stable three dimensional (3D) structure is one of most promising approaches in tissue engineering (Ma 2004). A wide range of materials are assigned to perform in such processes and among them, the scaffolds using polymeric materials play the most crucial role. Polymeric scaffolds are used in seeding and proliferation of cells, new tissue creation in 3D for various organs, etc. The PNCs inhibit characteristics like porosity, pore sizing and the high surface area which are acknowledged as the essential parameters for scaffold tissue engineering (Quirk et al. 2004). In addition to that the PNCs possess architectural qualities like pore shape, the morphology of pore wall, and interconnectivity between the pores of the polymeric scaffold. These qualities formulate as the base requirements for seeding of cells, cell growth and migration, transport of mass and formation of new tissue (Ma 2004).

The replacement of scaffolds composed of collagen with ultra-porous scaffolds composed of biodegradable polymers has been growing rapidly. The reason behind their rapid growth of biodegradable PNCs is their degradation with new tissue formation leaving no place for the foreign body. However, the challenging aspects of such scaffolds are the designing and fabrication of the customized biodegradable polymers with characteristics which endorses cell adhesion and porosity (Ma 2004). Consequently, the other aspects also include adequate mechanical properties matching with the hot tissue along with the rate of predictable degradation and biocompatibility (Sinha and Okamoto 2003). The scaffold polymeric material must possess biocompatibility as an essential criterion. The nanocomposite under biomedical usage must possess the ability of easy sterilization to avert infection and must not induce any inflammatory response nor show any cytotoxicity to immunogenicity. The scaffold used in the engineering of bone tissue requires a porosity of greater than 90% with a pore diameter of 100 μm. These parameters are essential for cell penetration and proper vascularisation of the ingrown tissue (Karageorgiou and Kaplan 2005). The biomaterials used in bone tissue engineering include bioactive ceramics like calcium phosphate and surface-grafted hydroxyapatite (Hench 2006; Kim et al. 2004). These ceramics display suitable biocompatibility and osteoconductivity due to the similarity in the structure and chemical composition of the material with the mineral phase of the native bone (Karageorgiou and Kaplan 2005). However, the disadvantage of these bioactive ceramics lies in the intrinsic brittleness and complexity in shaping them according to the shape of the target bone. These disadvantages are negotiated with the development of PNCs reinforced with bioactive ceramics. These polymer–ceramic composites provide an option of shape control and manipulation to occupy the bone defects and illustrate excellent bioactivity (Ahmed and Bodmeier 2009).

The use of CNTs/polymeric composites as scaffolds for bone engineering has lately developed a considerable buzz. The scaffolds used for tissue engineering serve as substrates in adhesion of cells, segregation, extracellular matrix (ECM) formation, proliferation and to guide tissue regeneration. The ideal scaffold to be used for tissue regeneration must inhibit sufficient mechanical characteristics. In this regard, CNTs exhibit more credibility in offering the required structural tissue scaffold reinforcement (Lee et al. 2008). By integrating a little quantity of CNTs with the polymer matrix, considerable enhancement in the mechanical property (strength) was observed (Wang et al. 2005). It was shown that MWCNTs blended with chitosan significantly enhanced the mechanical aspects in contrast to those with chitosan alone. The in vitro studies confirm the biological properties of CNT scaffolds. The CNT incorporated with porous thermoplastic polyurethane–multiwalled synthesized by thermally induced phase separation (TIPS) method has been reported for biological activity (Jell et al. 2008). This nanocomposite exhibits enhanced stiffness due to the integration of CNT. Biodegradable poly (lactic-co-glycolic acid) (PLGA)/carboxyl-functionalized multi-walled carbon nanotube (c-MWCNT) nanocomposites were reported by Lin et al. (2011). Rat bone marrow-derived mesenchymal stem cells (MSCs) were used to assess the in vitro biocompatibility of the nanocomposites. The osteoblast fabrication of the effective angiogenic factor vascular endothelial growth factor (VEGF) showed rise due to CNT loading, verifying its potential for scaffold engineering. The addition of CNT leads to the establishment of (MSCs) that hold and propagate on all the PLGA/c-MWCNT nanocomposite scaffolds. The in vivo biocompatibility of ultra-short SWNTs/biodegradable polymer nanocomposite scaffolds in a rabbit model has been reported by Sitharaman et al. (2008). The implants formed on poly (propylene fumarate) (PPF)-SWNTs displayed only mild inflammatory responses and increased connective tissue organization. The PPF-SWNTs nanocomposite scaffolds showed considerable bone in-growth after 12 weeks of implantation with increased collagen matrix production.

Besides CNTs, graphene-reinforced PNCs embrace the vast potential for tissue engineering scaffolds owing to their better mechanical and electrical properties. Graphene-based nanocomposites exhibit great potential for development of cells due to their biocompatibility (Park et al. 2011). The nanocomposite composed of graphene/polycaprolactone synthesized covalently having enhanced conductivity, and mechanical properties have been reported for bioactivity (Sayyar et al. 2013). Pristine PC1 was used in the evaluation of cell growth of fibroblast (L-929), neural (PC-12), and muscle (C2C12) cell lines on covalently linked graphene/polycaprolactone nanocomposite materials. It was observed that proliferation of cell lines on the graphene-based nanocomposite was similar to that of plastic-based tissue culture and hence proving the credentials of the graphene-based nanocomposite fabrication for tissue engineering. The other graphene-based nanocomposites used in tissue engineering include graphene oxide (GO)–chitosan hydrogel scaffolds (Depan et al. 2011), GO-PVA (Zhang et al. 2011), graphene-reinforced chitosan films (Fan et al. 2010), graphene–gelatin methacrylate (Shin et al. 2013), and chitosan–PVA nanofibrous scaffolds with graphene (Lu et al. 2012). These graphene-based

nanocomposites inhibit properties like enhanced mechanical strength, subordinate degradation rate, lesser toxicity rate, and better wound healing. These properties symbolize their noteworthy potential in cell adhesion and differentiation of proliferation.

The other nanocomposite reported for tissue engineering includes nanoclays. The incorporation of nanoclay with polymers leads to enhancement of the mechanical and physical properties of the polymeric matrix due to their anisotropy and high aspect ratio morphology (Gaharwar et al. 2012). The addition of nanoclay provides the control over the chemical and mechanical properties of the overall nanocomposite. The combination of PCL with halloysite nanoclay has been reported with improved mechanical strength desired for protein adsorption and cell adhesion (Wu et al. 2010). This nanocomposite, when incorporated with human mesenchymal stem cells (hMSCs), resulted in faster scaffolds proliferation than PCL scaffold alone. Silicate nanoparticle (Laponite RD) has been reported as an effective scaffold material in controlling the adhesion, spreading, and proliferation of fibroblast and preosteoblast cells on silicate cross-linked PEO surfaces (Nitya et al. 2012). The in vitro cell culture studies revealed that the rise in silicate concentration in PEO–silicate nanocomposite led to improvement in adhesion and proliferation of hMSCs to a significant extent. The induction of osteogenic differentiation in hMSCs in the absence of any growth factors using nanoclay has been reported recently (Gaharwar et al. 2010). The montmorillonite (MMT) nanoclay along with 5-aminovaleric acid resulted in an increased in the interlayer spacing and improvement in biocompatibility with respect to human osteoblasts. MMT modified clay and 5-aminovaleric acid combination were also used to formulate chitosan/polygalacturonic acid (Chi-PgA) composite scaffolds (Gaharwar et al. 2013).

5.2 *Drug Delivery*

The method of drug delivery comprises the processes by means of which a pharmaceutical compound is administered to attain therapeutic effect in humans or animals. The most common diseases treated by means of drug delivery are those of nasal and pulmonary routes. These routes are of prime importance when parental drug delivery is for protein and peptide therapeutics. There are several drug delivery systems which are studied for these routes. These systems include liposomes, proliposomes, microspheres, gels, prodrugs, and cyclodextrins (Tiwari et al. 2012). The biodegradable PNCs form a promising class of materials with great potential in fulfillment of the strict requirements on these drug delivery systems. The biodegradable PNCs possesses biocompatibility, the ability of transference into an aerosol, stability to the force generation during aerosolization, proper targeting (specific sites) of cells in an organ, drug releasing in a predetermined manner, and degradation during the set period of time.

The graphene-based PNCs have been extensively explored for drug delivery due to their high surface area, hydrophobic interaction, and π–π stacking. The chitosan–graphene-based nanocomposite has been reported for drug loadings like 5-fluorouracil

and camptothecin (CPT) (Rana et al. 2011). In another study, graphene nanosheets (GS) containing gelatin as a reducing and functionalizing agent were used for loading of doxorubicin (DOX), an anticancer drug (Liu et al. 2011). This graphene-based nanocomposite exhibited better drug loading ability due to the high surface area and relatively higher π interactions. This whole complex (graphene–gelatin–DOX) on fabrication with conjugating Rituxan (CD20 + antibody) with polyethylene glycol–nanographene oxide (PEG–NGO) showed high toxicity to MCF-7 cells through endocytosis (Sun et al. 2008). This nanocomposite complex loading tendered greater results due to non-covalent π–π stacking. In another study, DOX was loaded on functionalized reduced graphene oxide (rGO) with the incorporation of polyethylene glycol (PEG) along with the branched polyethyleneimine (BPEI) (Dembereldorj et al. 2012). The nanocomposite was developed to carry out stimuli response for intracellular cytosolic delivery of DOX. The response of DOX release was observed in near-infrared (NIR), acidic pH, and high intracellular levels of glutathione (GSH).

Apart from graphene-based nanocomposites, the nanoclay-based nanocomposites have also been reported for drug delivery. In polymer-based drug delivery systems, the control over the proliferation of entrapped drugs is a challenging aspect. The control over proliferation can be attained on the basis of the therapeutic effects of the drugs and their biological activity by means of controlling the drug release kinetics (Alexandre and Dubois 2000). This challenging aspect can be negotiated to a greater extent by using silicate-based PNCs due to their superior diffusion and barrier properties of small molecules. Polyurethane/MMT clay nanocomposite in the form of nanofibrous web film has been reported as a delivery system for chlorhexidine acetate (CA), a bactericidal agent (Saha et al. 2014). This nanocomposite provided a sustained drug release due to bulky and immobilized drug cation in the clay interlayer spacing leading to the hindrance of the exchange of the cationic species nearby the buffered media. The fabrications of clay-based poly(N-isopropylacrylamide) nanocomposite hydrogels have been reported for drug delivery due to their swelling behavior (Lee and Fu 2003). In another report, a controlled dexamethasone drug release has been reported when organically tailored silicate nanoparticles (Cloisite clay) were linked to poly(ethylene-co-vinyl acetate) (Kiliaris and Papaspyrides 2010). The drug delivery of this silicate-based nanocomposite was attributed to the degree of dispersion as well as the aspect ratio of the silicate nanoparticles (Cypes et al. 2003).

5.3 *Dental Implants*

The replacement of missing teeth can be done by various means. One of the most preferred methods to fill the missing teeth gaps is the dental implantation. The dental implant comprises of two parts: the root and the crown. The root in dental implant mainly uses titanium or zirconia to support the prosthetic crowns. Gold and glass materials have also been used in implant abutments. These materials are mostly used due to their corrosion and degradation properties (Bidra and

Rungruanganunt 2013). However, their poor attachment and limited bone or soft tissue support in addition to their cost are some of their limiting factors. Such limiting factors can be avoided by using PNCs. The most commonly used polymer in dentistry is a high-performance thermoplastic polymer PEEK. PEEK can be used in dental implants due to its high elastic modulus as compared to the bone and stress reduction shielding (AL-Rabab'ah et al. 2017). The radiolucent nature of PEEK provides the improved radiographic imaging of the pre-implant tissues and inhibits the bonding capability with composite materials and ceramics. PEEK has been widely used in orthopedic and spinal surgeries due to its mechanical strength (Kurtz and Devine 2007). However, combination of its biological and mechanical characteristics encourages its use as dental implant abutments (AL-Rabab'ah et al. 2017). The role of PEEK and other high impact polymers is to provide supporting framework for single crown to full arch reconstruction. PEEK possesses the ease of sterilization due to its temperature stability above 300 °C (Wiesli and Özcan 2015). During dental implant, PEEK is nanomodified using bioactive nanoparticles followed by their reinforcement on carbon or glass fibers (Roskies et al. 2016). The production of PEEK is readily attained using 3D printers to simulate pre-surgery conditions (Tan et al. 2016). PEEK-based materials can be used to replace partial or complete framework of the missing tooth.

5.4 Polymer Nanocomposites as Biosensors

The PNCs especially the conducting polymers are widely investigated for bio-sensing applications due to controlling capability on parameters like electrical, mechanical, structural, and bio-reagent loading (Malhotra et al. 2006). The conducting polymer-based biosensors cater the basic requirements for biomedical devices like biocompatibility, in vivo sensing, multi-parametric assays, continuous monitoring of metabolites or drugs, high information density and miniaturization. The polymers reported for bio-sensing include polyphenylene sulfide (PPS), polythiophenes, polypyrroles (PPy), poly-para-phenylene (PPP), poly(3, 4-ethylenedioxythiophene) (PEDOT), polyfuran, polyindole, polycarbazole, and polyaniline (PANI) (Borole et al. 2006). The PNCs can be used in four types of bio-sensing, viz. enzyme, microbial, immuno, and nucleic acid sensing (Dhand et al. 2007). In enzyme bio-sensing, the PNCs utilizes the specificity of an enzymatic reaction, thereby leading to the generation of an electric current or potential difference along an electrode for quantitative analysis (Kerman et al. 2003). The enzyme sensors depict the biochemical reactions and their corresponding impact on the current generation. The polymers used in such sensors are poly(aniline co-fluoroaniline) and PPy (Sharma et al. 2004; Tian et al. 2001). In microbial sensors, the PNCs sense the presence of microorganism and the polymers used for such sensing are PVA and poly(4-vinylpyridine) (Fang et al. 2003; Kwok et al. 2005). In immunosensors, the PNCs sense the presence of an analyte within minutes using small volumes of the specimen (Lei et al. 2005). This sensing uses

immunochemistry and electrochemistry to avail the results and the polymers used in such sensing are PANI and PPy (Tian et al. 2001; Porter 2000). Finally, in nucleic acid biosensors, PNCs are used in the diagnosis of the disorders (Grant et al. 2005). It is also called as deoxyribonucleic acid (DNA) sensing and the polymers used in such sensing are poly(thiophene-3-yl-acetic acid 1,3-dioxo-1,3-dihydro-isoindole-2-yl ester) and poly(9,9bis (6-N, N, N-trimethyl ammonium hexyl bromide) fluorine)-co-phenylene (Zhang et al. 2005; Wang et al. 2004).

6 Conclusions

This chapter is intended to provide an insight into the different types of polymeric materials based on the degree of crystallinity. The amorphous and semicrystalline polymers and their property optimization on the addition of other materials have been discussed. The different types of polymers and their prescribed medical usage are mentioned pointing their credibility as materials of great future ahead on the basis of the modifications and material optimizations. The addition of various fillers like graphene and CNTs and their applicability in biomedical engineering such as drug delivery and tissue culturing are listed. The examples of different PNCs belonging to the amorphous and semicrystalline and their corresponding applicability in biomedical engineering are elaborated, and finally, the biomedical enhancements and applications pertaining to these polymers are mentioned.

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Multi-functional Lipid-Based Polymer Composites for In Vivo Imaging, Tissue Healing, Cell Rejuvenation and Theranostic Applications

V. Raj and P. Priya

Abstract Since 1960s, lipids are broadly explored as fundamental models to understand and study the cell membranes, as carriers for delivering and protecting bioactive agents. Lipids and lipid-based polymer composites have been utilized in various fields of research including imaging, diagnosis, cosmetics, vaccines, drug delivery and tissue engineering. This provides a strategy that involves the application of specified cell types and structured scaffold biomaterials to produce living biological structures. To develop a new tissue, well-controlled stimulation of cultured cells is required through organized combination of mechanical signals and bioactive agents. In this chapter, we highlight the potential use of lipid and lipid-based biopolymer composites as a platform for the in vivo imaging, tissue engineering, cell rejuvenation and theranostic applications.

Keywords Lipid · Fatty acid · Liposome · Vesicles · Tissue engineering · Phospholipids · Polymer composites

1 Introduction

Lipid is a biomolecule that originates naturally and comprised of hydrogen, carbon and oxygen atoms, and some cases consist nitrogen, phosphorus, sulfur and other elements. It encompasses a group of naturally existing molecules that include waxes, sterols, fats, A, D, E and K fat-soluble vitamins, glycerides and phospholipids. Scientists widely define lipids as small molecules with hydrophobic or amphiphilic in nature and are soluble in nonpolar solvents or weakly polar organic solvents, including chloroform, ether, benzene and acetone. Lipids form structures such as unilamellar and multi-lamellar liposomes, vesicles,

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K. K. Sadasivuni et al. (eds.), *Polymer Nanocomposites in Biomedical Engineering*, Lecture Notes in Bioengineering,
https://doi.org/10.1007/978-3-030-04741-2_4

or membranes due to its amphiphilic nature in an aqueous environment (McNaught and Wilkinson 2009; Fahy et al. 2009).

Lipids possess fats and oils as a main components present in food. In the body, the metabolic, nutritional and structural significance of lipids is established by enormous examinations and analysis carried out in dissimilar biological models (cellular, animals and humans). Lipids provide instrumental contributions in the evolution of species having major role in the development, growth and functional maintenance of tissues. Nerve tissue consists of highest quantity of fatty acid, especially very long-chain polyunsaturated fatty acid is a clear example for lipid's biological importance.

Lipids perform a crucial role in the development and growth of the organism where the necessity of these fatty acids will be altered and depend on the age, biological and physiological state of each individual. Furthermore, lipids essentially have participation in both prevention and/or development of many diseases, particularly chronic noncommunicable diseases that affect the lipid requirements in humans. As food components, for various body functions, lipids are also important because they (i) are substantial in delivering organoleptic characteristics (texture, aroma, flavor and palatability); (ii) are carriers for fat-soluble pigments, dyes, vitamins and antioxidants; (iii) are emulsifying agents and/or endorse the stability of emulsions and suspensions.

2 Classification of Lipids

Biological lipids origin in part or wholly with combination of two different types of biochemical subunits, isoprene and ketoacyl groups. The classification of lipids is performed into eight categories: fatty acids, polyketides (obtained from condensation of ketoacyl subunits); sphingolipids, glycerolipids, saccharolipids, glycerophospholipids, prenol and from condensation of isoprene subunits, sterol lipids (Messias et al. 2018).

2.1 Fatty Acids

Fatty acids, fatty acid derivatives and their conjugates are a group of wide-ranging biological molecules synthesized by a fatty acid synthesis process that involves chain elongation of an acetyl coenzyme A (CoA) primer with malonyl-CoA or methyl malonyl-CoA groups. They consist of hydrocarbon chain with a carboxylic acid end group that convokes the molecule with insoluble nonpolar, hydrophobic end and soluble polar, hydrophilic end in water (Vance and Vance 2008). Typically, long carbon chain of 4–24 carbons may be unsaturated or saturated and they are

linked to functional groups such as oxygen, nitrogen, sulfur and halogen. If there is a presence of C=C double bonds, *cis* or *trans* geometric isomerism exists that affect the molecule's molecular configuration. Eicosanoids, predominantly derived from eicosapentaenoic acid and arachidonic acid, which include leukotrienes, prostaglandins and thromboxanes, are the examples of biologically noteworthy fatty acids. Fatty amides and fatty esters are categories of fatty acid lipid and N-acyl ethanolamines, such as the cannabinoid neurotransmitter anandamide, are examples of fatty amides. Important biochemical intermediates of fatty esters include components such as fatty acid thioester coenzyme A derivatives, carnitines and thioesteracyl carrier protein and wax esters.

2.2 Phospholipids

Phosholipids are referred as amphiphiles containing both hydrophobic and hydrophilic elements. In the presence of water, phospholipids self-assemble spontaneously into ordered liquid-crystalline lyotropic phases. Examples of lipid-related structures are lipid monolayers, lipid bilayers, cochleates, ribosomes, tubules, liposomes and micelles. Phospholipids may be synthetic or natural, whereas natural phospholipids may be acquired from various sources such as egg yolk and in turn synthetic phospholipids are also synthesized from natural lipids. Compared to synthetic phospholipids, natural phospholipids are less stable. Phospholipids in terms of the polar head groups are classified as phosphatidic acid (PA), phosphatidyl choline (PC), phosphatidyl glycerol (PG), phosphatidyl ethanolamine (PE), phosphatidyl inositol (PI) and phosphatidyl serine (PS). An unlimited types of phospholipids were well defined and characterized by modifying the polar and nonpolar regions of phospholipid molecules (Antimisiaris et al. 2007). Examples of synthetic lipids are 1,2-distearoyl-sn-glycero-3-phosphate (DSPA), dipalmitoyl phosphatidyl choline (DPPC), 1,2-dipalmitoyl-sn-glycero-3-phosphoglycerol (DPPG), dimyristoyl phosphatidyl choline (DMPC), 1,2-distearoyl-sn-glycero-3-phospho-(10-rac-glycerol) (DSPG), distearoyl phosphatidyl choline (DSPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), hydrogenated soy phosphatidylcholine (HSPC), (1-palmitoyl-2-stearoyl(5- DOXYL)-sn-glycero-3phosphocholine (SLPC) and 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) (Eibl and Kaufmann-Kolle 1995).

2.3 Glycerolipids

Glycerolipids are formed by joining fatty acids to tri-substituted glycerols by ester bonds, the most familiar fatty acid being the esters of glycerol (triacylglycerols),

also called as triglycerides. Lipids function as a food store in animal tissues, since it consists of bulk fat storage. Additional subclasses of glycosyl glycerols are differentiated by the presence of one or more sugar residues linked to glycerol via a glycosidic linkage (Coleman and Lee 2004). Digalactosyl diacyl glycerols and seminolipid are examples of this glycero lipids found in plant membranes and mammalian sperm cells.

2.4 Glycerophospholipids

Glycerophospholipids are abundant in nature and present as lipid bilayer of cells as a crucial constituents functioning in cell signaling and metabolism. Glycerophospholipid implies many derivatives of sn-glycero-3-phosphoric acid that holds at least one O-alkyl or O-acyl or O-alk-1′-enyl residue attached to a nitrogenous base polar head, an inositol or a glycerol unit and glycerol moiety. All this derivatives contains a glycerol core with same or different subunits of fatty acids (Farooqui et al. 2000). Carbon 1 is a polar found in tail portion consists of usually a saturated fatty acid. Carbon 2 is also an apolar found in tail portion consists of usually unsaturated fatty acid and appears "bent" in the *cis* conformation. Carbon 3 is a polar found in head portion consist of a phosphate group or an alcohol attached with a phosphate group. Phosphatidylserine (PS or GPSer), phosphatidyl choline (also known as PC, GPCho or lecithin) and phosphatidyl ethanolamine (PE or GPEtn) are examples of glycerophospholipids existing in biological membranes.

2.5 Sphingolipids

Sphingolipids are compounds that are synthesized from the amino acid serine, occupied with a sphingoid base backbone further converted into glycosphingolipids, phosphosphingolipids and other compounds. Ceramides are N-acyl-sphingoid base derivatives containing amide-linked fatty acids lacking additional head groups. Mammals contain sphingosine as a major sphingoid base and phosphosphingolipids present majorly in mammals. Ceramide is found in insects, whereas phosphoethanolamines and fungi mainly have phytoceramide phosphoinositols composition of mannose-containing head groups (Konrad Sandhoff et al. 2002). The glycosphingolipids are a diverse family of sphingolipids and ceramides composed of one or more sugar residues attached to the sphingoid base at the 1-hydroxyl position via a glycosidic bond. The simple and complex glycosphingolipids such as gangliosides having at least three sugar residues and cerebrosides are examples of glycosphingolipids.

2.6 Sterol Lipids

Sterol lipids are a subclass of steroids with a hydroxyl group at the 3-position of the A-ring. Animal sterol such as cholesterol and cholesterol derivatives along with the sphingomyelins and glycerophospholipids are also important constituents of membrane lipids (Russell 2003). Secosteroids consisting vitamin A of several types are characterized by fragmentation of the B ring core structure. Bile acids and their conjugates, cholesterol-oxidized derivatives in mammals are some more examples of sterol lipids produced in the liver. The plant counterpart's sterols are the phytosterols, such as stigmasterol, campesterol, brassicasterol and β-sitosterol.

2.7 Prenol Lipids

Prenol lipids are produced through the mevalonic acid (MVA) pathway mainly from the 5-carbon precursors such as dimethyl allyldiphosphate and isopentenyl diphosphate. Polyterpenes are prenol lipids with structure consisting more than 40 carbons. Carotenoids are simple essential isoprenoids that act as antioxidant and function as precursors of vitamin A (Kuzuyama and Seto 2003). Hydroquinones and quinones are another important biological class of molecules, containing an isoprenoid tail linked to a nonisoprenoid quinonoid core origin. Ubiquinones, vitamin K and vitamin E are also examples of this class.

2.8 Saccharolipids

Saccharolipids are compounds in which fatty acids are linked to a sugar backbone directly, and monosaccharide substitution takes place for glycerol backbone present in glycerolipids and glycerophospholipids. It forms structures biocompatible with cell bilayer membrane (Raetz et al. 2006). Acylated glucosamine lipopolysaccharides precursors of lipid A component are the most common glucosamine-based saccharolipid present in Gram-negative bacteria.

2.9 Galactolipids and Sulfolipids

Galactolipids are a category of glycolipids containing galactose sugar. In vertebrates, the galactolipid, galactocerebroside (GalC) and a sulfated derivative sulfatide are present in abundance along with some group of proteins in myelin, the membrane present around the axons of nervous system. The membranes of

chloroplast contain a large amount of monogalactosyl diacylglycerol (MGDG) and digalactosyl diacylglycerol (DGDG).

Sulfolipids are a category of lipids which contain a sulfur moiety functional group. One of the abundant constituents of sulfolipids is sulfoquinovose, acylated to form glycoside of sulfoquinovosyl and diacylglycerols. Sulfur cycle taking place in plants consist sulfoquinovosyl diacylglycerol, a plant sulfolipids as an important intermediate.

2.10 Polyketides

Polyketides are a class of secondary metabolites enclosing alternating methylene and carbonyl groups derived by polymerization of propionyl and acetyl subunits aided by a collection of classic enzymes as well as multi-modular and iterative enzymes called polyketide synthases that share mechanism analogous with the fatty acid synthesis. Most of polyketides produced are cyclic molecules which are primarily made from modification via chemical routes like oxidation, glycosylation or other processes. Polyketides or polyketide derivatives such as antibiotics, tetracyclines, erythromycins, insecticide spinosyn A and antitumor epothilones are generally used as antiparasitic, antimicrobial and anticancer agents.

2.11 Lipoproteins

A lipoprotein is described as a biochemical assembly that includes both proteins and lipids water-bound to the proteins called apolipoproteins forming a large spherical complexes. Many transporters, enzymes, antigens, structural proteins, toxins and adhesins are lipoproteins. They are categorized as high-density lipoproteins (HDL), intermediate-density lipoproteins (IDL) and low-density (LDL) lipoproteins. It is also possible to differentiate lipoproteins according to the proteins classification in serum protein electrophoresis as “alpha” and “beta” lipoproteins.

2.12 Liposomes

Liposomes are self-assembled vesicles containing a phospholipid bilayer varying between 15 and 1000 nm in diameter that have the capability of encapsulating hydrophobic compounds and aqueous solutions. Lipids resemble cells forming a tiny bubble structure of water-filled vesicles, called liposomes (Koynova and Tihova 2010; Gomez-Hens and Manuel Fernandez-Romero 2005; Singh et al. 2001; An et al. 2009). Liposomes have historically been utilized as: model

biological membrane systems to deeply analyze and comprehend the basic nature of cell membranes, in molecular biology and biochemistry in analytical methods, in imaging, in microfluidic technologies, in cosmetics and food technology, as drug delivery systems in pharmacology, nanogel production templates and in tissue engineering (Reineccius 1995; Xia and Xu 2005; Boerman et al. 2000; Voinea and Simionescu 2002; Kulkarni et al. 2010).

Liposomes are classified based on three aspects such as route taken for synthesis, number of bilayers formed in the vesicle and by dimensional magnitude of vesicles. Depending on the number of vesicles and bilayers present in structure of liposomes, they are classified as unilamellar vesicles (ULVs 25–1 mm) or multi-lamellar vesicles (MLVs, 0.1–15 mm) or multi-vesicular vesicles (MVVs, 1.6–10.5 mm). Moreover, depending on their dimension, unilamellar liposomes are further categorized as small unilamellar vesicles with size in range of (SUVs, 25–50 nm) and large unilamellar vesicles with size in range of (LUVs, 100–1 mm) (Akbarzadeh et al. 2013).

2.12.1 Preparation Methods

Mammals including humans apply various biosynthetic pathways both for formulation and break down lipids. But some lipids that are essential cannot be made in this route and must be consumed from the diet only. Many studies about the liposomes production method can be found in the literature (Vemuri and Rhodes 1995; Wagner and Vorauer-Uhl 2011). Common synthesis parameters for liposome production consists of high-pressure homogenization, thin-film hydration, detergent removal, reverse-phase evaporation, French press extrusion, ethanol injection, proliposome method, polyol dilution, double emulsions and freeze–thaw method (Laouini et al. 2012; Mozafari 2005). Depending on the particular method selected, MLVs or LUVs are produced. Even though all these techniques can be used for liposomes manufacture, just three of them are frequently used; they are ethanol injection method, film hydration and reverse-phase evaporation method. For the removal of solvent traces and detergent from liposomes, several techniques such as dialysis, gel filtration, centrifugation and vacuum have been proposed. For fast and environmental friendly production method of liposomes, an easy new method without the use of any dangerous processes or hazardous chemicals has been designated. This method involves the liposome constituents hydration in aqueous medium, further followed by heating liposome constituents up to a temperature of 1208 °C in the presence of 3% v/v glycerol (Huang et al. 2014).

2.12.2 Formulation and Functionalization

Cholesterol is a principal sterol biosynthesized by all animals cells and when combined with phospholipids make liposome membranes more stronger (Drummond et al. 1999). Cholesterol is essential for the maintenance and

stabilization of the bioactive agent present in the center core of the liposome. Surface properties of liposomes altered after coating with hydrophilic polymers such as polyethylene glycol (PEG) is used for this kind of job. "Sterically stabilized liposomes" (SSLs) or "stealth" liposomes are the liposome formulations modified with phospholipids, Chol and PEG (Woodle and Lasic 1992). PEGylated liposomes' surface functions as a protective steric barrier by inhibiting adsorption of proteins onto the liposome surface vehicles (Monteiro et al. 2014; Tsukanova and Salesse 2004). Nowadays, variety of natural synthetic polymers such as chitosan, heparin, dextran and poly(amino acid)s were introduced to replace PEG.

Fluorescent-labeled lipids are also used in the liposome formulations. Fluorescent-labeled lipids engulfed within the layers of lipid to form bilayer helps in triggering rapid membrane fusion, which able to facilitate fluorescence imaging of cell membranes and traffic processes of membrane (Kleusch et al. 2012).

Liposomes of different compositions with a particle size of approximately 90 nm were synthesized using Chol in different ratios along with cholesten-5-yloxy-N-(4-((1-imino-2-Dthiogalactosylethyl) amino) butyl) formamide (Gal-C4-Chol) and DSPC concentration of which was also varied and labeled with [3 H] cholesterol hexadecyl ether. In a comparative study between DSPC/Chol/Gal-C4-Chol (60:35:5) and DSPC/Chol (60:40) liposomes, DSPC/Chol/Gal-C4-Chol (60:35:5) liposome shows extensive hepatic uptake (Murao et al. 2002). Kawakami et al. used mannose receptor-mediated gene transfection to macrophages to synthesize mannosylated cholesterol derivative (Man-C4-Chol). Currently, for laboratory-scale production enormous methods are available, but only a few large-scale manufacturing techniques are in use (Kawakami et al. 2001).

2.13 Cubosomes

Cubosomes are distinctive micro- and nanostructured particles formed by amphiphilic macromolecules separated by lipid bilayers resulting in a cubic bicontinuous crystalline phase. Till date, six different cubosome structures displaying cubic like symmetry have been characterized (Q212, Q223, Q224, Q227, Q229 and Q230) (Vargas et al. 1992). Generally, a cubic phase is indicated by Qn where Q means cubic phase and n represents the number of the corresponding space groups. On the basis of structure, they can be divided into nonbicontinuous or bicontinuous groups. When compared with the cubosome parent bulk cubic phase gel, cubosomes have a lower viscosity and a larger surface area. Cubosomes exhibit good biological properties such as bioadhesivity, biocompatibility and biodegradability and are easily scaled up for manufacturing purposes for various applications (Spicer et al. 2001; Nanjwade and Yallappamaharaj 2014). At first, cubosome particles are formed using some techniques into a three-phase region containing a liposomal dispersion. Its formation entirely differs from liposomes and can concurrently accumulate lipid soluble, water-soluble and amphiphilic molecules as a three-phase region (Barauskas et al. 2005).

Monolein is the base precursor of cubosome formation, and it consists of three macroscopic cubic phase forms; precursor, bulk gel and particulate dispersion. Dispersion of the particles is performed using a number of different ways spray drying, sonication, spontaneous emulsification and high-pressure homogenization (Siekmann et al. 2002).

2.14 Hexosomes

Hexosomes are reverse-hexagonal, close-packed, rod-like micelle arrangements with infinite water layers covered by surfactants monolayer lacking the difficulty of the internal bicontinuous cubic-phase formation. Hexosomes can be prepared in a similar way as those for cubosomes by self-assembly in aqueous solutions.

2.15 Lipoplexes and Polyplexes

Lipoplexes are the compounds containing lipid and DNA, whereas the polyplexes is made up of cationic polymer and DNA. Polyvalent cations (Ca^{2+}, Mn^{2+}, $Co[NH_3]^{3+}$ and La^{3+}), polycations (basic proteins, polyethylenimines, spermin, histones and spermidin), polyvalent electrolytes (dendrimers and polypeptides), cationic lipid or polymers react and combine with negatively charged DNA to form complexes known as lipoplexes used for delivering nonviral vectors for gene therapy. Ewert et al. investigated that DNA gets inserted in hexagonally arranged cylindrical tubular lipid micelles to configure a honeycomb lattice possessing superior transfection efficiency in mouse embryonic fibroblasts than that of commercially available DOTAP-based complexes (Ewert et al. 2006). Preparation of lipoplexes is alike the synthesis of liposomes with slight alteration. Plasmid DNA is entangled into lipoplexes by a lot of techniques such as ethanol dilution method, reverse-phase evaporation, lipid hydration–dehydration techniques, ether injection and (Cudd and Nicolau 1985; Fraley et al. 1980; Baru et al. 1995; Morishita and Kaneda 2002; Maurer et al. 2001) detergent dialysis.

2.16 Tubules

Lipid tubules are made through rolling up of layers of lipids to form open end hollow cylinders having internal lumen diameter around 10–70 nm. Their formation phenomenon is similar to cell division mechanism occurring naturally through the self-assembling process. Tubules are also formed by some supplementary substances like bile, synthetic surfactants and inorganic materials (e.g., halloysite) via closely resembling method of self-assemble for lipid tubule formation (Shimizu et al. 2005). Self-assembled lipid tubules are hollow in cylindrical shape with

crystalline molecular order having excellent mechanical properties with average stiffness, flexibility and chemical functionality making them worthy for divergent applications such as biotechnological, drug delivery and nanofabrication. Cholesterol, glycolipids and its derivatives, phospholipids such as dipalmitoyl phosphatidylcholine and 1,2-Dimyristoyl-sn-glycero-3-phosphocholine (DMPC) are other lipids that often favorably form tubules (Yager et al. 1985).

2.17 Ribbons

Ribbons are termed as intermediate products formed by unstable precursors of tubules during tubule formation. These are long rectangular strips that curl along the surface of cylindrical tubules. Similarly, helical ribbons are spontaneously formed during dilution of bile, possibly due to cholesterol supersaturation (Konikoff et al. 1992) and also found in bile produced from gall bladder of humans. In nature, ribbons are found to be crystalline. Examples of some other materials forming helical ribbons are diacetylenic lipids, glutamates, bile and inorganic or organic chiral molecules.

2.18 Cochleates

Cochleates are solid particulates projecting lipidic supramolecular arrangements formed as a result of interaction between the main anionic lipid (especially phosphatidylserine) component and divalent cations such as calcium (Ca^{2+}). It is a unique multilayered structure containing alternate layers of cationic components and anionic phospholipids resulting as solid, large, continuous, lipid bilayer sheets with little or no internal aqueous space rolled up in a spiral. The stability of encochleated molecule is enhanced by continuous bilayer rolling of lipid. In drug delivery applications, instead of cationic divalent metals, drugs with positive charge such as tobramycin may lead to formation of cochleates alongside reaction with phospholipids.

ISCOM and ISCOMATRIX™

Immunostimulating complexes (ISCOMs) are a highly immunogenic formulation of microbial membrane antigens having cage-like structures developed in the early 1970s composed of lipid, cholesterol and immune-stimulating saponin (Quil A) (Horzinek and Mussgay 1971). These nanoparticulates showed good stability on storage and were roughly around 40–60 nm in diameter. ISCOMs are primarily categorized as traditional or more generally called classical and nonclassical ISCOMs or popularly known as ISCOMATRIX™ (Myschik et al. 2006). Traditionally, antigens were found to be enticed into the cage-like shape of ISCOMs, whereas for ISCOMATRIX, antigens were muddled within the lipid

cage-like formation in varying ratios for better immune stimulatory action. These antigens were incorporated using different association techniques such as lipid anchors (cholesterol derivative), electrostatic interaction and chelation technique (Mowat a and Reid 2001). Four different methods were used for the preparation of ISCOMs and ISCOMATRIX: solvent injection methods, dialysis, thin lipid film hydration and ultracentrifugation. Properties such as shape, structure and stability depend upon the proportion of preparation technique.

From a manufacturing viewpoint, the assembly of multiple molecular constituents with diverse physicochemical properties into complex composites could additionally complicate the scale of the synthesis. To overcome and facilitate the challenges in scaling up of the fabrication process, various methodologies of nanoengineering have currently been explored. For example, in order to reduce the laborious and time-consuming nanoprecipitation production process, sonication, a single step method was introduced. The production time required to produce PLGA nanoparticles by nanoprecipitation coated with lipid monolayer could be significantly lessened without disturbing their physicochemical properties by replacing the ordinary heating method by vortexing and solvent evaporation techniques using a single sonication bath. Multi-inlet vortex reactor (MIVR) is used to produce lipid–polymer hybrids by continuous flow-confined mixing protocol and has already been assessed for the large-scale manufacturing of a multitude functioning nanoparticles. MIVR geometry consists of two or four radically symmetric inlets in a cylindrical mixing chamber which establishes a continuous flow of antisolvent aqueous phase containing the dispersed lipids and organic phase containing the dissolved hydrophobic polymers leading to instantaneous self-assembly and nanoprecipitation of homogeneous lipid-coated polymer nanoparticles. Utilizing this rapid and efficient nanoparticle mixing method, increased production rates >10 g h^{-1} were achieved without satisfying the physicochemical characteristics of hybrid nanoparticles via the previously stated laboratory-scale sonication method. Alternatively, in recent years microfluidic-based perceptive has been adopted for the production of polymer nanoparticles on a larger scale via self-assembly with well-controlled and reproducible results. Valencia and coworkers used the Tesla micromixing for synthesizing lipid-coated PLGA nanoparticles (Valencia et al. 2010). To prompt rapid homogeneous mixing, separate hydrodynamic stream inlet focuses flow of aqueous antisolvent and organic solvent through a microchannel, which leads to development of (PEGylated) lipid–PLGA nanospheres. Overall, the methods covered here seem to further encourage to a greater probability of moving fast toward the clinical translation.

3 Lipid Functionalization with Polymeric Materials

Polymers are made by the combination of a number of small units which are indistinguishable and interchangeable known as monomers. Both synthetic and natural polymers have blossomed in recently owing to their distinctive style and

usage in various conventional fields. Polymers are embedded with lipids to enhance the properties of polymers but the polymeric materials also behave interlinked having their own properties which they combined with lipids.

Unsaturated polyester resins are synthetic polymers that are thermosetting in nature. They are cheaper materials, easily processable, easily available and have good balance in their mechanical, chemical and electrical properties with only negativity as the rigidity. Flexibility is introduced into them by mixing castor oil into them. Originally thermoplastic starch is rigid and brittle but fatty acids are mixed into it to overcome these demerits (Winkler et al. 2014). Alternatively, fatty acids also improve some softness of starch. Quinoa proteins are natural hydrophilic polymers, and its hydrophilicity is increased more after blended chitosan and sunflower oil (Abugoch et al. 2011).

Lipids are also incorporated in polymeric materials such as pectin which enriched the pathogenic properties and water resistance capability of biodegradable pectin materials. Natural waxes are incorporated with polymeric materials like silk fibroin, starch, cellulose and polyethylene, and this leads to their usage for food packaging, wound dressing, solid fuel and food packaging and boosted their tensile strength, flexibility, wettability, hydrophobicity and rate of combustion. Phospholipids after blending with cellulose acetate improve its solubility and antifouling property and accelerated their biological and drug delivery applications.

When thyme oil is used in blend form with the native polymeric materials like alginate, pectin, chitosan films, they can be used for food preservation and drug delivery applications with improved antimicrobial properties (Liakos et al. 2014; Perdones et al. 2016).

Pectin derivatives with different fatty acids are synthesized by acylation of polysaccharide alcoholic functions to generate pectin based materials. Chemical reaction is proceeded via mechanical milling of polysaccharide along with specific fatty acid anhydride in presence of K_2CO_3 catalyst and few drops of ethanol. Finally, ethyl acetate and solid reacted with 0.5 N HCl to remove the remaining fatty acids (Monfregola et al. 2011). Polyurethanes which combine with materials derived from vegetable oils like castor oil, canola oil, can be used as a scaffold in which isolated cells may be seeded which allows the cells to grow and proliferate until it forms a tissue which can then be implanted back to the patient (Auad et al. 2010).

4 Characterization of Lipid-Based Polymers

Some characterization techniques are used to identify and analyze the newly formed blends and composites. Like NMR is used to study the molecular structure, X-ray chromatography is used to determine the degree of crystallinity of the sample. DSC is used to establish the decomposition temperature and other thermodynamic parameters. IR spectroscopy is used to ascertain the type of bonding and kind of functional groups attached to the materials formed. Electron microscopy is used to

probe the deeper structure formation, morphology of materials. Raman spectroscopy is used to observe vibrational and rotational modes in a system. TGA measures the rate of change in mass of the samples with respect to temperature. Size exclusion chromatography categorizes the molecules depending on their granular size and weights. Florescence correlation spectroscopy is helpful to analyze the quantity of proteins within biological samples. SEM is used to determine the surface morphology.

5 Applications of Lipid-Based Polymer

5.1 Cell Rejuvenation and Tissue Engineering

Lipids are primary units in any living organisms as they have polar head group region which is connected to the hydrophobic tail via a backbone. Hence, scientists have been utilizing the advantage of the versatile properties and flexible characteristics of lipids to find new applications in various fields. Among the lipids, micelles and liposomes are the most primarily used lipid-based nanoparticles using which all other structures can be formed. These lipid-based materials offer stability, and hence, they could be used as novel biological membranes for model study. It is strongly believed that materials made up of phospholipids may be progressively used as tools for the exploitation of cell and tissue behavior and for reconstructive surgery controlled release of bioactive agents (Collier and Messersmith 2001).

Although liposomes have been extensively used in treatment of cancer and other medical conditions, its future prospects are not restricted to those therapeutic applications. Liposomes have been progressively used in different fields of research including the production of vaccines, cosmetics, imaging and tissue engineering (Nikalje 2015). Herein, we will focus on lipids as a biomaterial and review some applications of the liposomes, mainly in tissue engineering (TE), drug delivery and theranostic applications. It is expected that therapeutic liposome nanoparticles have the capability of dramatically improving the efficacy and reducing the side-effect profile of new as well as already found bioactive agents. Therefore, future holds the possibilities of combining liposomes with scaffolds medicinal usage.

5.1.1 Combining Liposomes with Scaffolds

Application of biomaterials in the field of drug release, scaffolding, tissue engineering and regenerative medicine has been advancing toward the nanoscale design strategies. Scaffolds with combination of drug-loaded nanoparticles are used for controlled release of bioactive agents temporally and spatially, leading to a local and sustained delivery. In recent times, there have been lots of researches on direct stem cell growth and associated fields. The sheathing of the bioactive agents inside

liposomes has an edge over other techniques but use of single liposomes has the limitation due to the absence of a three-dimensional mechanical support which is necessary for tissue regeneration (Santo et al. 2012).

Many types of scaffolds can be prepared by different techniques using natural and synthetic polymers. Tissue engineering scaffolds can be designed in a more efficient way to control the release pattern of bioactive agents physically and chemically (Rambhia and Ma 2015). Particularly, hydrogels exhibit an immense potential as smart and stimuli-responsive biomaterials. Stimulation of tissue regeneration by the delivery of bioactive agents from scaffolds is still challenging due to the complex processing associated with scaffolds. There is a better control of release profile, when the bioactive agent is encapsulated into hollow nanofibers. Due to presence of some complications during nanofiber preparation, the method did not allow for easy large-scale production.

All these phenomena combine the advantageous characteristics of liposomes and polymer matrices with the aim of developing biomaterials to segregate and sustain liposomes at a local tissue site. Liposomes which are sensitive toward stimulus have the ability to master chemical reactions ensuring the rapid formation of in situ biomaterials such as polymers, minerals and mineral/polymer composites (Westhaus and Messersmith 2001). Since, liposomes are highly sensitive molecules different ways to paralyze liposomes at the surface of the scaffolds. It can be done nonspecifically, in which liposomes are engrossed at the surface; or specific immobilization in which liposomes are covalently bound at the surface thus increasing their stability. To obviate the need for chemical conjugation, scaffold system is used. To simplify liposome adsorption, scaffold surfaces are coated with several extracellular matrix proteins, which are able to reduce the amount of required DNA and transfect a greater number of cells. Recently, a chemical modification of electrospun polycaprolactone (PCL) nanofiber meshes (NFMs) was reported which facilitates the immobilization of liposomes loaded with bioactive agents onto their surfaces. Dexamethasone and plasmid DNA, pDNA-encoding RUNX2-loaded liposomes were covalently attached to the SH groups available at the exterior of electrospun NFMs. It was concluded that the percentage of liposomes crippled is mainly controlled by the quantity of SH groups accessible at the surface of nanofibers (Monteiro et al. 2014). Liposomes can also be incorporated into the nanofibers by coaxial electrospinning.

Tissue regeneration not only depends on the bioactive agent itself, but also on the various parameters such as spatiotemporal gradients, concentration, target cell type and combination with other GFs. Bioactive agent-loaded liposomes when fused with scaffolds leads to enhancement like: (i) better and stable concentration; (ii) numerous bioactive agent delivery; and (iii) spatial patterning (Mufamadi et al. 2011). The delivery of bioactive agent by the liposome–scaffold device can be done by two ways: (i) by the incorporation of the proper bioactive agent-loaded liposomes into the scaffold; growth/differentiation factor and (ii) by the incorporation of the DNA (or RNAi) into liposomes.

5.1.2 Growth/Differentiation Factor Delivery

The tissue regeneration method involves complex cataracts of bioactive agents such as cytokines, GFs and other molecules. GFs are endogenous polypeptides that function as the cell-surface receptors involving organized cellular activities such as differentiation, migration and proliferation (Quaglia 2008). The GF therapeutics outcome mainly depends on the delivery modes. Furthermore, finding the better way to stimulate the accurate differentiation of stem cells is one of the important challenges in tissue engineering. So far, the most ordinary method involves the use of concoctions of growth/differentiation factors in the culture medium. To endorse the preferred regenerative outcome, combination of suitable signaling molecules should be delivered by controlled release systems. For example, bone morphogenetic protein 2 (BMP-2) is encapsulated to stimulate the osteogenic differentiation, on the other hand to promote the chondrogenic differentiation transforming growth factor b (TGF-b) is attached to it.

Liposomes are used as an animal model for demonstrating cartilage repair with some success. They are injected directly into the joint cavity for a period of some weeks. Transforming growth factor beta 1 (TGF-b1) is released from liposomes without any side effect with an improved local efficacy and release kinetics. Increased retention time of collagen/hydroxyapatite (HA) composite scaffold was observed during subcutaneous implantation in rats after coating liposomes with bisphosphonate. The BMP-2 entrapped bisphosphonate-coated liposomes are employed in local delivery (Wang et al. 2012). The poly (2-hydroxyethyl methacrylate) fibrous scaffold immobilized with fetal bovine serum loaded liposomes positively improved the chondrocyte proliferation and adhesion (Rampichová et al. 2012). Biological assays showed that the electrospun PCL NFMs immobilized with Dex-loaded liposomes surface has not displayed any sorts of cytotoxic consequences on human bone marrows which are basically derived mesenchymal stem cells (hBMSCs). Osteogenic differentiation of hBMSCs was achieved by them (Monteiro et al. 2015).

Bone formation is clinically approved by the RhBMP-2 growth factor. Due to shorter biological half-life and trouble in retention at regions of local delivery, large bolus doses are necessary to prompt bone healing. RhBMP was formulated into cubic phase gel enhanced sustained release, adhesion and local retention. In addition, cubic gels showed an improvement in bone repair in six weeks in Wistar rats (Issa et al. 2008).

Lipid tubules entrapped with proteins such as DNA, TGF-b1, cytokines BMPs and NGF have also been studied. Peptides or proteins encapsulated inside tubules show insignificant proteolysis by trypsin (Meilander et al. 2001). Jain et al. developed agarose scaffold containing hollow cylindrical multiple lipid bilayers inside microtubules encapsulated with trophic factors, such as BDNF. Agarose hydrogels and release of BDNF from gel in a sustained manner found to help in repair of spinal cord after six weeks of implantation with very minimal inflammatory response (Jain et al. 2006).

5.1.3 Therapeutic Gene Delivery

The in vivo stem cell differentiation uses growth/differentiation components which has some shortcomings such as time-consuming, denaturation during encapsulation, use of GFs, short half-lives, complications in differentiating the cells into one particular heredity and long time periods to acquire the differentiated cells. To overcome these limitations in controlling stem cell differentiation, gene therapy such as encoding a set or a peculiar proteins is carried out. Therefore, gene therapy may be a good approach involving encoding transcription factors for a specific or to a set of proteins. Transcription factors describe the expression of all natural splice variants occur in a sequence that may organize regulations of cataract of multiple different genes.

Initially, gene therapy was envisaged to replace a hereditary genetic defect in which functioning gene was inserted into the host cell genome or, more recently, a new function is provided for genes in a cell overexpressing GFs (Winn et al. 2005). PDNA enters into the nucleus and gets intercalated in host cell DNA and transformed into messenger RNA (mRNA). Therefore, GFs or therapeutic proteins are produced outside of the nucleus using the cell machinery.

Stem cell differentiation can be controlled in another way by the delivery of RNAi. As RNAi functions by binding to nucleic acids, hindering gene transcription and translation or by the insertion of small interfering RNAs (siRNAs), micro-RNAs (miRNAs) or small hairpin RNAs (shRNAs) for eradication of target mRNAs and silencing genes of interest (Yau et al. 2012). The main benefit of this tactic is that the targeted genes are silenced by RNAi trigger without inclusion into the host genome. Therefore, there is a huge substantial growth in this field from the last decades, due to its massive potential in treating various diseases by replacing or altering missing or defective genes or silencing undesirable gene expression.

The ex vivo process is a genes' delivery technique which involves direct insertion of genes into the target cell. The ex vivo technique commonly uses antilogous cells recovered from the patient's body. Viral vectors such as retrovirus or lentivirus are broadly used to transfer the genes into stem cells because of their higher transduction efficiency and transgene expression. To transfect cells, both viral and nonviral vectors are used as carriers. Viral vectors are preferred to express the transfer of gene for the time span of a patient's life, whereas the nonviral vectors are considered when the therapeutic genes are required to be transferred for shorter duration (Pornpattananangkul et al. 2010). Although viral vectors are more effective, they occupy some disadvantages such as high manufacture cost, safety concerns, lacking of desired tissue selectivity, immunogenicity of the virus proteins and recombination development of infectious viruses.

Therefore, there is a requirement of a superior delivery system that not only safeguards the nucleic acids and facilitates and their cellular uptake, but also should enhance the efficiency of the delivery. Nonviral delivery systems including liposomes have relatively lesser transfection efficiency, but they have been recommended due to their safety, low cost production and higher pDNA size entrapment. Moreover, in formulation design, nonviral vectors are very flexible and can be easily tailored to interact with the DNA cargo.

Liposomes are contemplated in the cell biology as first nonviral delivery systems. Development and evaluation of numerous cationic lipids were undertaken for the purpose of transfection of cell and for gene delivery (Woodle and Scaria 2001). Cationic liposomes interact with negatively charged cell membranes lead to higher transfection efficiency. A leading commercial reagent lipofectamine is generally used to transfect cells. Cytotoxicity, lack of colloidal stability combined with small duration of gene expression in in vivo gene therapy, has been cited as the demerits of cationic liposomes which had hindered its future growth and research (Samal et al. 2012). Liposomes in combination with gene and scaffolds may contribute to overcome the disputes of toxicity, gene silencing efficiency and long-term expression. Explicitly, delivery of gene-loaded liposomes through scaffold may lessen their contact to immune cells, enrich cellular uptake with a sustained delivery.

Liposome–scaffold system may be used as gene delivery system in spatially localized, efficient and cell-controlled TE applications. Tissue vascularization was developed for delivery of VEGF encoded genes applying bone marrow stromal cells. Drugs (liposomes loaded with DNA encoding the 165 amino acid form of VEGF) were injected into rat skin for nursing of wound healing (Liu et al. 2004). A plasmid expression vector containing VEGF was served as a wound bed of rat abdominal skin flaps in a fibrin and new vessel formation was observed in histological analysis. The fibrin-mediated administration of a VEGF-A plasmid topically enhanced flap survival rate by seven days. PDNA-encoding RUNX2-laden into liposomes were covalently deactivated at the exterior of PCL nanofibers (Michlits et al. 2007). Furthermore, in medium free of osteogenic supplementation, hBMSCs osteogenic differentiation was accomplished by the overexpression of other osteogenic markers.

5.1.4 Magnetite Cationic Liposomes

Magnetic nanoparticles that can react and affect the anionic cell membranes are known as magnetite cationic liposomes (MCLs). Its numerous applications include usage in hyperthermic treatments, regenerative medicine strategies and TE. The biocompatible and nontoxic nature are the main properties of magnetic cationic liposomes that can be injected into tissue by the application of an external magnetic field which slowly accumulate in the organ or target. They are attracted by applying highest magnetic flux density for stimulating cell sorting and bioactive agent targeting. For instance, magnetic nanoparticles loaded into liposomes may exemplify a new modality for bone tissue regeneration and therapeutic angiogenesis (Ishii et al. 2011).

5.2 In Vivo Imaging Applications

Early and timely detection and treatment of the diseases can only be possible with the usage of age cutting therapeutic agents. Conventional and traditional methods

often undergo insufficient delivery of the bio active agents to the target tissues or cells, or create toxic side effects. To overcome these limitations, much effort has been dedicated in current years toward developing superior nanocarriers to increase their delivery efficiency. Incorporating both diagnostic and therapeutic agents into a single delivery system is another effective approach for simultaneous detection and therapy. To achieve these objectives, targeting ability with highest specificity and high stable, theranostic systems are needed to be established without the involvement of therapeutic agents in the system.

For targeted drug delivery, the surfaces of liposomes have been altered for detection of disease biomarkers and associated ligands with the help of receptors. Present-day imaging agents, such as Gd^{3+}, ^{18}F and ^{64}Cu, have been incorporated into phospholipid bilayer for nuclear imaging and magnetic resonance imaging (MRI). To date, hundreds of drugs and imaging agents including chelating agents, fluorophores, nanoparticles, proteins and peptides as well as antimicrobial agents and anticancer agents, oligonucleotides and vaccines and have been incorporated into liposomes for a wide-ranging theranostic applications.

Early detection of diseases and its stages such as cancer is a major factor of clinical outcome. As a result, the development of new analytical assays or diagnostic agents for detection of diseases has been noteworthy. Composition of liposomes and its control has generated tremendous interest toward the recognition of biomarkers and diseases in vivo.

5.2.1 Liposomes as Nanocarriers of Imaging Agents

Liposomes have been extensively used in medical imaging techniques, including magnetic resonance, fluorescence, nuclear and ultrasound imaging applications. For all of these techniques, liposomes offer highest stability, bioavailability and performance of prevailing contrast agents.

Fluorescence Imaging

Fluorescence imaging is the most broadly used diagnostic technique. It allows for visual imagining of gene expression, locating biomolecule and activities associated with enzymes in tissues. Liposomes with upgraded pharmacodynamics and pharmacokinetic characteristics assist the delivery fluorescence imaging agents specifically to the target area. PEG-coated quantum dots (QDs) encapsulated inside the aqueous phase of DOPC-supported liposome-hybrid nanoparticles for cancer imaging purpose were developed. The hybrid nanoparticles exhibited superior retention properties and enriched tumor penetration in both subcutaneous solid tumors and tumor spheroids. The hybrid formulation is compatible without further modification with various types of water-soluble quantum dots. Radioactive tracer europium complexes using liposomes were recently developed. Er^{3+}-doped Y_2O_3 (Y_2O_3:Er^{3+}) nanoparticles into liposome-hybrid nanoparticle showed strong NIR

fluorescence at 1550 nm under 980 nm excitation. These liposomes were subjected to several surface modifications, and positively charged Y_2O_3:Er^{3+} nanoparticles were successfully loaded inside negatively charged, DPPG-supported by modified liposomes.

Magnetic Resonance Imaging (MRI)

MRI is a noninvasive, extensively used imaging technique for medical applications. It is primarily used to identify the nuclear spins of hydrogen atoms present in water using radio frequency pulses, and to image noninvasive throughout the whole structure and physiological processes. Liposomes with fluorophores are able to load a large number of various MRI contrast agents simultaneously that allow controlled release and effective delivery of these probes for enriched imaging. Recently, a stimuli-responsive thermosensitive liposome was developed by a mixture of 1-myristoyl-2-stearoyl-sn-glycero-3-phosphocholine (MSPC), 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine (DPPC), 1,2-distearoyl-sn-glycero-3-phospho ethanolamine (DSPE)-PEG loaded with doxorubicin (DOX) and MRI contrast agent Gd-DTPA. The simultaneous delivery of DOX and Gd-DTPA allows drug release and monitor instantaneously, with triggerable release by localized heating in the tumor environment. Another important paramagnetic MRI contrast agent, ferrimagnetic iron oxide (FMIO) nanoparticles, has been utilized for the development of liposomal MRI probes. The liposomal FMIO nanoparticle cluster (ferriliposome) has the capability of targeting both tumor microenvironment and tumors through external magnetic field.

Ultrasound Imaging

In medical field, ultrasound imaging is another noninvasive diagnostic imaging technique, which has the characteristics similar to sound waves with frequencies greater than >20,000 Hz. Ultrasound imaging is implemented by administering ultrasound pulses into tissue and measuring the echoes caused by the tissue at various reflection angles. Acoustic liposomes (ALs) are liposomes containing perfluoropropane gas. Acoustic liposomes with an approximate diameter of 100–200 nm can be used as drug carrier along with passive localization to tumor tissue. It is achieved through improved permeability and retention effect. When the acoustic liposomes are coupled with high-frequency ultrasound (HF-US), they can be used to analyze antitumor efficacy and drug delivery efficiency (Ferrara et al. 2009). Recently, Kodama and coworkers developed a cisplatin-loaded, DSPC-supported AL to evaluate the antitumor effects using HF-US imaging on angiogenesis. With this method, the authors were able to track and map the flow of ALs in blood vessels and microvessel structures (Kodama et al. 2011).

Nuclear Imaging

Nuclear imaging is a technique in which small molecules are used as radioactive tracers. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are two basic types of nuclear imaging methods. PET detects gamma rays emitted from positrons annihilation ^{64}Cu radioactive isotopes, whereas SPECT detects gamma rays emitted from isotopes such as 99 m Tc directly (Rahmim and Zaidi 2008). A number of liposomes have been reported on encapsulated radionuclide tracers inside the aqueous compartment or chemically engineered lipid bilayer. The hydrophilic model drug fluorophore Alexa Fluor 750 has been encapsulated in the liposome formulations of ^{18}F or ^{64}Cu-labeled lipids. After liposomal treatment, FVB mice were used as model organism with bilateral Met-1 tumors. They were scanned and photographed with micro-PET and optical imaging in vivo techniques. Nine various types of radioisotopes functionalized liposomes formulations loaded with Alexa Fluor 750 were tested. It was found that in comparison to the free drugs, lower osmolarity in the aqueous portion along with cholesterol within the lipid bilayer highly resulted in much higher tumor accumulation. In live animal models, the combination of optical imaging techniques and PET will be helpful in screening the flow of liposomal vehicles through systemic delivery. The synergistic effect of the combination therapy of bimodal radio chemotherapeutic ^{188}Re-liposome-DOX showed larger tumor inhibition and higher median survival time than any other liposome (Chang et al. 2017).

6 Concluding Remarks

Liposomes are vesicular structures constructed with lipid bilayers resembling the biological lipid membrane and are created in aqueous solutions. When the liposomes emerged on the surface as the potential drug carrier, a lot of researches have been directed to achieve effective delivery system of therapeutic bioactive agents. However, there are some limitations to overcome. For instance, new strategies have to be developed to overcome the rapid blood clearance of PEGylated liposomes. The concept of triggered and stimuli-responsive controlled release in drug delivery is very promising, and effective research has to be dedicated to validate its applicability in vivo, in humans. Large-scale manufacturing techniques and advanced industrial technologies are required for producing sterile, well-characterized and stable products.

In this chapter, we have highlighted some applications of liposomes in theranostic, imaging, drug delivery and tissue engineering. Liposomes can be regarded as a versatile candidate to provoke the differentiation of stem cells through the release of bioactive agents. However, procedure of conventional method to provoke the overexpression of lineage-specific proteins relies on the usage of growth/differentiation factor combinations with suboptimal outcomes. Liposomes can regulate growth/differentiation factor release and do not show any side effects.

Liposomes mainly depend on the delivery of nucleotides (i.e., pDNA and RNAi). The incorporation of pDNA into the host cells genome enriches biocompatibility issues in the framework of tissue engineering, where differentiated cells are used for successive in vivo applications. The combination of liposomes with scaffolds appears to be a good method to solve this limiting factor. We strongly trust that lipid-based polymer composites may play a major role in biomedical applications such as tissue engineering, drug delivery, imaging and theranostics.

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Biomedical Applications of Electrospun Polymer Composite Nanofibres

Kalim Deshmukh, Sowmya Sankaran, M. Basheer Ahamed and S. K. Khadheer Pasha

Abstract Electrospun polymeric nanofibers (PNFs) play a pivotal role in every facet of science, engineering, and technology. Electrospinning (ES) is the technique that endows non-woven fibers in the nanometer scales and that owns superior properties including high surface areas, mechanical strength, easy processability, mass production, and ease of functionalization. This technique has a great versatility to be altered in different ways for synergizing material properties with different morphology, in order to fulfill the requirement of desired applications. In general, the precursor materials used for producing electrospun nanofibers (NFs) are natural and synthetic polymers, ceramics, or composites. These precursors are carefully selected based on the nature and the structure of desired tissues regeneration. The application of electrospun PNFs in the biomedical field is very vital. It is a well-known fact that all the tissues and organs such as bone, tendons, cartilage, skin, and dentine of living beings comprise fibrous structures in the nanometer range. This chapter attempts to make an overview of the recent advances in electrospun polymeric composite NFs for biomedical applications.

Keywords Electrospun nanofibers · Drug delivery · Tissue engineering · Wound dressing

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K. K. Sadasivuni et al. (eds.), *Polymer Nanocomposites in Biomedical Engineering*, Lecture Notes in Bioengineering,
https://doi.org/10.1007/978-3-030-04741-2_5

1 Introduction

Of late, the biomedical industry has been witnessing the challenge of developing novel materials and equipment that will prove beneficial to both the patients and the healthcare industry. This can be attributed to the fact that the patients are consistently looking for quality medical treatment, whereas the healthcare professionals and insurance companies are constantly seeking for simple and economical diagnosis and treatments. In this bottleneck situation, the unification of biology and nanotechnology sectors is highly anticipated to revolutionize the research and development of biomedical field by making use of new and unique physical, chemical, and biological properties of the material at the nano-regime (10^{-9} m) via the fine-tuning of the matter in the nanometer (nm) scale and by directly applying the nanomaterials to biological sites/targets. Presently, the nanomaterials are developed for myriads of biomedical and biotechnological applications such as tissue engineering, drug delivery, enzyme immobilization, biosensors, wound healing, and implants (Menaa 2011).

The electrospinning (ES) technique involves the formation of an electric field in between a positively charged syringe that contains a polymer solution and a grounded collector, as shown in Fig. 1a (Barnes et al. 2007). Generally, a polymer jet is formed when the electrostatic charges overcome the dominant surface tension created by the pendent droplet-shaped polymer solution oozing at the positively charged metallic tip of the syringe (Fig. 1b). The continuously charged jet strands of polymer solution start to accelerate from the metallic tip of the syringe to that of the grounded collector and deposit in the collector to form the polymeric nanofibers (PNFs). The grounded collector can be flat plate collector, rotating drum collector, mesh collector, etc., which decides the orientation or alignment of the nanofibers (NFs) to form unique structures with respect to morphology and mechanical properties (Barnes et al. 2007; Liu et al. 2017). Figure 2 represents the flowchart of the electrospun NFs for biomedical applications (Weng and Xie 2015).

Tissue engineering or regenerative medicine is a multidisciplinary field that synergies the knowledge of biology, medicine, material science, and engineering fields (Agarwal et al. 2008; Greiner and Wendorff 2007). Generally, the main aim of tissue engineering is to understand and apply from basics to advanced level of these multidisciplinary fields, for constructing and controlling realistic 3D physiological substitutes such as restoring, maintaining, and recovering the normal functions of affected tissues and organs. It is anticipated to have tremendous potential to enhance the healthy and quality life of humans by means of regenerating, maintaining, and improving the functions of tissues and organs. It has been proven best in replacing the naturally harvested tissues and organs in reconstructive and transplantation surgery (Kanani and Bahrami 2010). The scaffolds produced in tissue engineering bestow excellent support for the damaged cells that fail to stimulate an immune response caused due to injury, disease, or congenital defects via regenerating new extracellular matrix (ECM). The natural ECM is composed mainly of carbohydrate polymers such as proteins and glycosaminoglycans

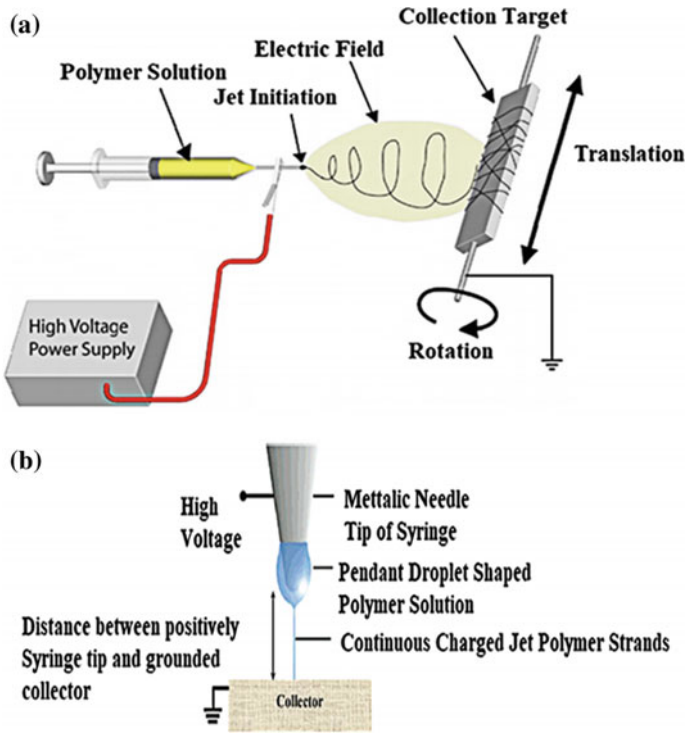

Fig. 1 **a** A pictorial representation of ES technique to depict the basic components and working process (Barnes et al. 2007). Copyright 2007. Reproduced with permission from Elsevier Ltd. **b** Formation of continuously charged jet of polymer strands between the pendant droplet-shaped polymer solution from the positively charged metallic syringe tip and the grounded collector (Liu et al. 2017). Copyright 2017. Reproduced with permission from Elsevier Ltd.

(GAGs), and it is used to segregate tissues, create a supportive meshwork all around the cells, and more importantly, offer excellent anchorage to the cells. Figure 3 highlights the basic concept involved in the tissue engineering field (Law et al. 2017). In this field, the stem cell from a slice of healthy tissue is isolated and then the harvested stem cells are in vitro cultured and expanded till the required number of cells is procured. After which, the stem cells are implanted in 3D polymeric scaffolds (or constructs) to produce an engineered tissue that can be transplanted back into the patients. However, it is to be noted that there are several types of tissue engineering techniques which may add or skip the steps depicted in Fig. 3. For instances, the cultured and expanded stem cells can be directly transplanted into the patient without seeding them on the 3D constructs (Law et al. 2017).

The ES technique bestows loosely attached 3D porous nanofibrous mats possessing high porosity and large surface area that can very well mimic the natural ECM structure making it an outstanding candidate for tissue engineering applications. The basic requirement for any scaffold material to be useful for the tissue

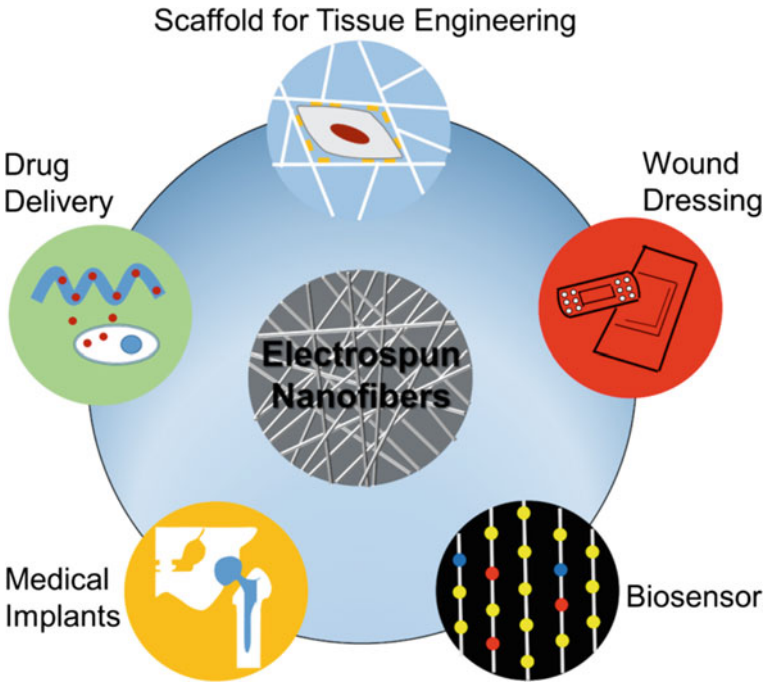

Fig. 2 A schematic illustration of the biomedical applications of electrospun NFs. Adapted from Weng and Xie (2015)

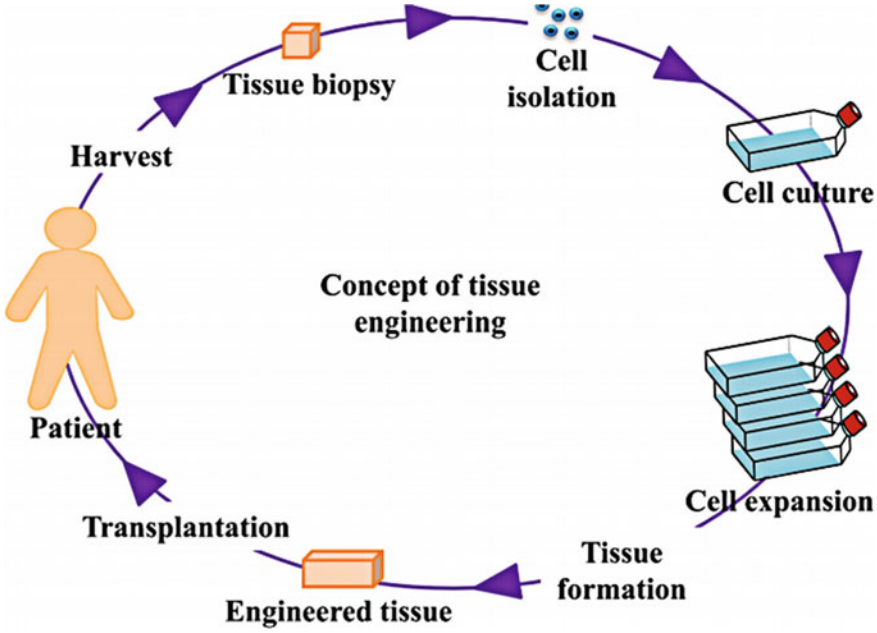

Fig. 3 Basic tissue engineering strategy (Law et al. 2017). Copyright 2017. Reproduced with permission from Springer

engineering applications is biodegradability and biocompatibility; i.e., the scaffold materials should have the ability to degrade with time, to be replaced with newly restored cells or tissues; and also be readily acceptable by the natural tissues. The next vital requisite in tissue engineering that influences the cell binding is the scaffold architecture. The scaffolds architecture in the nano-range holds high surface area that absorbs proteins and also offers additional sites to cell membrane receptors (Stevens and George 2005). Thus, the fate of the interactions of the tissue-engineered scaffolds in the cell environment purely depends upon its composition, i.e., synthetic or natural form of biopolymers. The tissue-engineered scaffolds are inserted into the body realizing the body as "self" which enable the damaged cells of the body to heal itself and to reinstate the "neo-native" functional tissues (Barnes et al. 2007).

To date, the benefits of ES technique for tissue engineering applications are focused upon two main reasons. The first reason is the production of non-woven nanofibrous mats from biomaterials that can mimic physical dimensions such as geometry and morphology in unison with the natural ECM in nano-dimensions. This necessitates the proper selection of biomaterials keeping in view of the degradation time and mechanical properties of the scaffolds which depend on the type of desired scaffolds, type of tissues to be restored, and time of regeneration. The biomaterials used for ES can be made from natural polymers, namely silk, nylon, wool, chitosan (CS), chitin, starch, protein, cellulose, and synthetic polymers, including polyvinyl alcohol (PVA), polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), polyethylene glycol (PEG), polyethylene oxide (PEO) and polyurethane (PU). These biomaterials are designed to check and regulate the growth, differentiation, and organization of cells at the time of formation of functional tissues. The second main reason is the ease in the modification of the ES apparatus keeping in mind the specific requirement of mimicking the ECM in order to enhance the cell proliferation and cell differentiation (Agarwal et al. 2008).

For the drug delivery applications, the ES process bestows excellent flexibility to choose a diverse range of suitable materials. The materials selected can be biodegradable or non-degradable in nature for controlling the drug release that can occur either via diffusion alone or via the diffusion and scaffold degradation. Almost all drugs including proteins, anticancer agents, antibiotics, RNA, and DNA can be loaded into electrospun nanofibrous scaffolds. Different ES techniques can be used in a limitless manner, particularly for tissue engineering as well as drug delivery applications. The drug loaded into the polymer or polymer composites can be done by coatings, embedding, and encapsulation. Figure 4 displays the ES process for drug and molecule incorporations into the NFs. In general, the different methods of drug and molecule encapsulations in the ES process include co-ES, side-by-side ES, multi-jet ES, coaxial ES, emulsion ES, and surface immobilization. These drug loading methods can greatly aid in regulating the kinetics of drug release (Liu et al. 2017; Sill and Recum 2008).

A wound dressing is the most important part of the biomedical field which owns benefits such as excellent protection, decent appearance, exclusion of exudates, and halting the growth of an exogenous microorganism. One of the astounding features

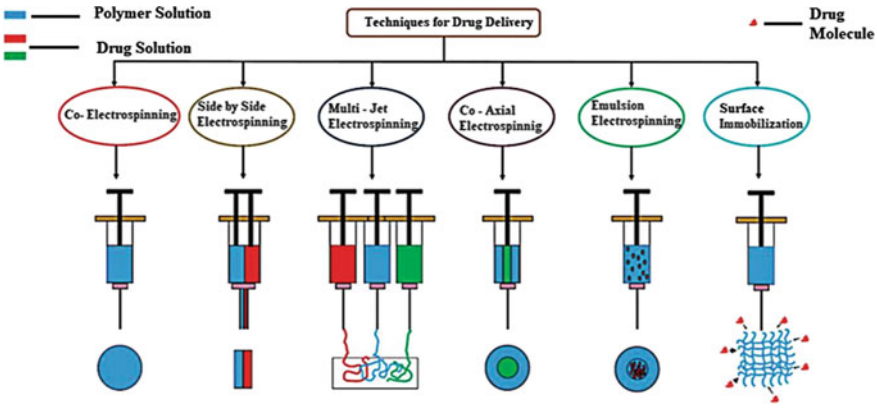

Fig. 4 Different methods of loading drugs in ES process (Liu et al. 2017). Copyright 2017. Reproduced with permission from Elsevier Ltd.

of a wound dressing is the coagulation of any type of open wounds such as traumatic, chronic, or thermal wounds. The other key attributes of antimicrobial wound dressings include creating a moist environment for improving the rate of healing, possessing broad-spectrum antimicrobial activity inclusive of active defense against antibiotic-resistant bacteria, etc. (Jones et al. 2004; Wright et al. 2002; Leaper 2006; Boateng et al. 2008; Gallant-Behm et al. 2005). Figure 5 shows five subsequent wound healing phases, i.e., hemostasis and inflammation phases, migration phase, proliferation phase, and maturation phase. In the hemostasis and inflammation phases, the neutrophils infiltrate into the wounded site. In the next phase, i.e., migration phase, the epithelial cells invade the wounded site. In the proliferation phase, the epithelium fully envelops the wound. In the final phase, i.e., maturation phase, most of the fibroblasts and capillaries created at the initial stages disappear (Boateng et al. 2008).

The inherent properties of NFs include high surface area and high porosity that offer steadfast initial signaling pathways and pull the fibroblasts to the derma layer separating critical ECM components for repairing the damaged tissues. The electrospun nanofibrous mats also enhance the cell attachment and cell proliferation in the wound healing mechanism. The non-woven form of electrospun NFs is generally very effective for wound healing applications, as it has tiny pores to block the permeation of bacteria. The high surface area of electrospun NFs aids in efficient dermal drug delivery and absorption of fluid (Chen et al. 2008).

In recent years, there are several featured review articles reported on the electrospun polymeric composite NFs for biomedical applications. For instance, Manea et al. (2016) have highlighted the importance of selecting basic materials for producing polymeric NFs for suitable medical applications. A critical literature survey on the application of ES technique in the biomedical field was carried out by Jesus et al. (2016). Venugopal et al. (2011) have provided the brief review on the recent advances in the biomedical applications of electrospun NFs, wherein a special

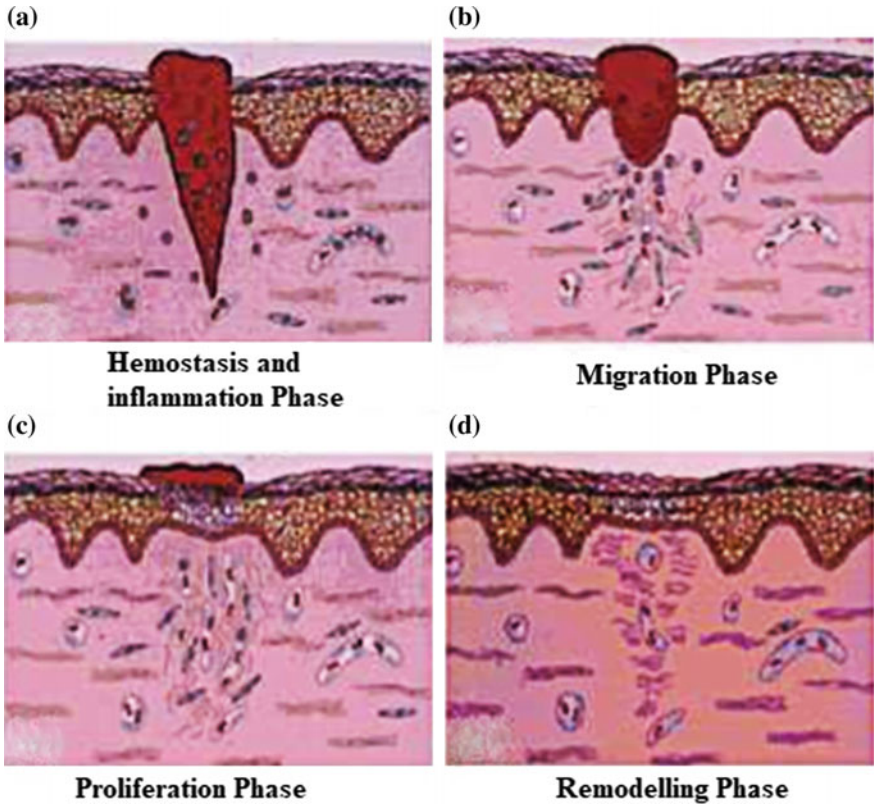

Fig. 5 Consecutive cascade of events in wound healing (Boateng et al. 2008). Copyright 2008. Reproduced with permission from Wiley Interscience

attention was given to electrospun polymeric nanofibrous scaffolds for tissue engineering of bone, cartilage, blood vessels, skin, and nerves. Leung and Ko (2011) have outlined the different ES processes developed for fabricating NFs for tissue regeneration and drug delivery application. The recent advances and the new perspectives on the smart electrospun NFs for controlled drug release were reviewed by Weng and Xie (2015). Hassiba et al. (2016) provided an overview of recent advances in NFs synthesis via the ES technique for wound healing/wound dressing applications.

In the forthcoming section, an attempt has been made to critically review the polymer-based electrospun composites nanofibers for biomedical applications, specifically tissue engineering, drug delivery, and wound dressing. The insulating polymers such as PVA, PLA, PGA, polylactic-co-glycolic acid (PLGA), PCL, PEG, PU, polyethyleneimine (PEI) and conducting polymers such as polypyrrole (PPy), polyaniline (PANI), poly(3,4-ethylenedioxythiophene) (PEDOT) have been selected as a base polymer for the review.

2 Biomedical Applications of Various Polymer-Based Electrospun Composite Nanofibers

2.1 Biomedical Applications of Polyvinyl Alcohol-Based Electrospun Composite Nanofibers

Polyvinyl alcohol (PVA), a well-known linear synthetic polymer, possesses unique properties such as water solubility, easy processability, biodegradability, and film-forming capacity (Pawde and Deshmukh 2008; Marin et al. 2014; Muppalaneni and Omidian 2013). PVA can be readily used for blends and composites preparation with a variety of natural and renewable polymers. PVA is commercially synthesized by the hydrolysis of polyvinyl acetate (PVAc) in two steps, viz. free radical polymerization of vinyl acetate to PVAc and partial or full hydrolysis. The structural property of PVA is largely dependent on its molecular weight and the degree of hydrolysis. Despite the type of hydrolysis, the tacticity of PVA is one of the most important structural considerations that are primarily decided by the starting material and the method of synthesis. The hydrolysis is atactic if the PVA is produced from polymerization of vinyl acetate and vinyl trifluoroacetate. The radical polymerization of vinyl formate yields syndiotactic PVA, and the cationic polymerization of benzyl vinyl ether results in isotactic PVA. By increasing the molecular weight and degree of hydrolysis, the properties such as viscosity, solvents resistance, adhesive and tensile strength and film-forming ability drastically get improved (Muppalaneni and Omidian 2013; Marten 2002; Baker et al. 2012; Deshmukh et al. 2016a, b, c, d; Mohanapriya et al. 2016a, b, 2017).

The degree of hydrolysis and tacticity primarily decides the glass transition and melting temperature of PVA (Muppalaneni and Omidian 2013). PVA is colorless and odorless in nature with the melting temperature around 180–228 °C, exhibiting glass transition temperature ~85 °C. PVA structure is highly stable and chemically inert due to its crystallization making it relatively safe and biocompatible (Baker et al. 2012). The simple structure and unique features of this polymer have been identified for potential applications in textile, paper, adhesives, food, biomedical, and pharmaceutical industries (Hassan and Peppas 2000). The resistance of PVA against various organic solvents and its solubility in water paves way for many potential applications (Marin et al. 2014). Food and drug administration (FDA) has allowed PVA to be used in close contact with food products. PVA films, in fact, display extraordinary barrier properties for food packaging. It is highly useful biomaterial in medical devices because of its biocompatibility, non-carcinogenicity, swelling properties, and bio-adhesivity (Pawde and Deshmukh 2008; Deshmukh et al. 2017a; Pawde et al. 2008).

Agarwal and Pramanik (2016) prepared CS/PVA blend nanofibrous scaffolds (NS) via free surface ES for tissue engineering application. The average diameter of the NFs was observed to be 269 nm. The NS showed excellent features such as swelling, strength, and biodegradability. Asran et al. (2010) prepared biodegradable blend scaffolds of PVA and polyhydroxy butyrate (PHB) for skin tissue engineering

application. It was reported that as the PVA content increased, the rate of degradation was also subsequently increased. The biocompatibility tests of PHB/PVA NFs were carried out using the human keratinocyte cell line (HaCaT) and fibroblasts. The adhesion, the proliferation of HaCaT cells, and fibroblasts were enhanced in pure PHB NFs, whereas increasing the PVA content in PHB stimulated the HaCaT cell growth while inhibiting the growth in fibroblasts. Thus, the bio-selectivity was altered using different compositions of PVA and PHB. Shalumon et al. (2009) prepared a biocompatible and bioactive carboxymethyl chitin (CMC)/PVA blended NS. The evaluation of cytotoxicity and cell attachment studies of the NS was accomplished using human bone marrow mesenchymal stem cells (hMSCs) by MTT assays. The cell attachment and cell spreading in the NS were witnessed using the cell attachment studies. The CMC/PVA NS supports cell attachment, cell adhesion, and proliferation, making it useful for tissue engineering (Jayakumar et al. 2010).

Silica (SiO_2)/PVA composites were electrospun to form NFs using an indigenous ES set up. The optimized ES parameters include an applied voltage of 30 kV, tip–collector distance of 12 cm and flow rate of 1 ml/min. A comparative study of electrospun pristine PVA and SiO_2/PVA NFs was made. The SEM image of both the electrospun PVA NFs and the SiO_2/PVA composite NFs is shown in Fig. 6. The diameter of pure PNFs was about 100–500 nm while the SiO_2 incorporated PVA was about 100–700 nm. The presence of SiO_2 renders better fiber mats paving way for tissue engineering as well as textile applications (Sasipriya et al. 2013; Deshmukh et al. 2017b).

Taepaiboon et al. (2006) loaded four types of nonsteroidal anti-inflammatory drugs (NSAIDS) into electrospun PVA NF mats for transdermal drug delivery (TDD) applications. The four model drugs such as sodium salicylate (SS), diclofenac sodium (DS), naproxen (NAP), and indomethacin (IND) were individually mixed with the PVA solutions under constant stirring for 4 h. The viscosity, surface tension, and the conductivity of prepared solutions were measured prior to

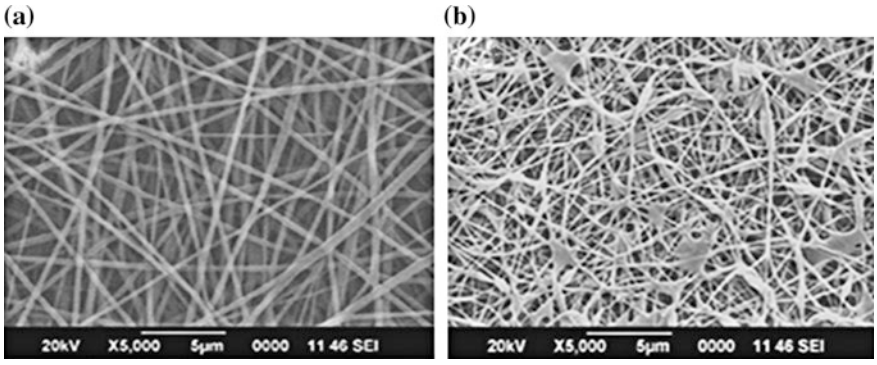

Fig. 6 SEM image of **a** electrospun PVA NFs, **b** SiO_2/PVA NFs (Sasipriya et al. 2013). Copyright 2013. Reproduced under creative common license

electrospinning. These solutions were later electrospun to get NFs with an average diameter of 130 nm. The drug encapsulation efficiency of PVA NFs was observed to be in the range of 81–98%. The release characteristics of these model drugs from as spun PVA mats were carried out by total immersion method in which the SS drug-loaded PVA mat exhibited a burst release characteristics resulting from the high solubility of SS drug in an aqueous medium. The highly porous nature of the PVA NF mats contributed to high swelling in an aqueous medium. In general, for DDS, one of the factors that control the release of a drug is the swelling behavior of the hydrogel carrier (Rujiravanit et al. 2003). The PVA matrix absorbs water and swells causing the solvation of the SS drug molecules leading to the rapid removal from the matrix (Taepaiboon et al. 2006). Ketoprofen drug was dissolved in a small quantity of methanol, followed by mixing with the PVA solution containing fully hydrolyzed PVA in deionized water. A known quantity of surfactants such as Triton X-100 and acetic acid was added to ES with fully hydrolyzed PVA entrapping the ketoprofen. For cross-linking, the drug incorporated PVA matrix was treated with methanol which discarded the burst release of drug from the fiber mat. Also, the methanol stabilized fiber mat, displayed a slow drug discharge for two weeks. The extent of PVA hydrolysis also has some additional influence on the drug release rate (Kenawy et al. 2007).

Currently, several natural polymers have been checked and used as drug delivery systems (DDS). For instance, Yang et al. (2007) fabricated electrospun gelatin/PVA composite NS and investigated the effect of gelatin/PVA ratio, cross-linking time of glutaraldehyde vapor, and the amount of drug incorporated on the drug release profile of raspberry ketone (RK). The outcome of the analysis is that the burst release of the drug was witnessed in the first hr and became constant after 2 h. Zulkifli et al. (2013) fabricated hydroxyethyl cellulose (HEC)/PVA nanofibrous mats using ES process. HEC is a well-known biocompatible water-soluble polymer. PVA is chosen as a polymer for producing electrospun NFs because of its good fiber forming capacity, biocompatibility, and good chemical resistance. The 5 wt% concentration of HEC and 15 wt% concentration of PVA were blended in different weight ratios 50:50, 40:60, and 70:30 of HEC to PVA and electrospun to form the NFs with an applied voltage of 25 kV, tip to collector distance of 12 cm and a humidity of 50%. The nanofibrous mat was then treated with glutaraldehyde to form water-insoluble NFs. Human fetal osteoblastic (hFOB) cells were subjected to cell culture studies for a period of 14 days which revealed enhanced cell adherence and proliferation of hFOB on NS. The authors concluded that the cross-linked HEC/PVA fibers seem to be a relevant candidate for a variety of biomedical applications.

Zhou et al. (2008) evaluated the in vitro of electrospun N-CECS/PVA NF mats for skin regeneration scaffolds using L929 cells. Indirect cytotoxicity examination of the nanofibrous mats revealed non-toxicity to the L929 cells. The result from cell culture studies revealed that the NF mats boosted the cell attachment and proliferation in L929 cells. Hence, this novel electrospun mat can serve as a wound dressing material for skin regeneration. Chellamani et al. (2012) developed a special wound care product made of CS/PVA blended NFs. The CS/PVA weight ratio of

80/20, 70/30, 60/40, and 50/50 was used to electrospun the NFs. CS/PVA NFs as a wound dressing material exhibited very high moisture transmission, excellent antimicrobial activity, the complete absence of any of the cytotoxicity effects, and extraordinary odor absorbing capacity. Among the four different weight ratios, 50/50 CS/PVA NFs offered better results mainly because of its lower diameter. Even after 72 h of CS/PVA NFs in contact with the wounds of rat, no skin irritation was observed. Also, the total time taken for wound healing by CS/PVA NFs was 50% faster than that encountered in open wounds.

Kang et al. (2010) formed the PVA NFs with the mean diameter of 240 nm from ES of 10 wt% PVA aqueous solution. The as-spun PVA NFs were heated at 150 °C for 10 min for improving the physical cross-linking and the water resistance of PVA NFs. CS is coated on the heated PVA (H-PVA) NFs mat in order to construct biomimetic NF wound dressings. The CS-coated PVA (C-PVA) NFs mat exhibited better tensile properties and low hydrophilicity than the H-PVA NFs mat. The wounded portion of the rats was applied with C-PVA and H-PVA to observe their effect. Faster wound healing was noticed in C-PVA and H-PVA as compared to the control sample. The histological assessment and mechanical stability test concluded that the C-PVA NFs mat is more efficient as a wound healing accelerator in comparison with H-PVA NFs mat. The open wound healing test and histological assessment revealed that C-PVA mat more effectively renewed the damaged skin; however, the difference in H-PVA mat was not too remarkable. The tensile property of C-PVA was greater than H-PVA because of the inter-fiber bonds formed due to CS coating. These outcomes recommend the C-PVA NFs as a promising candidate for biomedical applications. A novel electrospun quantized chitosan (QCS)/PVA blend NFs with an average diameter of 60–200 nm was reported by Ignatova et al. (2006). The NF mats were subjected to UV irradiation for cross-linking using triethylene glycol diacrylate (DA) leading to stabilization of the NFs against disintegration in water (Jayakumar et al. 2010). Electrospun CS/PVA blended NS exhibited better physicochemical and biological properties in comparison with pure PVA NS for nerve tissue engineering applications. Adding CS to PVA scaffolds stimulates better proliferation of nerve cells, which in turn improves the biocompatibility of the blend scaffolds (Alhosseini et al. 2012; Gholipour et al. 2009).

Yeum et al. (2011) reported the study on silver nanoparticles (Ag NPs)/montmorillonite (MMT)/PVA composite NFs with 7.5 wt% concentration of PVA, 5 wt % of MMT, and 5 wt% of Ag NPs. Most of the MMT platelets were exfoliated with orderly distribution within the fiber mat and their orientation being along the fiber axis. The exfoliated MMT NPs enhance the thermal stability and tensile strength of the electrospun NFs. The well-dispersed Ag NPs offer good antibacterial performance to the NFs. The inference drawn from the study was that the NFs can be used for wound dressing, filtration, reinforcement in the polymer matrix, and protective clothing applications. Wound dressing materials prepared from silver nitrate ($AgNO_3$)/PVA aqueous solution was electrospun into non-woven webs which were subjected to heat or UV radiation treatments resulting in a reduction of the Ag ions into Ag nanoparticles. The crystallinity of the electrospun PVA fiber was improved on heat treatment and hence made the web insoluble in moisture environment.

The Ag ions are a very effective antimicrobial agent for wound and burn healing functions deactivating the bacterial proteins and nucleic acids to their negatively charged components. Also, Ag ions generate O_2 that has the capability to destroy the cell wall membrane of the bacteria. Thus, the electrospun $AgNO_3$/PVA nanofibrous webs can be considered as a potential wound dressing materials (Duan et al. 2007). Iodine/PVA blends today are extravagantly used as antiseptic products. PVA NFs with iodine usually disinfect the skin treated with medicine. Iodine/PVA blend NFs can be easily generated using ES process (Matuseviciute et al. 2012). The iodine prominently influences the structure of the electrospun non-woven mat making it suitable for the biomedical application such as skin and wound healing and also in drug release.

El-Aassar et al. (2016) successfully prepared an antibacterial electrospun NFs using PVA, pluronic F127 (Plur), and PEI blend reinforced with TiO_2 NPs for wound dressing applications. The TiO_2 NPs were synthesized using the sol–gel method. PVA-Plur-PEI blended NFs with the concentration of 0.01, 0.03, and 0.05% TiO_2 NPs were prepared using ES. The surface microstructure and diameter of the blend NFs were dependent on Plur concentration. By adding TiO_2 NPs, the fiber diameter of the blend NFs was gradually reduced. The TiO_2/PVA-Plur-PEI NFs had better antibacterial properties than PVA-Plur-PEI NFs against gram-negative bacteria. Thus, TiO_2/PVA-Plur-PEI NFs have promising future in advanced wound treatments, treatment of skin infections and also in tissue regeneration. Halloysite nanotubes (HNT)/PVA NS were found useful in numerous biomedical applications such as in bone tissue engineering, DDS, wound dressings, targeted tissue transportation systems, soft biomaterial implants due to their biocompatibility, non-toxicity, non-carcinogenicity, smoothness, and flexibility (Moreno et al. 2011; Deshmukh et al. 2017c). Table 1 depicts various biomedical applications of electrospun PVA composite NFs.

2.2 *Biomedical Applications of Polylactic Acid-Based Electrospun Composite Nanofibers*

PLA belongs to the biodegradable, aliphatic polyester family which stands second in the highest consumption volume of any bioplastic. It is commonly prepared from α-hydroxyl acids such as polyglycolic acid (PGA) and/or poly(mandelic acid) and can also be derived from renewable resources which include cornstarch, tapioca, and sugarcane. PLA is a thermoplastic polymer possessing high strength and high modulus. Generally, it is used for industrial packaging and in the biocompatible and bioabsorbable medical devices (Khoo et al. 2016; Garlotta 2001; Lasprilla et al. 2012). The structure of PLA can be modified by polymerization of a controlled mixture of L- or D-isomers to obtain high MW polymers both crystalline and amorphous which are mainly used as food contact agent as it is approved safe by FDA (Conn et al. 1995).

Table 1 Biomedical applications of electrospun PVA composite NFs

ES type	PVA-based composite NFs	Biomedical applications	References
Traditional ES	PHB/PVA	Skin tissue engineering	Asran et al. (2010)
Traditional ES	CMC/PVA	Tissue engineering	Shalumon et al. (2009) and Jayakumar et al. (2010)
Traditional ES	SiO_2/PVA	Tissue engineering	Sasipriya et al. (2013)
Traditional ES	Ketoprofen/PVA	Drug delivery	Kenawy et al. (2007)
Traditional ES	RK/gelatin/PVA	Drug delivery	Yang et al. (2007)
Traditional ES	HEC/PVA	Tissue engineering, drug delivery, medical prostheses	Zulkifli et al. (2013)
Traditional ES	CS/PVA	Wound healing	Chellamani et al. (2012)
Traditional ES	CS/PVA	Wound dressing, tissue engineering	Kang et al. (2010)
Traditional ES	Ag NPs/MMT/PVA	Wound dressing	Yeum et al. (2011)
Traditional ES	$AgNO_3$/PVA	Wound dressing	Duan et al. (2007)
Traditional ES	Iodine/PVA	Wound healing, drug release	Matuseviciute et al. (2012)
Traditional ES	PVA-Plur-PEI/TiO_2	Wound healing, tissue regeneration	El-Aassar et al. (2016)

PLA is prepared using lactic acid (LA). LA is a basic block of PLA which can be produced by two methods, i.e., petrochemical feedstock and carbohydrate fermentation. The fermentation of natural products such as rice and corn was the common process to synthesize LA (>90%). The PLA is synthesized in multistep, starting with the production of lactic acid, followed by lactide formation and ends with its polymerization (Moreno et al. 2011). LA monomers can be converted into PLA using any of the three polymerization processes including polycondensation, ring opening polymerization (ROP), and azeotropic dehydration condensation reaction of which ROP allowed the production of a high MW PLA more economically. Hence, ROP is a suitable processing method (Hamad et al. 2015). PLA is easily degraded by hydrolysis of the ester bond on abiotic degradation. The particle isomer ratio, size, shape, and the temperature of hydrolysis decide the rate of degradation. The glass transition (T_g) and melting temperature of PLA homopolymer are about 55 and 175 °C, respectively.

The properties of high MW PLA are similar to polystyrene, which includes colorless, glossy, and stiffness. PLA hydrolyzes to harmless, natural products when properly disposed off (Garlotta 2001). PLA is regarded both as biodegradable and as biocompatible when in contact with living tissues. PLA can be considered as an environmentally friendly material as long as the LA is derived from renewable sources by fermentation. PLA has occupied a strong position in the biomedical applications, namely tissue engineering scaffolds, DDS, orthopedic device, wound

dressing and healing agent due to its excellent biodegradability, mechanical, thermal, barrier properties, processability, and low cost. Different PLA types can be used to prepare a range of biomedical devices such as degradable sutures, drug release systems, and porous scaffolds for cellular applications (Conn et al. 1995; Hamad et al. 2015; Lim et al. 2008). PLA, a bioplastic, usually derived from biomass is used commonly to make plastic films, bottles, and biodegradable medical devices.

Hydroxyapatite (HA)/PLA composite NFs prepared via ES showed excellent mechanical strength as a substrate for bone tissue regeneration (Takenaka et al. 2004). Superparamagnetic nano-Fe_2O_3/nano-HA/PLA NFs produced using ES process was tested on white rabbit model with lumbar transverse defects which induced the formation of bone tissues and remodeling (Meng et al. 2013). Wojasinski et al. (2014) prepared composite nano-HA/poly L-lactide (PLLA) NFs using ES. The composite nanofibrous mat was prepared by applying 17 kV and maintaining a relative humidity of 40–52%. The resulting nano-HA/PLLA composite NFs showed very good chemical resistance and high porosity, making it suitable for bone replacement application, dental filling, and bone tissue engineering. Prabhakaran et al. (2009) analyzed the electrospun PLLA, HA/PLLA, and HA/collagen/PLLA substrates for bone tissue regeneration. PLLA NFs possess controlled degradation which is very useful for tissue engineering and drug delivery therapies. The in vitro assays reported that introduction of HA in poly P-lactide (PPLA) matrix improved the cell proliferation to a greater extent compared to PLLA scaffolds. Furthermore, the presence of collagen has enhanced the cell attachment as well as cell proliferation of HA/collagen/PLLA NS. This NS was tested on osteoblastic cells which revealed a very good growth and adherence with mineral depositions 57% greater than in the HA/PLLA NFs.

Hoveizi et al. (2014) functionalized the surface of PLA scaffold with gelatin to increase the cell adherence and proliferation on the scaffold and also biocompatibility. The PLA and gelatin at varying compositions (gelatin: PLA at 7:3 and 3:7) were dissolved in hexafluoroisopropanol (HFIP). The FTIR and SEM analysis revealed that modified gelatin/PLA (3/7) scaffold is more relevant for attachment of fibroblasts and viability in comparison with pristine PLA NFs or gelatin NFs. Thus, culturing fibroblast on gelatin/PLA scaffold can improve skin wound healing. Gelatin modified PLA scaffold was tested on rat wound to study the structural properties and cytocompatibility of scaffolds. The average diameter of about 350 nm of electrospun gelatin/PLA NFs was more desirable to mimic the natural ECM. The cell adhesion and proliferation were considerably improved for the gelatin/PLA NFs. After 21 days, the formation of new tissues on the fibroblast cultured with gelatin/PLA blend NS was confirmed using histopathological analyses. Thus, the authors have developed simple, novel, and effective NFs that will potentially increase the reliance of PLA scaffold in the tissue engineering and wound healing applications. Xu et al. (2009a) fabricated CS/PLA blend NFs using ES which are suitable to mimic ECM providing a native environment to the cells for tissue engineering applications.

Single-walled carbon nanotubes (SWCNTs)/PLA biodegradable NS have been fabricated by Zhang et al. (2005a). The in vitro assay revealed that the SWCNTs loaded NS permits cell growth with no hostile effect on cell proliferation. Valente et al. (2016) created PLA fibers of both alignments, i.e., random and aligned membranes, via ES and sterilized them under UV, ethylene oxide (EO) and γ-radiation. UV and γ-radiation exposed PLA fibers did not show any morphology or alignment variation without any significant change in the physical properties. However, the wettability was slightly increased. The EO exposed PLA fibers exhibited changes in fiber orientation and morphology with 28% increase of polymer crystallinity. In vitro studies reveal that both UV and γ-radiation treated PLA fibers permits adhesion and proliferation of MG63 osteoblastic cells with a growth pattern highly sensitive to random or aligned orientation. Thus, the UV and γ-sterilized PLA fibers can be suggested for biomedical applications where the fiber morphology and alignment are of prime importance. Chen et al. (2007) prepared the electrospun blends of nano-TiO_2/PLA NFs loaded with the daunorubicin (an anticancer drug for drug delivery in targeted cancer cells). Nano-TiO_2/PLA NFs showed a decent biocompatibility and a high surface area which helps in loading and accommodating a large number of drug molecules. Tetracycline hydrochloride (TCH) which is a hydrophilic antibiotic was encapsulated into the PEG/PLA NFs core using emulsion ES. These NFs exhibited a stable release rate along with no initial burst release and also proper protection of loaded active agent (Rieger et al. 2013). Spasova et al. (2008) electrospun PLA and PEG/PLA mats coated with CS for wound healing application, i.e., for immediate hemostatic activity.

Electrospun PLA fibers were loaded with ketoprofen drug whose structure is shown in Fig. 7 (Park and Lee 2011). Porous PLA NFs were fabricated by phase separation technique during the ES. The release of the ketoprofen drug from the NFs displayed higher release rate at body temperature (37 °C) than at room temperature (20 °C). The release effect increased as the ketoprofen content increased. The ketoprofen/PLA NFs release pattern exhibited a rapid release initially, i.e., in the first few hours with subsequent slower release rates. After 360 h, ketoprofen/PLA NFs with 1% ketoprofen exhibited 73 and 86% release of the ketoprofen drug at 37 and 20 °C, respectively, whereas the NFs containing 8% ketoprofen exhibited 43 and 39% drug release at 37 and 20 °C, respectively, as depicted in Fig. 8 (Park and Lee 2011).

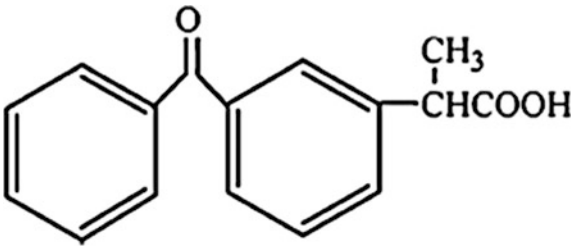

Fig. 7 Chemical structure of ketoprofen drug (Park and Lee 2011). Copyright 2010. Reproduced with permission from Springer Ltd.

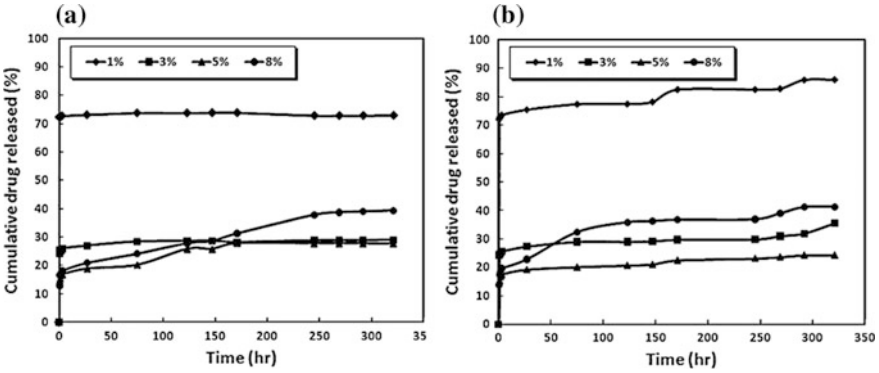

Fig. 8 Release profile of in vitro ketoprofen drug from electrospun PLA NFs in phosphate buffer 7.4 at **a** 20 °C and **b** 37 °C (Park and Lee 2011). Copyright 2010. Reproduced with permission from Springer Ltd.

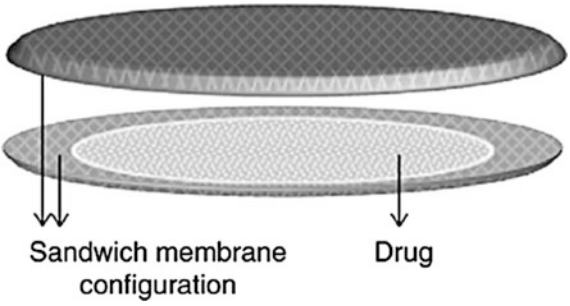

Fig. 9 Illustration of PLA/ibuprofen/PLA sandwich membrane (Immich et al. 2013). Copyright 2013. Reproduced with permission from Elsevier Ltd.

Immich et al. (2013) proposed a study on electrospun ibuprofen/PLA-based sandwich nanomembranes for evaluating and quantifying the transport mechanism that controls the release of drugs in the sandwich mat. The operation conditions during ES process include applied voltage of 10 kV, the flow rate of 2 mm/h, the tip–collector distance of 8.5 cm and with spinneret opening diameter of 0.4 mm, to yield PLA NFs. The drug was dispersed in the first electrospun PLA membrane after drying and solidification. The second membrane layer was electrospun on the first layer containing the drug (Fig. 9). The thickness of the ibuprofen/PLA nanomembranes is a very crucial factor for controlling the drug delivery. Thicker membrane exhibited slower mass transference. The choice of thickness of PLA membrane and ibuprofen concentration can be fixed on the basis of intended therapy. Thinner membranes are appropriate for treatments that require less control over the release of an initial dose of ibuprofen drug. However, the dense and thick membranes are highly recommended for treatments that require higher control over the release of a low dose ibuprofen. The PLA-ibuprofen-PLA sandwiched membrane was cultured on HeLa cells (cells from cervix carcinoma) and was tested for cell viability and toxicity. The test confirms that PLA displayed no harmful effects

on HeLa cells. Thus, the prepared PLA sandwiched membrane can be used as drug carriers without causing any effect on human cells or tissues.

Ultrafine PVA/PLA NFs were formed using coaxial ES with PVA as the core and PLA as the shell. During the ES process, the voltage of 20 kV was applied and the tip–collector distance kept was 13 cm. The NFs with homogeneous and smooth surface morphology were obtained. The core–shell NFs have some crystallinity and porosity with an average diameter of 200 nm which is purely dependent on the ES parameters. The core–shell fiber diameter increases from 1 to 2 µm when the PLA solution flow rate is increased. The contact angles (Fig. 10) of ultrafine NFs obtained from the core–shell ES were lesser than that of monolithic PLA NFs, which demonstrated that the PVA/PLA (core–shell) NFs have improved hydrophilicity, showing application potential for controlled release of bioactive molecules (Goncalves et al. 2015).

The electrospun PEO/PLA NFs were loaded with two different anticancerous drugs, hydrophilic doxorubicin hydrochloride (DOX) and lipophilic paclitaxel (PTX). The results indicated that the most soluble hydrophilic DOX exhibited faster drug release. The in vitro assay for cytotoxicity revealed higher inhibition and apoptosis of the cells in NFs containing dual drug when compared to single drug-loaded NF system. This suggests a promising future of multi-drug delivery of NFs for combined therapies (Xu et al. 2009b). Ultrafine PEG/PLA NFs were loaded with both hydrophobic PTX and DOX, via emulsion ES where an increase in the release rate was observed due to the presence of DOX (Xu et al. 2008). Sun et al. (2006) reported the coaxial ES of polyvinylpyrrolidone (PVP)/PLA (sheath/core) NFs with fiber diameter ranging between 400 and 500 nm and total core diameter in the range 200–300 nm for drug delivery applications.

Yang et al. (2008) analyzed and reported the impact of fiber structure on the release profiles and structural stability of encapsulated proteins (Lysosomes and Bovine Serum Albumin (BSA)). These proteins were encapsulated into the

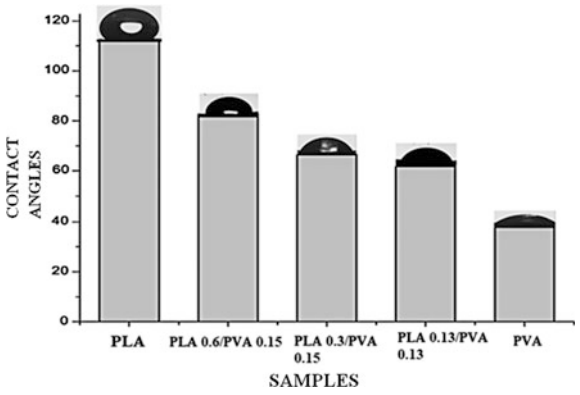

Fig. 10 Contact angles of electrospun PVA, PLA, and PVA/PLA core–shell NFs (Goncalves et al. 2015). Copyright 2015. Reproduced under creative common license

core-shell PLA NFs serving as a scaffold for controlled release of bioactive proteins in tissue engineering. The PCL/PLA sheath NFs encase the BSA containing nerve growth factor in the core via coaxial ES. The growth factors were well protected by the sheath polymers and therefore showed a near zero-order release mechanism over time. This is contrary to the initial burst release over a day in blends of BSA/polymer NFs where the growth factor was directly incorporated. This reveals that the sheath plays a key role in establishing the molecular diffusion path and also controlling the growth factor release (Zhang et al. 2006).

Hardiansyali et al. (2015) prepared CS/PLA blends NFs via ES using solvents such as chloroform, water, acetic acid, and ethanol. The average diameter of the NFs reduced as the CS content was increased. The CS/PLA NFs displayed excellent antibacterial activity against *Escherichia Coli* (*E. Coli*). Also no cytotoxicity to the mouse fibroblasts L929 cells was observed which signifies the cytocompatibility of blended NFs. Thus, the CS/PLA NFs exhibited excellent antibacterial activity as well as non-cytotoxicity to the mammalian cells making it a potential candidate for tissue engineering, wound dressing, and also as DDS. Table 2 depicts various biomedical applications of electrospun PLA composite NFs.

Table 2 Biomedical applications of electrospun PLA composite NFs

ES type	PLA-based composites NFs	Biomedical applications	References
Traditional ES	HA/PLA	Bone tissue regeneration	Takenaka et al. (2004)
Traditional ES	Nano-Fe_2O_3/nano-HA/PLA	Bone tissue repair	Meng et al. (2013)
Traditional ES	HA/collagen/PLLA	Bone tissue regeneration	Prabhakaran et al. (2009)
Traditional ES	Gelatin/PLA	Tissue engineering	Hoveizi et al. (2014)
Traditional ES	Daunorubicin-nano TiO_2/PLA	Drug delivery	Chen et al. (2007)
Emulsion ES	TCH-PEG/PLA	Drug delivery	Rieger et al. (2013)
Traditional ES	PLA NFs and PEG/PLA	Wound healing	Spasova et al. (2008)
Traditional ES	Ketoprofen/PLA	Drug delivery	Park and Lee (2011)
Traditional ES	Ibuprofen/PLA	Drug delivery	Immich et al. (2013)
Coaxial ES	DOX and PTX—PEG/PLA	Multi-drug delivery	Xu et al. (2008)
Emulsion ES	BSA/Lysosomes/PLA	Tissue engineering	Yang et al. (2008)
Coaxial ES	BSA/PCL/PLA	Drug delivery	Zhang et al. (2006)
Traditional ES	CS/PLA	Tissue engineering, wound dressing, DDS	Hardiansyah et al. (2015)

2.3 *Biomedical Applications of Polyglycolic Acid-Based Electrospun Composite Nanofibers*

PGA, a well-known linear, biodegradable and thermoplastic polymer belongs to the family of the aliphatic polyester. The copolymers of PGA such as poly (lactic-co-glycolic acid) (PLGA), poly(glycolide-co-caprolactone), and poly (glycolide-co-trimethylene carbonate) are extensively used for synthesizing absorbable sutures. PGA possesses melting point around 225–230 °C, T_g around 35–40 °C with an elevated degree of crystallinity (45–55%) (Middleton and Tipton 2006). The solubility of PGA is unique in a sense that the high MW PGA is not soluble in most of the common organic solvents such as acetone, chloroform, dichloromethane, ethyl acetate and THF due to its high crystallinity while the low MW PGA is more soluble. Moreover, the PGA is highly soluble in fluorinated solvents such as HFIP and hexafluoroacetone sesquihydrate (Blomqvist et al. 2002). PGA can be synthesized via different methods such as polycondensation of GA, ROP of glycolide and solid-state polycondensation of halogenoacetates. The simplest method of PGA synthesis is the polycondensation of GA, but this method is not efficient as it yields a low MW product. In this process, the GA is heated to a temperature of 175–185 °C and at an atmospheric pressure, until the water distillation comes to an end. Thereafter, the pressure is decreased to 150 mm Hg, maintaining the same temperature for about 2 h, and forming the low MW PGA.

The ROP of glycolide is the most common method to produce high MW PGA (Fig. 11). Glycolide is a cyclic diester of glycolic acid. ROP of glycolide is catalyzed with the help of different catalysts such as antimony, zinc, and tin compounds. Stannous octoate ($SnOct_2$) is the most frequently preferred catalyst since it has been approved by FDA. Catalysts such as aluminum isopropoxide, calcium acetylacetonate, and several lanthanide alkoxides have also been identified for PGA preparation. In this method, the catalyst is added to the glycolide at a temperature of 195 °C under a nitrogen atmosphere for a reaction time of about 2 h. Then, the temperature is increased to 230 °C for a period of half an hr. The high MW polymer is obtained after solidification (Takahashi et al. 2000). Kahikara et al. (2007) prepared PLLA and PGA by ROP with tin (II) 2-ethyl hexanoate as a catalyst. Implantable medical devices such as anastomosis rings, pins, rods, plates, and screws have been created using PGA (Middleton and Tipton 2006). The potentiality of PGA for tissue engineering and control drug delivery applications has been

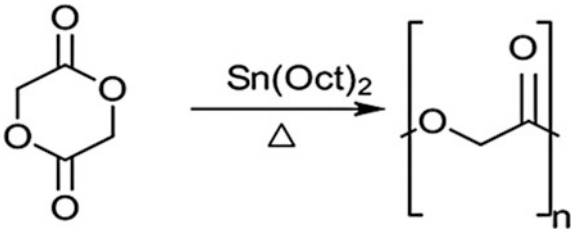

Fig. 11 Synthesis of PGA from glycolide through ROP (Kaihara et al. 2007). Copyright 2007. Reproduced under creative common license

explored. Tissue engineering scaffolds made from PGA in the form of non-woven meshes have been commonly used.

Hajiali et al. (2011), prepared gelatin/PGA blended NFs using ES. The gelatin/PGA was blended at 0, 10, 30 and 50 wt% ratios to form electrospun NFs. The biocompatibility assay of prepared gelatin/PGA NS was cultured on human umbilical vein endothelial cells and human umbilical artery smooth muscle cells for evaluating the cell attachment and viability. Gelatin/PGA NFs with 10 wt% of PGA enhance the endothelial cells while the gelatin/PGA NFs with 30 wt% improved smooth muscle adhesion, viability, and penetration in comparison with other prepared (0% and 50 wt%) NF blends. It was observed that with increasing gelatin content, the mechanical properties of the NS were highly improved since the interaction between PGA and gelatin increased. Thus, it was concluded that the addition of gelatin into PGA enhances both the mechanical and biological properties of PGA making it suitable for vascular tissue engineering and regeneration in vivo applications.

PCL/PGA composite NFs via ES were fabricated using various compositions for soft tissue engineering applications (Aghdam et al. 2012). The average diameter of the NFs increased because of the addition of PGA to PCL. As the amount of PGA increased in the PCL/PGA blend, a simultaneous increase in the hydrophilicity and water uptake of the NF scaffolds was observed similar to PGA NFs. The dynamic mechanical thermal analysis (DMTA) and tensile properties revealed a significant increase in the mechanical properties of the PCL/PGA NFs due to an increase in the PGA content. Athanasiou et al. (2007) examined the effect of porosity of the electrospun PLA/PGA (50:50) copolymer NFs on in vitro characteristics of an osteochondral biodegradable implant. Nanofibrous specimens were fabricated with three porosities: (i) 0% (low) (ii) 33% (medium), and (iii) 75% (high) porosity. These specimens were placed in the phosphate-buffered saline at 37 °C for 8 weeks or more until the complete degradation was accomplished. The results analyzed from various characterization techniques such as SEM, PH, and molecular weight loss measurements, and the mechanical test indicated that the porosity highly influences the implants structural properties, i.e., low porous implants, were prone to larger losses in MW than the medium or high porous implants. A significant mass loss of the specimens was observed between 4 and 6 weeks. The mechanical assay showed that at the 0 weeks, the high and low porous specimens were two to three times stiffer than the medium porous specimens. PH measurements revealed that with an increase in porosity, the implant becomes less acidic, i.e., low porosity > medium porosity > high porosity (in terms of acidic levels of implants). Thus, the low porous implants experience faster degradation due to more acidic nature than medium or high porous specimens, hence leading to a short span of functional life of the low porous implants. This faster degradation in low porous implants can be attributed to improved autocatalysis in the implants as they are not able to clear the acidic degradation by-products.

Park et al. (2006) prepared electrospun biodegradable and biomimetic chitin/PGA blended NS for tissue engineering. The average diameter of the as-spun NFs was around 140 nm. The degradation study (in vitro) of chitin/PGA NFs was

Table 3 Biomedical applications of electrospun PGA composite NFs

ES type	PGA-based composites NFs	Biomedical applications	References
Traditional ES	Gelatin/PGA	Vascular tissue engineering, Regeneration in vivo applications	Hajiali et al. (2011)
Traditional ES	PCL/PGA	Soft tissue engineering	Aghdam et al. (2012)
Traditional ES	PLA/PGA	Osteochondral bsiodegradable implants	Athanasiou et al. (2007)
Traditional ES	Chitin/PGA	Tissue engineering scaffolds	Park et al. (2006) and Jayakumar et al. (2011)

carried out in phosphate-buffered saline (pH ∼ 7.2). The hydrolytic cleavage of PGA in the as-spun NFs was observed that is mainly due to the presence of chitin which is hydrophilic in nature. The cytocompatibility and cell behavior assay of chitin/PGA NFs were evaluated using normal human epidermal fibroblasts (NHEF) seeded on the NF scaffolds. The chitin/PGA NFs with the composition of 75/25 and BSA coating exhibited extraordinary cell attachment and spreading on NHEF, making it potential tissue engineering scaffolds (Jayakumar et al. 2011). In vitro degradation studies on non-porous ultrafine PLLA/PGA NFs were carried out by You et al. (2005). The degradation rates of the prepared ultrafine PLLA/PGA NFs were remarkably decreased with increasing content of PLLA since the PLLA has lower degradation rate as compared to PGA. Their inference on degradation rate was that the non-porous PGA > porous PGA/PLLA (90/10) > porous PGA/PLLA (50/50) > porous PGA/PLLA (30/70) which was mainly because of autocatalytic hydrolysis. Table 3 shows various biomedical applications of electrospun PGA composite NFs.

2.4 Biomedical Applications of Polylactic-co-Glycolic Acid-Based Electrospun Composite Nanofibers

PLGA has been approved by FDA for a variety of biomedical applications due to its excellent biodegradability and biocompatibility (Makadia and Siegel 2011; Danhier et al. 2012; Kim et al. 2003). PLGA with varying MW ranging from 10 to 100 KDa and molar ratios of lactide to glycolide is available globally. PLGA is commonly synthesized by ring opening copolymerization using twelve different monomers, i.e., the cyclic dimers of glycolic acid and lactic acid. PLGA is an amorphous polymer with degradation rates of 50–100 days or even up to 1 year in some cases. The fastest half-life degradation of PLGA copolymers with 50:50 lactide: glycolide is between 50 and 60 days (Ansary et al. 2014). PLGA is soluble in several organic solvents. It can also be easily electrospun into nano-/micro-fibrous mats to form a randomly oriented, non-woven scaffold. It is hydrophobic in nature when compared

to the natural ECM and hence cannot interact with cells and does not have the required functional groups for bonding with the biologically active molecules. PLGA has subunits that contain elevated levels of methyl functional groups making it even more hydrophobic (Croll et al. 2004). PLGA can be synthesized in different weight ratios of lactide and glycolide during polymerization (e.g., 75:25 PLGA contains 75% lactic acid and 25% glycolic acid). Lower MW (<10 KDa) PLGA can be synthesized from the polycondensation of LA and GA at temperatures greater than 120 °C under the complete water removal conditions (Gentile et al. 2014). ROP combines lactide and glycolide using metal catalysts (tin (II) 2-ethyl hexanoate, tin (II) alkoxides, or aluminum isopropoxide) at the high temperature ranging between 130 and 220 °C to yield high MW PLGA. The $SnOct_2$ is the most commonly used catalyst and a food additive (Kowalski et al. 2000).

Recently, Li et al. (2011) proposed a novel mechanism to yield a repeating sequence of PLGA with different tacticities using 1,3-diisopropylcarbodiimide (DIC) and 4-(dimethylamine) pyridinium p-toluenesulfonate (DPTS) as initiators. The resulting PLGA with a sequence and stereochemistry was highly controlled that allowed to tailor and reduce the hydrolysis rate (Gentile et al. 2014). The crystallinity of PLGA mainly depends on its block structure and molar ratios and the T_g of PLGA range from 40 to 60 °C. PLGA containing higher lactide contents can be easily soluble in chlorinated solvents while the PLGA with higher glycolide contents can be dissolved readily in fluorinated solvents such as HFIP (Pavot et al. 2014). Lactide-rich PLGA copolymer is less hydrophilic in nature as LA is more hydrophobic than GA and thereby the degradation rate is more gradual. Generally, the degradation rate will be slower for polymers with low MW, high hydrophilic nature, high amorphous nature, and also for copolymers with higher glycolide content (Mirakabad et al. 2014; Kim et al. 2004). The LA and GA under normal physiological conditions are produced as by-products of various metabolic pathways in the body. The toxicity in the body is almost negligible; since PLGA undergoes degradation by simple hydrolysis in the body, making it ideal for drug delivery, bone regeneration, etc. Also, PLGA can be used for producing various biomedical devices (Pavot et al. 2014; Mirakabad et al. 2014). One of the main advantages of PLGA NS is that they can be easily complexed with hydrophilic molecules for modifying the surface and internal morphology of the NFs for delivering a payload of hydrophilic/hydrophobic drugs. The morphology, porosity, and composition of PLGA can be altered by controlling its degradation kinetics (Stevanoviae et al. 2007).

PLGA in the microspheres and nanoparticles form is extensively used for sustained drug release such as anticancer, antibiotics, peptide, and protein drugs (human growth hormone, BSA, insulin, lysozymes). PLGA is highly biocompatible and biodegradable polyester that is commonly used as a biomaterial for a variety of DDS in the form of blends, films, matrices, microspheres, nanoparticles etc. PLGA nanoparticles are used for delivering various drugs such as antipsychotics, anesthetics, antibiotics, antiparasitics, antitumors, hormones, and proteins (Gilding and Reed 1979). The MW of PLGA influences the mechanical strength of the polymer used for formulating a drug delivery device. The physical property also affects the

degradation rate and hydrolysis of PLGA. The crystallinity of the PLGA directly influences the mechanical properties, swelling behavior, hydrolysis, and biodegradability (Mirakabad et al. 2014; Lee et al. 2014).

Xin et al. (2007) synthesized PLGA via ES with 85:15 molar ratio of PLA: PGA. The PLGA non-woven fibers were obtained with an average diameter of 760 ± 210 nm and tested for viability, growth, and differentiation of hMSCs, their osteogenic (hMSCs-Ob) and derivatives of chondrogenic (hMSCs-Ch). The SEM micrographs demonstrated that the PLGA NFs were well attached to the hMSCs, hMSCs-Ob, and hMSCs-Ch. The authors suggested the electrospun PLGA MFs for tissue engineering applications. Wang et al. (2014) fabricated recombinant fibronectins (rFN)/Cadherin (CDH) loaded collagen/PLGA NS and estimated their effects on the differentiation and adhesion of hMSCs. The scaffold efficiency was assessed by investigating the viability, morphology, and osteogenic gene expression levels of hMSCs. The rFN/CDH discharge from PLGA NFs was examined using liquid chromatography–mass spectroscopy. Both rFN and CDH improve the osteogenesis and cell adhesion. It was noted that the controlled and sustained discharge of rFN/CDHs improves the proliferation of hMSCs and also induces osteogenic gene expression. The hMSCs differentiation into osteoblasts may be induced by rFN/CDHs, and hence, the rFN/CDH loaded collagen/PLGA NFs have great potential in bone tissue engineering.

Ajalloueian et al. (2014) prepared a novel CS/PLGA blended NFs through an emulsion ES process with PVA as an emulsifier. The extraction of PVA from the as-spun NFs resulted in CS/PLGA NFs as the final product. The CS content in PLGA solution was adjusted from 0 to 33%. It was found that the CS/PLGA nanofibrous mats are more hydrophilic in nature than the pure PLGA nanofibrous mats. Further, the tensile strength of CS/PLGA NFs in dry and wet conditions is 4.94 and 4.21 MPa implying that these NFs are very much strong for various biomedical applications. Also, the CS/PLGA NFs enhance the fibroblast attachment and proliferation as compared to neat PLGA NFs as revealed from cell structural studies. Thus, the authors concluded that the CS/PLGA NFs can be potentially used for skin tissue regeneration. Heo et al. (2014) prepared HA/PLGA NFs via ES and the morphological studies revealed that the PLGA NFs resembled the natural ECM and also showed the presence of HA. The cell adhesion test showed that the gelatin adheres well to the electrospun NFs. The electrospun HA/PLGA NFs used along with gelatin are suitable for bone repair applications.

Yu et al. (2015) used carbon nanotubes (CNTs) as carriers to load an anticancer drug (DOX) which was then incorporated into PLGA NFs via ES to form a DOX @ CNTs/PLGA NFs (Fig. 12). The release profiles of DOX-loaded NFs were studied, and the in vitro antitumor effectiveness on HeLa cells was detected. The release of DOX was sustained and controlled from the electrospun NF mats, making it suitable for biomedical applications where the drug molecule is required to maintain long-term effectiveness against cancer. The release profiles also revealed that the DOX can be incorporated into inner cavities or on the outside surface of the CNTs, so as to hinder the initial burst release of DOX. The electrospun DOX @ CNT/PLGA NFs also effectively restricts the cell viability of HeLa cells in vitro

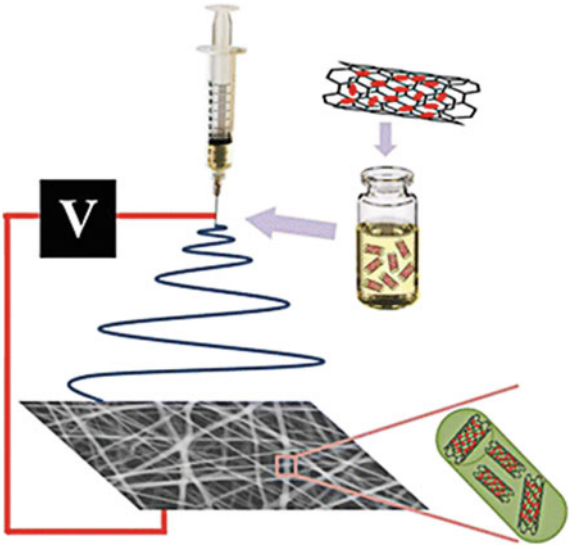

Fig. 12 ES process of DOX @ CNTs/PLGA composite NFs (Yu et al. 2015). Copyright 2015. Reproduced under creative common license

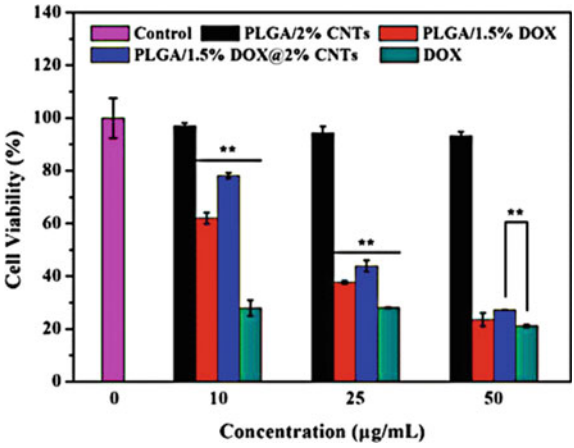

Fig. 13 Cell viability of HeLa cells of various specimens with different DOX concentrations (Yu et al. 2015). Copyright 2015. Reproduced under creative common license

(Fig. 13). Electrospun DOX @ CNTs/PLGA composite NFs can be used for chemotherapy in clinical cancer treatment because of the long-term drug release. Wei et al. (2012) synthesized a fluorescein isothiocyanate–dextran (FITC-D)/PLGA NF composite scaffolds which were dissolved in water and emulsified into the PLGA/oil phase for emulsion ES process. The core–shell structure of the prepared NFs helped in the controlled release of the model drug from the NFs. In the first 2 weeks, the burst release profile was up to 60% after which the NFs displayed a release profile of about 1% for the next 4 consecutive weeks. Thus, the electrospun FITC drugs loaded PLGA NFs exhibited a release profile suitable for site-specific drug release systems (Thangamani et al. 2017).

Khalil et al. (2013) prepared and characterized electrospun Ag NPs/PLGA composite NFs for biomedical applications. Ag NPs of particle size 5–10 nm were incorporated into PLGA matrix without any chemical and structural modifications to form an organic–inorganic nanocomposite. The ES parameters were controlled by optimizing the applied voltage to 20 kV, tip–collector distance of 14 cm, and solution feed rate of 0.5 ml/h to form Ag NPs/PLGA NFs. The size of the NFs was 50–100 nm. The authors suggested the use of Ag NPs/PLGA composite NFs as an internal aid for water/air filter membranes and for long-lasting antimicrobial wound dressings. Woo et al. (2010) examined the porous electrospun PLGA NFs containing (1,3)-(1,6)-β-D-glucan (β-glucan) and their influence on adhesion, proliferation, migration, collagen gel contraction, cytotoxicity assay of adult human dermal fibroblast (aHDF) and adipose tissue-derived stem cell (ADSC). The pure β-glucans and the porous β-glucan/PLGA NFs supported and improved the cellular responses, proliferation, and migration of HDFs and ADSCs. The cytotoxicity assay revealed that the porous β-glucan/PLGA NFs are biologically safe for enhancing wound healings. Song et al. (2012) fabricated and analyzed the dual drug-loaded mesoporous silica nanoparticles (MSNs)/PLGA composite NF mats via ES. The dual model drug, viz. fluorescein (FLU) and rhodamine B (RHB), was loaded into the MSNs/PLGA during the ES process. The schematic diagram of the ES process wherein the dual drugs are loaded into the MSNs/PLGA NFs are depicted in Fig. 14.

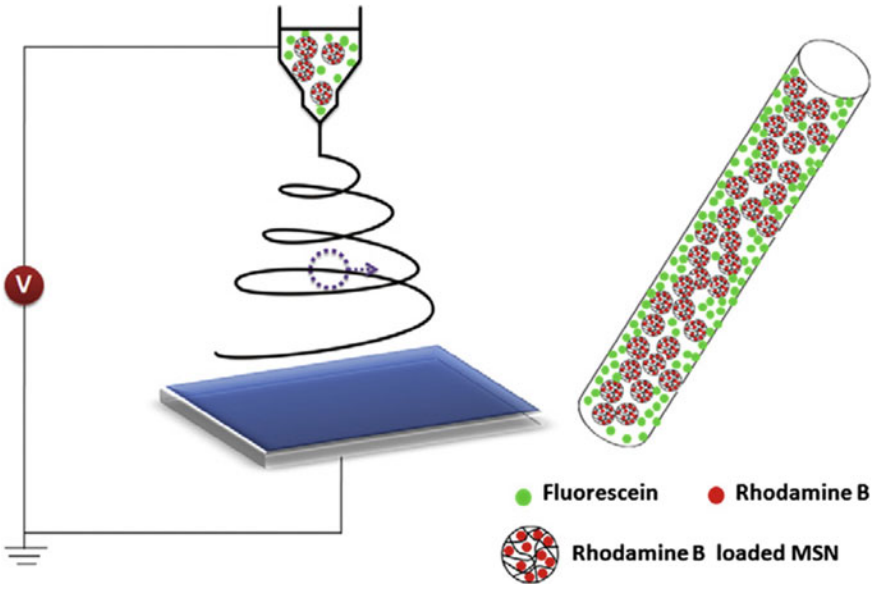

Fig. 14 Schematic diagram of the ES process wherein the dual model drugs are loaded into the MSNs/PLGA NFs (Song et al. 2012). Copyright 2012. Reproduced with permission from Elsevier Ltd.

The amount of FLU was kept constant throughout the experiment (5% wt%), whereas the different amount of RHB was loaded to MSNs (5, 15, and 25% wt%) to study their releasing properties. The release profiles of the dual model drug-loaded electrospun NF mats revealed that the FLU and RHB discharge from the FLU/RHB-loaded MSNs/PLGA NFs exhibit separate and distinct profiles. It was observed that most of the FLU was discharged promptly during the 324 h of the trial period while the RHB displayed controlled and sustained release behavior over the given trial period. The sustained release of RHB in the given trial period was because of the presence of MSNs in the NF mats. The release rates were evaluated depending on the location of the drugs in the electrospun NF mats. The FLU was located in the PLGA matrix, and hence, the release rate was rapid. The RHB displayed a sustained release behavior, mainly because of the hindrance from the MSNs and polymer matrix around the MSNs. The MSNs content in the dual drug-loaded mats controls the RHB release rate. The dual drug-loaded electrospun MSNs/PLGA NF mats when compared to the single drug-loaded system is expected to show different release kinetics which can be used for functional wound dressing and tissue engineering applications. Several biomedical applications of electrospun PLGA composite NFs are given in Table 4.

Table 4 Biomedical applications of electrospun PLGA composite NFs

ES type	PLGA-based composites NFs	Biomedical applications	References
Traditional ES	PLGA	Tissue engineering, 3D carrier vehicle for lineage specific cells	Xin et al. (2007)
Coaxial ES	rFN/CDHscollagen/PLGA	Bone tissue engineering	Wang et al. (2014)
Emulsion ES	CS/PLGA	Skin tissue regeneration	Ajalloueian et al. (2014)
Traditional ES	HA/PLGA	Bone repair	Heo et al. (2014)
Traditional ES	DOX @ CNTs/PLGA	Chemotherapy in clinical cancer treatment, drug release	Yu et al. (2015)
Emulsion ES	FITC-Dextran/PLGA	Site-specific drug release systems	Wei et al. (2012)
Traditional ES	Ag NPs/PLGA	Internal aid for water/air filter membranes, wound dressing agents	Khalil et al. (2013)
Traditional ES	β-glucan/porous PLGA	Wound healing	Woo et al. (2010)
Traditional ES	FLU and RHB-MSNs/PLGA	DDS, functional wound dressing, tissue engineering	Song et al. (2012)

2.5 *Biomedical Applications of Polycaprolactone-Based Electrospun Composite Nanofibers*

PCL is biodegradable polyester with a melting point ~60 °C and T_g about −60 °C. PCL can be shaped or molded with bare hands. It can also be reheated, reshaped again and again (Mohamed and Yusoh 2016). It resembles nylon when it gets hardened. PCL is considered as non-hazardous, biodegradable and can be colored with fruit colors. The modulus of elasticity is typically around 440 MPa with the tensile strength approximately around 16 MPa. PCL, which is compatible with most of the materials, is usually mixed with starch for lowering its cost and increasing its biodegradability. ROP using catalyst ($SnOct_2$) is a common method of preparing PCL (Woodruff and Hutmacher 2010). Although PCL evokes a very mild inflammatory response, the intrinsic hydrophobic nature of PCL limits the cell attachment and growth (Choong et al. 2004). For enhancing the hydrophilicity of PCL homopolymer, it is copolymerized with hydrophilic blocks (Li et al. 2002). This copolymerization of PCL with a hydrophilic block enhances cell attachment and hydrophilic degradation. PCL-PEG-PCL triblocks at particular compositional ratios of PCL: PEG offers excellent support for human endothelial cell growth. In the human body, PCL undergoes hydrolysis of its ester linkages and gets degraded, thereby conquering immense attention as an implantable biomaterial. It has been found that the degradation rate of PCL is much slower than that of PLA. PCL has been declared as a safe polymer by FDA and can be used in the human body, for example, drug delivery device, suture, or adhesion barrier (Mohamed and Yusoh 2016). It is also used as scaffolds for tissue repair, guided bone, and tissue regeneration (GBR). Numerous drugs have been encapsulated within PCL beads for controlled discharge and targeted drug delivery. PCL has been vastly used in dentistry field as a night guard component and in the root canal filling due to its excellent biodegradability (Hirashi et al. 2007). Because of its hydrophobicity, PCL degrades very slowly and hence becomes a potential candidate for applications such as controlled DDS and implants for orthopedic surgery (Cohn et al. 2002).

Boakye et al. (2015) fabricated Keratin/Magnesium oxide (MgO)/PCL composite NFs by ES with diameters of as-spun NFs ranges from 0.2 to 2.2 μm. Keratin was successfully extracted from human hair by modifying the usual methods. The novel Keratin/MgO/PCL composite NFs possessing suitable structural and mechanical property is highly suggested for tissue engineering. Lee et al. (2008) fabricated collagen (type 1)/PCL NFs using ES for vascular tissue engineering applications. The obtained NS displayed very good biocompatibility, cell growth, and cell proliferation in vivo. Fujihara et al. (2005) prepared a GBR membrane using $CaCO_3$/PCL composite NFs via layer-by-layer (LBL) ES. The GBR membrane obtained using LBL ES method constituted of two layers of a $CaCO_3$/PCL and a layer of PCL NFs for mechanical support having high tensile strength. Hiep et al. (2010) synthesized PLGA/PCL copolymer NFs with different compositions. The cytocompatibility test revealed that the biocompatibility of electrospun NF mats was enhanced with increasing content of PLGA. SEM micrographs clearly

showed the in vitro adhesion and proliferation of fibroblast cells on the prepared NF mats. The enhancement in the mechanical properties of the electrospun NFs was observed due to the increasing concentration of PLGA, making it a trustable biomaterial for biomedical applications.

PCL with and without TiO_2 was electrospun to form NFs with a diameter of 200–800 nm (Ghosal et al. 2014). The NFs were coated with collagen solution (10 and 20 mg/ml) by overnight soaking. The collagen-coated NS exhibited improved hydrophilicity when compared to the uncoated ones. The collagen coating improved the cell adhesion and proliferation. However, the presence of collagen decreases the tensile strength of the scaffold to some extent. Vaz et al. (2005) fabricated bilayered electrospun NS consisting of PLA as the sheath and PCL as the core for bio-mimicking the morphological and mechanical features of a native blood vessel scaffold. The NS cultured on a mouse fibroblasts and human myofibroblasts supported proper cell attachment, spread, and growth. Zhang et al. (2005b) performed the ES method for fabricating ultrafine gelatin NFs and ultrafine gelatin/PCL NFs for investigating the efficiency of NS for bone marrow stromal cell culture. The scaffolds were suitable for surface adhesions and cell migrations up to 114 μm inside the scaffolds.

Repanas et al. (2015) created PEG/PCL NS using ES for evaluating its suitability as a DDS. In this study, dipyridamole (DPA) is used as a model drug. PEG-containing two different chain lengths were used. A comparison between the DPA loaded NFs and without DPA loaded NFs was studied. The DPA loaded NS and that with higher MW was smooth in nature having an average diameter of around 586.75 ± 204.79 nm. Young's modulus was around 0.61 ± 0.05 mm with an ultimate tensile strength (UTS) as 16.79 ± 3.08 MPa. DPA contained in NFs usually undergoes two stages of cumulative release: an initial burst followed by slower Fickian diffusion (release exponent $n = 0.432$). Liao et al. (2006) incorporated bovine and platelet-derived growth factor bb (PDGF-bb) in aligned PCL NFs by coaxial ES for demonstrating the controlled release and bioactivity retention. Zhang et al. (2006) successfully incorporated model protein (fluorescein isothiocyanate-conjugated bovine serum albumin (fitcBSA)) and PEG into the PCL NFs using ES. The fitcBSA loaded into PCL was simply achieved by changing the inner flow rate and keeping constant outer flow rate. Core–sheath fitcBSA-PEG/PCL blended NFs exhibited better sustainability when compared to normal electrospun fitcBSA-PEG/PCL NFs. Zhang et al. (2004) prepared core–shell NFs with PCL as the sheath and gelatin as the core. PCL NFs are encapsulated with two different types of medically pure drugs, i.e., gentamycin sulfate (GS), a water-soluble antibiotic to kill bacteria, and resveratrol (RT), an alcohol-soluble antibacterial antioxidant present in several types of plants using coaxial ES for drug delivery. The release profile of RT and GS was controlled and sustained with no burst release (Huang et al. 2006a).

Chellamani et al. (2014) successfully created PCL NFs and TCH/PCL NFs via ES for assessing their antibacterial properties, in vitro drug release study and wound healing ability. The TCH was added into 15% PCL solutions at varying concentrations of 0.5, 1, 1.5, and 2%. The ES setup was optimized with an applied voltage

Table 5 Biomedical applications of electrospun PCL composite NFs

ES type	PCL-based composite NFs	Biomedical applications	References
Traditional ES	MgO/PCL NFs and K/MgO/PCL	Tissue engineering	Boakye et al. (2015)
Layer-by-layer (LBL) ES	$CaCO_3$/PCL	Guided bone regeneration	Fujihara et al. (2005)
Traditional ES	TiO_2/PCL	Tissue engineering	Ghosal et al. (2014)
Coaxial ES	PLA/PCL	Vascular scaffolds	Vaz et al. (2005)
Traditional ES	Gelatin/CS/PCL	Wound healing	Zhang et al. (2005b)
Traditional ES	DPA-PEG/PCL	Drug delivery	Repanas et al. (2015)
Coaxial ES	Bovine and platelet PDGF-bb/PEG/PCL	Drug delivery	Liao et al. (2006)
Coaxial ES	fitcBSA/PEG/PCL	Drug delivery	Zhang et al. (2006)
Coaxial ES	GS/RT/PCL	Drug delivery	Huang et al. (2006a)
Traditional ES	TCH/PCL	DDS, wound healing	Chellamani et al. (2014)

of 20 kV, tip–collector distance of 10 cm and solution flow rate of 3 ml/h. The morphology of both drug-free and drug-loaded PCL NFs remained unaltered. The TCH-loaded PCL NFs inhibited the bacterial growth and healed the wound 50% faster than standard wound dressing procedure. This indicates that TCH-loaded PCL NFs can perform a dual role as a DDS and also as a wound healing agent. The incorporation of 1,7-bis (3,4-dimethoxyphenyl)-5-hydroxy-1,4,6-heptatrien-3-one into collagen/PCL electrospun NFs facilitates cell migration, growth, and differentiation which is suitable for wound healing applications (Chong et al. 2013). The biomedical applications of various electrospun PCL composite NFs are discussed in Table 5.

2.6 Biomedical Applications of Polyethylene Glycol-Based Electrospun Composite Nanofibers

PEG or PEO is a water-soluble and non-toxic polyether which possesses numerous applications from industrial manufacturing to medicine. PEG, in its common form, is a linear or branched polymer having hydroxyl groups. As different applications need varying chain lengths, PEG and PEO possess MW roughly below 20,000 g/mol and above 20,000 g/mol, respectively. The physical properties of PEG and PEO are different while their chemical properties are almost similar. The different forms of

PEG are available, and their properties mainly depend upon the initiator used during polymerization. Monofunctional methyl ether PEG or methoxypolyethylene glycol (MPEG) is the most commonly used initiator (French et al. 2009; Roberts et al. 2002). The purification and separation of PEG are very difficult, and hence, its cost is ten to thousand-fold greater than that of polydispersed PEG (Winger et al. 2009).

PEG is synthesized by reaction of ethylene oxide with water, ethylene glycol or its oligomers with acidic or basic catalysts used for initiating the reaction. Ethylene glycol and its oligomers are preferred as a precursor in comparison with water because they permit the formation of low dispersity polymers. The ratio of reactants decides the polymer chain length. The polymerization mechanism can be anionic or cationic depending on the catalyst used. For PEG with a low polydispersity, anionic reactions are preferred. Anionic ROP of ethylene oxide is a common method used for the synthesis of PEG (Roberts et al. 2002; Winger et al. 2009; Louis 2012). In pharmaceutical products, PEG is often used as an excipient (Smolinske 1992). PEG is being used in lubricating eye drops (Kovar et al. 2009) and also finds application in chemical, biological, commercial, and industrial sectors. The covalent grafting of PEG derivative onto molecules called as PEGylation specifically enhances the water solubility and biocompatibility which is useful for developing drugs (Ni et al. 2011). PEGylated products especially used for medical applications undergo extensive characterization analysis to check regulatory compliance (Bai and Liu 2014; Baker et al. 2014).

Ni et al. (2011) blended the hybrid amphiphilic PEG and hydrophobic PLA to form NS. The authors observed that PLA/PEG NS showed improved regular and continuous morphology in comparison with pristine PLA fiber mats. Mesenchymal stem cell cultured on prepared PLA/PEG NS favored attachment and proliferation. The MSCs also penetrated through the interstitial pores in the NS and thus bonded exceptionally well with the surrounding. The prepared NS was implanted into the thigh muscle pouches of rats that presented a very good biocompatibility making it useful for bone tissue engineering application. Talebian et al. (2014) prepared a novel hybrid of CS/1.2 wt% PEO and bioactive glass (BG) via ES. The addition of BG into CS/PEO NFs improved the mechanical property as well as hydrophilicity of the NS as evaluated from tensile strength and water contact angle measurements. MTT assay was used for assessing the in vitro cell viability of hMSCs on NFs. This cell adhesion test revealed that the hMSCs were viable at several points on the BG/CS/PEO NS. The BG present in the NS improved the alkaline phosphate activity of hMSCs cultured NS after 14 days when compared to that of pure CS and PEO NS. The authors recommended the BG/CS/PEO NS relevant for tissue engineering applications.

PLLA/PEG NFs were successfully electrospun with fiber diameter ranging between 100 nm and 6 μm (Spasova et al. 2007). The cytocompatibility assay of the NS was tested on human dermal fibroblasts cells and the osteoblast-like cell line MG63. It was observed that both the types of cells attached uniformly and almost equally with the PLLA/PEG NS. For scaffolds containing higher PEG content (PLLA/PEG $\sim$ 70/30), the long-term culturing of osteoblasts-like cells tends to

organize in tissue-like structure. Thus, the PLLA/hydrophilic PEG NFs can be suggested as promising new biocompatible scaffolds for tissue engineering applications. Polyhydrobutyrate (PHB) and PHB/PEO NFs with various concentration of chlorhexidine (CHX) were synthesized for drug delivery applications (Fernandes et al. 2014). The antibacterial activity of electrospun PHB and PHB/PEO NFs in the presence and absence of CHX against *Escherichia Coli* (*E. Coli*) and *Staphylococcus aureus* (*S. Aureus*) were investigated. The antibacterial assay revealed that electrospun NFs containing CHX displayed excellent bactericidal activity. PHB/PEO containing 1% CHX exhibited higher CHX discharge levels and equivalently good antibacterial activity in comparison with PHB/PEO containing 5 and 10 wt% CHX. The NFs containing 1 wt% CHX were assessed for bacterial performance by colony forming units (CFU) wherein 100 and 99.69% reductions of *E. Coli* and *S. Aureus,* respectively, were accomplished.

PCL NFs (sheath portion) with PEG incorporated PDGF-bb (core portion) were fabricated via coaxial ES. The synthesized NFs containing the growth factor were released in a controlled manner for about 2 months retaining its biological activity. Also, the discharge of the growth factor was highly dependent on the MW of PEG (Xu et al. 2005). Xu et al. (2006) incorporated the anticancer drug BCNU (generic name: carmustine) into electrospun PLLA/PEG NF mats with an average diameter of 690–130 nm dependent on the drug loading concentration of 5–30 wt%, respectively. The increase in BCNU loading increases the release rate and initial burst release. The authors examined the impact of BCNU release from the PLLA/PEG NF mats on the rat glioma C6 cells. The BCNU loaded NF mats exhibited anticancer activity for a period of 72 h while the unloaded NF mats exhibited no anticancer activity and the naked BCNU lost its anticancer activity after 48 h. The authors also concluded that the drug encapsulation within the NFs protected it from degradation, and also the controlled release rate of BCNU from the NF mats was observed. Mirzaei et al. (2014) incorporated genipin into CS/PEO solution (90/10) to prepare electrospun NFs which were exposed to water vapor for complete cross-linking. The cytotoxicity of genipin cross-linked NFs was tested on human fibroblast cells which exhibit least toxic effects on fibroblast cells and the moderate amount in genipin. A decent interaction between the fibroblast cells and genipin cross-linked NFs was observed making CS/PEO electrospun NFs as a potential candidate for tissue engineering and wound dressing scaffolds. Xu et al. (2010) successfully incorporated TCH into PLA/PEG NFs via ES, without losing its bioactivity. The drug-loaded NS exhibited controlled release of TCH for a period of 6 days. Antimicrobial studies of TCH-loaded NFs inhibited the *S. Aureus* growth. As the content of antibiotic drug increased in the electrospun membranes, its antibacterial effectiveness was enhanced. The electrospun NFs provide mechanical barriers and have the capacity to deliver the antibiotics in a sustained manner, making it useful for wound dressing of ulcers caused by diabetes or any other disease such as malignant wounds. The various biomedical applications of electrospun PEG composite NFs are given in Table 6.

Table 6 Biomedical applications of electrospun PEG composite NFs

ES type	PEG- or PEO-based composites NFs	Biomedical applications	References
Traditional ES	PLA/PEG	Tissue engineering	Ni et al. (2011)
Traditional ES	CS/BG/PEO	Tissue engineering	Talebian et al. (2014)
Traditional ES	PLLA/PEG	Tissue engineering	Spasova et al. (2007)
Traditional ES	CHX loaded PHB/PEO	Drug delivery	Fernandes et al. (2014)
Coaxial ES	PDGF-bb/PCL/PEG	Drug delivery	Xu et al. (2005)
Traditional ES	BCNU/PLLA/PEG	Drug delivery for cancer treatment	Xu et al. (2006)
Traditional ES	Genipin/CS/PEO	Wound dressing, tissue engineering	Mirzaei et al. (2014)
Traditional ES	TCH-loaded PLA/PEG	Wound dressing for ulcers caused by diabetes or any other disease, malignant wounds	Xu et al. (2010)

2.7 *Biomedical Applications of Polyurethane-Based Electrospun Composite Nanofibers*

PU contains organic units joined by carbamate or urethane link that is available in the form of both thermoset and thermoplastic. The urethane linkages in PU backbone may also contain ester, ether, urea, and aromatic rings. PU is generally prepared by chemical reaction of a di/polyisocyanate and a diol or polyol. Usually, the isocyanate and polyols used for making PUs contain two or more functional groups. The use of isocyanates in making PUs is minimized because of their toxicity. Recently, non-isocyanate-based PUs (NIPUs) have been included as a separate important class of PUs to lessen the severity of health and environment issues. PU has been used for making high resilience foam seats and gaskets, durable elastomeric wheels and tires, synthetic fibers, hard plastic parts such as in electronic instruments, condoms, and high-performance adhesives (Delebecq et al. 2013).

Unnithan et al. (2012) incorporated ciprofloxacin HCl (cipHCl) model drug into the Dextran/PU NFs using ES for testing the antibacterial activity. The interaction parameters such as viability, proliferation, and attachment between the fibroblasts and the Dextran/PU NS and cipHCl/Dextran/PU NS were examined. The drug-containing NS exhibited favorable cell interaction with the fibroblasts. The nanofibrous mat showed a very decent bacterial activity against both gram-positive and gram-negative bacteria. The authors suggested this biomaterial scaffold for wound dressing applications. Unnithan et al. (2014) blended PU, cellulose acetate (CA), and Zein to prepare NFs having a diameter around 400–700 nm via ES. The PU was blended with CA and Zein to obtain good hydrophilicity, excellent cell

attachment, proliferation, and blood clotting ability. The streptomycin sulfate was loaded into the NFs to examine its antimicrobial ability against the gram-negative and gram-positive bacteria. The viability, proliferation, and attachment between fibroblasts and the CA/PU NFs and CA/Zein/PU NFs were also investigated. The blood clotting ability was very much enhanced in CA/Zein/PU NFs in comparison with the pure PU NFs. It was also found that the presence of CA and Zein in the NFs enhanced its hydrophilicity, bioactivity and offered a moist environment for the wound to recover fast (Deshmukh et al. 2017d).

The synthetic PU and natural gelatin were blended into NFs via simple ES method which produced a mean diameter of 0.4–2.1 μm (Kim et al. 2009a). When the gelatin content was gradually decreased, there was an increase in contact angle with a concurrent decrease in water uptake of the prepared gelatin/PU NS. An increase in the gelatin content increases the cell proliferation. The NS exhibited elastic nature due to the increasing content of PU. The authors suggested the gelatin/PU blended NS to be useful in a wound dressing. Wang et al. (2012) prepared PU, heparin loaded gelatin blazered NFs using ES for examining its biocompatibility. PU is known for its elastic and mechanical properties but exhibits hydrophobicity. Gelatin improves the endothelial cell proliferation. Heparin is a highly sulfated linear glucosamine that functions to prevent thrombosis. The PU formed the external layer while the gelatin-heparin formed the inner layer of the NF from ES process. Higher platelet adhesion to external PU layer was observed in comparison with the inner heparin layer which shows that the probability of clot formation within the NS is lesser. Figure 15 depicts the SEM micrographs of the adhesion of platelet on the PU NS and cross-linked gelatin-5 wt% heparin NS, respectively.

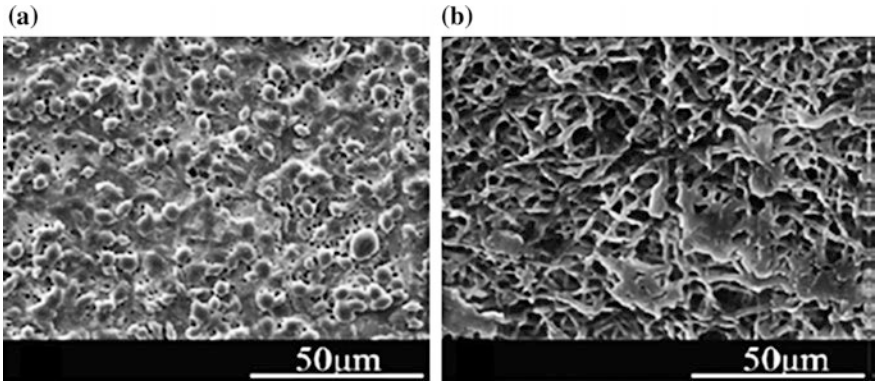

Fig. 15 SEM micrographs of platelet adhesion on **a** PU NS and **b** cross-linked gelatin-5 wt% heparin NS (Wang et al. 2012). Copyright 2012. Reproduced with permission from Springer Ltd.

Wang et al. (2016a) prepared a blend of PU, Keratin, and Ag NPs' NFs using ES for wound dressing applications. Keratin was obtained by extraction from human hair. The extracted Keratin was chemically modified using nondiabetic acid to yield S-carboxymethyl Keratin which was mixed with PU and electrospun. Then, the Ag NPs were prepared in situ to obtain Ag NPs/Keratin/PU NF mats. The addition of Keratin accelerated the fibroblast cell proliferation. The Ag NPs loaded into the NFs did not alter the cytocompatibility. Also, the Ag NPs/Keratin/PU NF mats exhibited good antibacterial activity. The NF mats accelerated wound recovery than that of conventional gauze sponge dressing. It was observed that the synthesized Ag NPs/Keratin/PU NF mats exhibited excellent biocompatibility, antibacterial activity, and negligible inflammatory responses, making them suitable for wound dressing applications. Kim et al. (2014) loaded the biocompatible Propolis (a natural resin) loaded PU NFs using ES. The small quantity of Propolis in the PU matrix improved the hydrophilicity and mechanical strength of the NF membranes. The cytocompatibility and cell behavior assay of the NF mats revealed that the fibroblasts were well seeded to the matrix. The results also claimed that the addition of Propolis into PU matrix increased its cell compatibility. Also, it was found that the NF mats had efficient antimicrobial performance. These desirable properties of the synthesized Propolis/PU NFs offer a promising role in wound dressing and skin tissue engineering. Verreck et al. (2003) loaded drugs Itraconazole and Ketanserin into PU solutions to form NS for wound healing applications. Nanoclay (MMT)/PU nanocomposite NFs were synthesized using ES. Antiseptic drug (Chlorhexidine Acetate) was loaded on to nanoclay which was further incorporated into PU NFs for topical drug delivery applications. The main aim of this study was to understand the release behavior of loaded NFs using nanoclay (Saha et al. 2014). Table 7 depicts various biomedical applications of electrospun PU composite NFs.

Table 7 Biomedical applications of electrospun PU composite NFs

Type of electrospinning (ES)	PU-based composite NFs	Biomedical applications	References
Traditional ES	CA/Zein/PU	Fast wound recovery	Unnithan et al. (2014)
Traditional ES	Gelatin/PU	Wound dressing	Kim et al. (2009)
Coaxial ES	Heparin/gelatin/PU	DDS	Wang et al. (2012)
Traditional ES	Ag NPs/Keratin/PU	Wound dressing	Wang et al. (2016a)
Traditional ES	Propolis/PU	Wound dressing, skin tissue engineering	Kim et al. (2014)
Traditional ES	Itraconazole/ ketanserin/PU	Wound healing	Verreck et al. (2003)
Traditional ES	Chlorhexidine/ nanoclay/PU	Drug release systems	Saha et al. (2014)

2.8 Biomedical Applications of Polyethyleneimine-Based Electrospun Composite Nanofibers

PEI contains repeating units of an amine group and two carbon aliphatic CH_2–CH_2 spacers. Linear PEI (L-PEI) contains secondary amine groups and the branched PEI (B-PEI) contains primary, secondary, and tertiary amino groups. In a totally branched chain, a dendric form of the amino group was reported (Yemuland and Imae 2008). The melting temperature of L-PEI ranges from 73 to 75 °C. The monomer unit of PEI is very simple which consists of a 3-membered ring (i) the 2 corners of the molecule possesses –CH_2 linkages and (ii) the third corner consists of the secondary amine group (=NH). This monomer can be transformed into a highly branched polymer with about (i) 25% primary amine groups, (ii) 50% secondary amine groups, and (iii) 25% tertiary amine groups, in the presence of a catalyst. ROP of aziridine is used for the production of B-PEI (Zintchenko et al. 2008). The post-modification of polymers such as poly(2-oxazolines) can be used to synthesize L-PEI. Furthermore, the hydrolysis of poly(2-ethyl-2-oxazoline) yields L-PEI (Brissault et al. 2003). PEI is used for enhancing the attachment of weakly anchoring cells in cell culture. PEI being a cationic polymer easily gets attracted to the negatively charged outer surfaces of cells, enabling stronger attachments between the cells and the plates coated with PEI (Liu and Liu 2015; Saraf et al. 2010).

Kim et al. (2009b) prepared the PCL/PEI blend NFs via ES to overcome the limitation of high hydrophobic nature of pristine PCL NFs. The PEI being a cationic polymer enhances the cell adhesion. The fiber diameter of the as-prepared NF mats ranges between 150.4 ± 33 and 220.4 ± 32 nm. The PCL/PEI NFs exhibited a good mechanical property, adequate porosity and improved hydrophilicity. The excellent hydrophilic properties of PEI improved the cell adhesion and cell proliferation of the as-spun NF mats, making it suitable scaffolds for tissue engineering applications. Wu et al. (2015) fabricated a novel biocompatible PVA/CO_2 modified PEI (CO_2-PEI) composite NFs using ES process. The CO_2 is used for modifying the surface of the PEI for reducing the cytotoxicity of the PEI. The fiber diameter ranges from 265 ± 53 nm to 423 ± 80 nm. The cytotoxicity assay of the as-spun NF mats was evaluated using the cell growth and proliferation of normal mice Schwann cells which revealed that the NS promoted the cell growth and proliferation. Fan et al. (2016) prepared electrospun PVA/PEI NFs modified with folic acid (FA). Here, the authors cross-linked the PVA/PEI NFs by exposing it to glutaraldehyde vapor which was then modified with FA through PEG spacers and then acetylation of the fiber surface through PEI amines. Despite the surface modification of the prepared FA-modified NFs, its morphology remained smooth and uniform. The hemolysis assay confirmed the good hemocompatibility of the FA-modified NFs. The quantitative cell counting assay and confocal microscopy results bespeak that the FA-modified PVA/PEI NFs were suitable specifically for capturing cancer cells overexpressing FA receptors. Hence, the authors suggested that the FA-modified PVA/PEI NFs can be potentially used for capturing circulating tumor cells during cancer cell diagnosis.

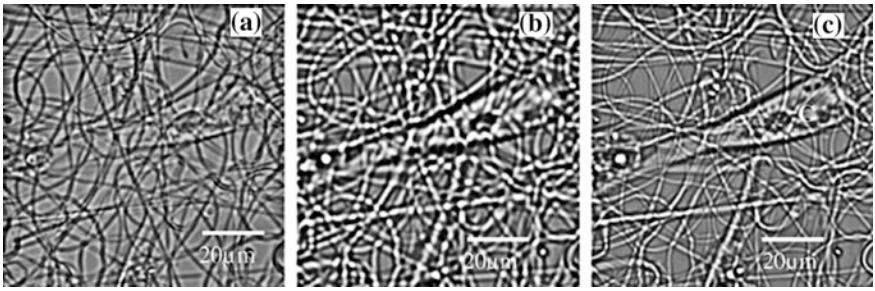

Fig. 16 DIC images **a** focused on the top view of NHF cells, **b** focused on the 3D L-PEI NS where the cell is inserted into pores, after 5 days of culture, **c** focused on the NHF cells (Khanam et al. 2007). Copyright 2007. Reproduced with permission from Elsevier Ltd.

Vongsetskul et al. (2012) prepared composite NFs of polymethyl methacrylate (PMMA)/PEI particles embedded in PVP using ES method. 18% w/v aqueous PVP solution was blended to 2% w/v PMMA/PEI particles with different pH concentrations. The prepared solution was electrospun with applied voltages (10, 12, 14, and 16 kV), tip–collector distance of 10 cm, yielding fibers with a diameter in the range of 141–353 nm. It can be noted that the ES at pH 2 concentration of PMMA/PEI with an applied electrical voltage of 14 kV produced smaller and uniform composite NFs, potentially useful in biomedical applications as DDS. Khanam et al. (2007) fabricated a novel biocompatible NS of cross-linked L-PEI with succinic anhydride (SA) and 1,4-butanediol di-glycidyl ether. The PEI non-woven NF mats were obtained with the diameter range of 687–1000 nm and were tested on normal human fibroblast (NHF) cells for examining their interaction and growth. The SEM, optical and fluorescence microscopy was used for studying the growth pattern of NHF cells in the NS. Figure 16 shows the differential interference contrast (DIC) images of the L-PEI NS and NHF cells. The fluorescence analysis bespeaks that the NHF cells were very well attached, spread throughout, and supported by the cross-linked L-PEI NS (Fig. 17). The authors unraveled the potential of this biomaterial scaffolds for tissue engineering application. The high surface to volume ratio of L-PEI electrospun NFs favored cell attachment by mimicking the 3D native ECM which is capable to serve as skin substitutes. Table 8 depicts the biomedical applications of electrospun PEI composite NFs.

2.9 Biomedical Applications of Polypyrrole-Based Electrospun Composite Nanofibers

The intrinsic conducting polymers (ICPs) have been given immense attention as advanced materials in the recent years. One such polymer is PPy which has been used for various applications due to its good environmental stability, simple

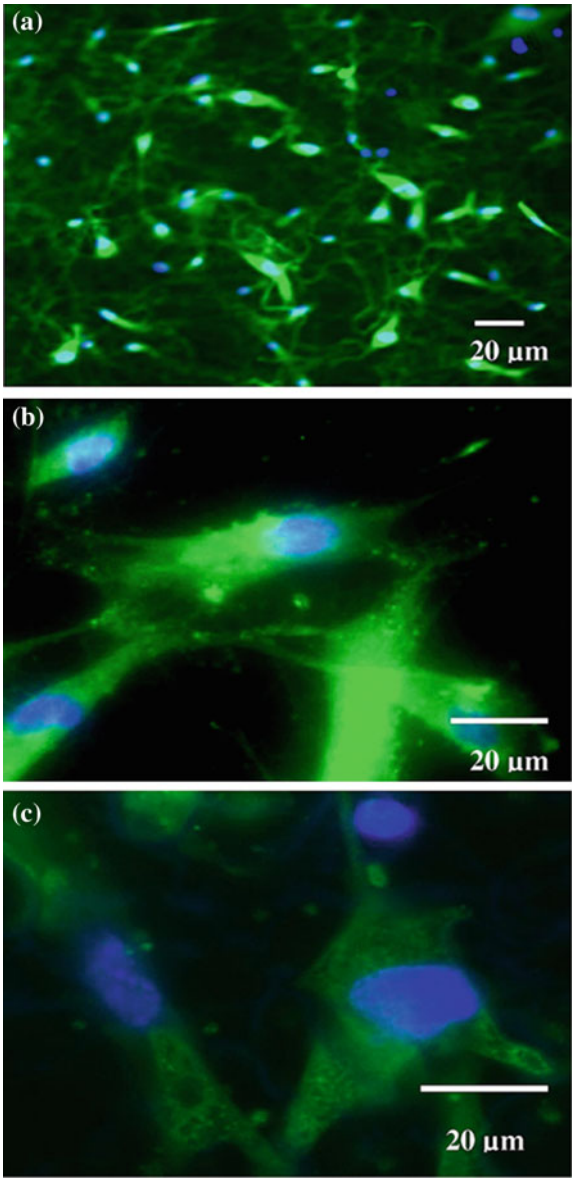

Fig. 17 Fluorescence microscopy images of fixed NHF cells on L-PEI NS at magnifications **a** 10X, **b** 40X, **c** 60X (Khanam et al. 2007). Copyright 2007. Reproduced with permission from Elsevier Ltd.

synthesis, and higher conductivity in comparison with other conducting polymers (Wang et al. 2001; Nagaraj et al. 2018). The facile synthesis of PPy includes an oxidative chemical or electrochemical polymerization of pyrrole (Huang et al. 2014; Balint et al. 2014; Kaur et al. 2015). In the oxidative polymerization process, the first step includes one-electron oxidation of pyrrole to a radical cation, which then couples with another radical cation to yield the 2,2-bi-pyrrole. The repetition

Table 8 Biomedical applications of electrospun PEI composite NFs

ES type	PEI-based composite NFs	Biomedical applications	References
Traditional ES	PCL/PEI	Tissue engineering	Kim et al. (2009)
Traditional ES	PVA/CO_2 modified PEI	Tissue engineering	Wu et al. (2015)
Traditional ES	FA-modified PVA/PEI	Cancer cell capturing applications	Fan et al. (2016)
Coaxial ES	PMMA/PEI	DDS	Vongsetskul et al. (2012)
Traditional ES	SA/1,4-butanediol di-glycidyl ether/L-PEI	Skin tissue engineering	Khanam et al. (2007)

process leads to longer chains. Electrochemical synthesis method is generally preferred for research purposes because of its simplicity, control on material thickness, geometry and location, easy doping during the process itself, wide range of available dopant ions and the geometry and location, easy doping during the process itself, wide range of available dopant ions and the generation of good quality films. Depending on the dopant type and extent, the electrical conductivity of PPy can be increased from 10^{-12} to 10^{2} S/cm (Balint et al. 2014). The unique electrical property and facile synthesis of PPy make it relevant material for biomedical applications; for instance, PPy biosensors modulate cellular activities such as cell adhesion, migration, DNA production, and protein secretion (Huang et al. 2014). PPy is considered as an excellent smart biomaterial because of its rapid stimulus responsiveness, good biocompatibility and chemical stability and excellent conductivity. Currently, the PPy is used in numerous applications such as fuel cells, corrosion protection, computer displays, and microsurgical tools and as a biomaterial in neural tissue engineering, neural probes, nerve guidance channels, and blood conduits (Kaur et al. 2015; Deshmukh et al. 2015).

Sudwilai et al. (2014) prepared a new biomaterial by coating electrospun PLA with a PPy conducting polymer for neural tissue engineering. The cytotoxicity assay of PPy-coated electrospun PLA NS is found to be non-toxic in nature. The NS supported the migration of neural progenitor cells. Under electrical stimulation, the neurons devised from progenitor displayed long neurite outgrowth. PPy-coated electrospun PLA NFs also exhibited good biocompatibility with neural progenitor cells. This nanofibrous material can be used as a potential candidate for controlling progenitor cell behaviors and also may enhance neural repair. Lee et al. (2009) prepared electrically conductive NFs and examined its effect on electrical stimulation. PPy was grown on random and aligned electrospun PLGA NFs to form conductive meshes. In comparison with non-coated PLGA control meshes, the PPy-coated electrospun PLGA nanofiber meshes (Fig. 18a) favored the growth and differentiation on rat pheochromocytoma 12 (PC 12) cells and hippocampal neurons. This suggests that PLGA/PPy conductive NFs may be suitable as neuronal tissue scaffolds. The SEM image of the single strands and section of PLGA/PPy NFs is shown in Fig. 18b. PC12 cells were stimulated electrically with a potential of 10 mV/cm on PLGA/PPy scaffolds, which showed 40–50% longer neurites with

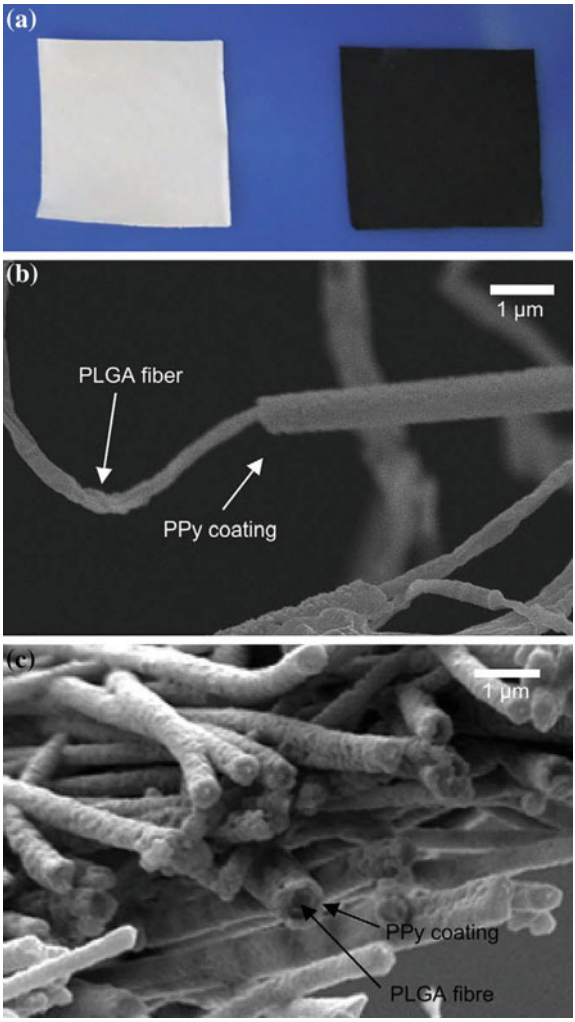

Fig. 18 **a** Photograph of electrospun pristine PLGA nanofibrous mat (white) and electrospun PPy-coated PLGA NF mats (black); SEM image of **b** single strands and **c** section of PLGA/PPy NFs (Lee et al. 2009). Copyright 2009. Reproduced with permission from Elsevier Ltd.

40–90% more neurite formation as compared to unstimulated cells tested on the same scaffolds. The section of PLGA/PPy NFs is magnified in SEM image (Fig. 18c). It was also noted that the aligned PLGA/PPy NFs stimulated cells with longer neurites and more neurite containing cells in comparison with pure PLGA/PPy NFs. This study suggests a synergistic effect of electrical stimulation and topographical guidance in PPy-coated PLGA NFs and its potential use as neural tissue engineering scaffolds and for neural interfacing. Aznar-Cervantes et al. (2012) successfully coated silk fibroin NFs and microfibers with PPy uniform films by polymerization method for biomedical applications. The results displayed that potential of both uncoated and coated PPy electrospun silk matrices to support ahMSCs (adult hMSCs) or human fibroblasts (hFb) adherence and proliferation

Table 9 Biomedical applications of electrospun conducting PPy composite NFs

ES type	PPy-based composite NFs	Biomedical applications	References
Traditional ES	PLA/PPy	Nerve tissue engineering	Suwilai et al. (2014)
Traditional ES	PLGA/PPy	Neural tissue engineering,	Lee et al. (2009)
Traditional ES	Silk fibrion/PPy	Tissue engineering	Aznar-Cervantes et al. (2012)

in vitro. It was found that the bioactivity of fibroin mesh was better than the PPy-coated silk fibroin NS. Table 9 shows several biomedical applications of electrospun conducting PPy composite NFs.

2.10 Biomedical Applications of Polyaniline-Based Electrospun Composite Nanofibers

PANI, which is also known as aniline black, is the second most important conductive polymer after PPy. Based on its level of oxidation, it exists in three forms (i) fully oxidized pernigraniline base (PB), (ii) half oxidized emeraldine base (EB), and (iii) fully reduced leucoemeraldine base (LB). Among them, EB is the most stable and conductive form of PANI. The benefits of PANI are numerous which includes easy synthesis, low cost, high environmental stability, and the capacity to electrically shift between its conductive and resistive states by doping and de-doping process (Wang et al. 2016b). The use of PANI in biomedical fields is limited mainly because of its poor processability, lack of flexibility and non-degradability, resulting in chronic inflammation after implantation and low cell compatibility. The processing of PANI is challenging as it is poorly soluble in most of the available solvents (Kaur et al. 2015). PANI also has excellent electrical, optical, mechanical, and magnetic properties. The oxidation and protonation state of PANI control its electrical properties. There are humongous routes for preparing PANI which includes chemical routes, i.e., hard and soft physical template synthesis and several lithographic techniques (MacDiarmid 2001). There are numerous limitations in using these preparation techniques, namely requirement of post-synthesis process, relatively poor size control and morphology uniformity, the poor orientation of nanostructure arrays and high cost, has hindered their production on an industrial scale. It is found that physical routes such as ES will be suitable for mass production when compared to above-mentioned chemical routes.

The potential applications of PANI include in electrical devices, flash welding, sensors and actuators, rechargeable batteries, electromagnetic shielding devices and biomedical applications (Huang et al. 2006b). PANI is one of the most useful conducting polymers that have tremendous potential to be used as conductive

substrates for tissue engineering applications (Li et al. 2006). The tunable electroactivity of the PANI has been quite recently explored in the biological field. The pure PANI and its blended form have been found to support cell growth. PANI has been investigated as a suitable biomaterial in biomedical research fields as the oxidative state of PANI can be varied easily (Tiwari et al. 2013). PANI, like many other conductive polymers, is not naturally biodegradable. However, it can be made biodegradable by forming composites, blending PANI with a biodegradable polymer, altering its backbone to permit degradability or preparation of short PANI chains for gradual erosion (Molapo et al. 2012). Blending PANI with a biodegradable or a biocompatible polymer via ES to form NFs is found to be very useful in tissue engineering applications (Gizdavic-Nikolaidis et al. 2010). Conducting polymers usually contracts upon reduction and expand after oxidation, i.e., a reversible electrochemical response. This unique feature permits the controlled release of various kinds of drugs. Till date, only a few works have been reported on electrospun PANI blends, particularly for controlled drug delivery applications.

Li et al. (2006) prepared electrospun gelatin/PANI NS for tissue engineering applications. The gelatin/PANI was electrospun for different volume ratio of 85:15, 70:30, 55:45, and 40:60, respectively. The prepared solutions were electrospun with an applied voltage of 10 kV and the tip–collector distance of 10 cm. It was observed that an increase in the PANI content from 0 to 5% w/w reduces the fiber diameter. These observations show that addition of few percentage of PANI to gelatin results in the complete change of the physicochemical properties of gelatin. The results clearly show that the electrospun conducting gelatin/PANI NFs was cultured on H9C2 rat cardiac myoblasts which resulted in high biocompatibility, readily supported cell attachment, migration, and proliferation. The authors recommended the novel conductive gelatin/PANI NF materials as a biocompatible scaffold for tissue engineering.

Prabhakaran et al. (2011) fabricated blends of PLLA/PANI NFs via ES in the ratio of 85:15 with a fiber diameter of 195 ± 30 nm. This NF mats exhibited a conductance of 3×10^{-9} S/cm using 2-point probe measurement. It was observed that the in vitro electrical stimulation of the nerve stem cells cultured on PLLA/PANI NS with an applied electrical potential up to 100 MV/mm for 60 min led to extension of neurite outgrowth in comparison with the cells grown on non-stimulated scaffolds. The neurite elongation was observed due to the electrical stimulation of conducting NS on the nerve stem cells demonstrating its application in nerve tissue regeneration. Mckeon et al. (2010) successfully prepared poly(D,L-Lactide) (PDLA)/PANI NFs using ES to examine its conductivity and biocompatibility. Only at 25 wt% of PANI in the NF blends, promising results were observed. Specifically, at this wt% the NS was able to conduct a current of 5 mA with an electrical conductivity of 0.0437 S/cm. This novel NS was able to attach and proliferate on primary rat muscle cells, though the NFs degraded during the process. This primary degradation and shrinkage restrict the NS to be used in biomedical application but it seems to be useful as a biocompatible coating on sensor devices, etc. (Llorens et al. 2013).

Table 10 Biomedical applications of electrospun conducting PANI composite NFs

ES type	PANI-based composites NFs	Biomedical applications	References
Traditional ES	Gelatin/ PANI	Tissue engineering	Li et al. (2006)
Traditional ES	PNIPAm/ MWCNTs/ PANI	Tissue regeneration	Tiwari et al. (2013)
Traditional ES	PLLA/PANI	Nerve tissue regeneration	Prabhakaran et al. (2011)
Traditional ES	PDLA/PANI	Biomedical applications, biocompatible coating on sensor devices	McKeon et al. (2010) and Llorens et al. (2013)
Traditional ES	PCL/CSA/ sPANI	Cardiac tissue regeneration	Borriello et al. (2011)

Borriello et al. (2011) fabricated composite NFs substrate prepared using polyaniline synthesized (sPANI) in the laboratory, doped with camphor sulfonic acid (CSA) and PCL via ES process and investigated the prepared NFs for cardiac tissue regeneration. The conductivity assay revealed that sPANI short fibers offered a highly effective transfer of electrical signal due to the spatial arrangements of the electroactive phases to form a percolative network. Thus, the PCL/sPANI electrospun NF membranes potentially mimic the morphological or functional features of cardiac muscle ECM. The PANI needles offered conductive signals and thus stimulated the cardiogenic differentiation of hMSCs into cardiomyocyte cells which were observed using the biological tests. These primary studies on electroactive biodegradable substrates pave a broad way to a new class of synthetic patches that support the regeneration of damaged myocardium (Llorens et al. 2013). Electrospun poly(N-isopropylacrylamide) (PNIPAm)/CNTs/PANI NFs were investigated by Tiwari et al. (2013). PNIPAm, MWCNTs, and PANI offered balanced hydrophilic functions, mechanical strength, and conductance, respectively, to the NS and hence supported an excellent cell proliferation and viability suitable for tissue regeneration applications. Table 10 depicts the biomedical applications of various electrospuns conducting PANI composite NFs.

2.11 Biomedical Applications of Poly (3,4-ethylenedioxythiophene)-Based Electrospun Composite Nanofibers

PEDOT is a derivative of polythiophene (PT) and it is the third most studied conjugated polymer. PEDOT is normally synthesized by the polymerization of the 3,4-ethylene dioxythiophene. PEDOT, in comparison with PT, has a dioxyalkylene bridging group across 3- and 4-positions of its heterocyclic ring which is

responsible for its low band gap, low reduction and oxidation (redox) potential, good electrical and environmental stability, good electrical and thermal conductivity, and good optical transparency in its conducting state than PPy (Pyshkina et al. 2010). The insolubility nature of PEDOT was evaded by using it with water-soluble polyelectrolyte, namely polystyrene sulfonic acid (PSSA), which acts as a charge balancing dopant during the polymerization, resulting in PEDOT: polystyrene sulfonate (PEDOT: PSS) which is a water-soluble conducting polymer having high conductivity, high visible light transmissivity, and excellent stability (Mohanapriya et al. 2016a).

Groenendaal et al. (2000) classified the production of PEDOT derivatives into three types of polymerization reaction, which includes (i) oxidative chemical polymerization of 3,4-ethylenedioxythiopene (EDOT)-based monomers, (ii) electrochemical polymerization of EDOT-based monomers, and (iii) transition metal mediated coupling of dihalo derivatives of EDOT. The chemical oxidative polymerization of EDOT monomer is carried out using oxidizing agents such as $FeCl_3$ or $Fe(OTS)_3$. The electrochemical polymerization requires only a very small quantity of monomers and short polymerization times which results in both electrodes supported and freestanding films. PEDOT has well-established biocompatibility, and presently, it is being used in biosensing and bioengineering applications such as neural electrodes, nerve grafts, heart muscle patches. PEDOT can be fabricated in various nano-structural forms such as nanofilms, nanorods, and NF mats (Huang et al. 2014).

Sharma et al. (2015) investigated the PEDOT composite and temperature responsive PNIPAm NS for tissue engineering. The pristine PNIPAm NS and PNIPAm/PEDOT composite NFs were synthesized via normal ES technique. The biocompatibility of the PNIPAm/PEDOT NFs was studied by seeding the L929 fibroblast cells on the NF surfaces. The result revealed that the PNIPAm/PEDOT NFs exhibit highest cell growth with 98% which indicates its potential to be used as a scaffold for tissue engineering. Chang et al. (2016) used ES method for preparing NF composite membranes of PLA and a natural polymer namely poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV). These NF membranes were made conductive by dipping it with PEDOT: PSS solution. Using MTT assay, in vitro cell cytotoxicity and cell viability of the PEDOT: PSS-coated PLA/PHBV NFs and uncoated PLA/PHBV NFs were studied by attaching the NFs to the surface of human skin fibroblast (HSF cells). Uniform NFs with no beads were produced for 20% w/v PLA/PHBV with a 50:50 weight ratio. The wettability and surface roughness of PLA/PHBV NF membranes coated with PEDOT: PSS were greatly enhanced in comparison with the uncoated membrane. The obtained results for cell viability from MTT assay revealed that the conductive PEDOT: PSS-coated PLA/PHBV NF membranes will be highly useful for tissue engineering as compared to their uncoated counterparts.

Jin et al. (2013) developed a novel and facile technique for creating PEDOT NF mats via ES in combination with in situ interfacial polymerization. The as-spun PEDOT NF mats exhibited enhanced mechanical properties with a tensile strength of 8.7 ± 0.4 MPa, Young's modulus 28.4 ± 3.3 MPa and excellent flexibility.

Table 11 Biomedical applications of electrospun conducting PEDOT composite NFs

ES type	PEDOT-based composites NFs	Biomedical applications	References
Traditional ES	PNIPAm/PEDOT	Tissue engineering	Sharma et al. (2015)
Traditional ES	PLA/PHBV/PEDOT: PSS	Tissue engineering	Chang et al. (2016)
Traditional ES	PEDOT	Tissue engineering, cell culture, implanted electrodes, drug delivery	Jin et al. (2013)
Traditional ES	MWCNTs/PCL/ PEDOT	Skeletal muscle cell alignment and regeneration	McKeon-Fischer et al. (2015)

The surface of PEDOT NF mats was cultured to human cancer stem cells (HCSCs) for three days to examine the cellular morphology and proliferation. The results bespeak that the PEDOT NF mats had similar biocompatibility to tissue culture plates (TCP). These PEDOT NF mats possess remarkable electrical conductivity (7.8 ± 0.4 S/cm) along with excellent mechanical properties and biocompatibility, making it a suitable material for biotechnological applications such as electroactive substrates, drug delivery, cell culture, and implanted electrodes. Mckeon-Fischer et al. (2015) created a conducting, biocompatible scaffold having superior mechanical properties for regenerating skeletal muscle. In this study, PEDOT NFs along with the PCL were electrospun to form conductive NS. As the PEDOT content was increased, the NS resulted in ribboning, increased in fiber diameters, and unaligned NFs during ES. This was circumvented by sonicating the PEDOT NPs prior to ES process, which resulted in decrease conductivity and enhanced mechanical properties. To increase the conductivity of the NS, MWCNTs were added in the ratio of 1:10 1:2, 3:4, and 1:1 to the PEDOT: PCL solution. The addition of MWCNTs slightly affected the scaffold conductivity and enhanced the elastic modulus, yield stress of the scaffold. The NS was attached to the rat muscle cell which was active for the 1:10, 1:2, 3:4, and 1:1 PCL: PEDOT scaffolds. It was observed that the 3:4 scaffolds had the lowest level of metabolic activity. It was also found that the scaffolds were cytocompatible. The authors suggested the need for further advancement of the fabrication method for producing more highly aligned scaffolds that have potential to promote skeletal muscle cell alignment and eventual regeneration. Table 11 depicts the various biomedical applications of the electrospun conducting PEDOT composite NFs.

3 Conclusions

The recent advances and state-of-the-art progress in ES technique for biomedical applications including tissue engineering, wound healing, and drug delivery have been discussed in this chapter hoping that the information provided will help in

planning future research endeavors in both ES and biomedicine fields. The coaxial or emulsion ES has promising benefits of sustained drug release and reduces the initial burst release commonly encountered with the polymer/drug blends. Designing new collectors can enhance the geometry; control the fiber alignment, mechanical, and biological properties of the scaffolds. Also, the surface modification of electrospun NFs can further improve the scaffolds interaction with cells. Novel NS prepared from ES can be readily used for steadfast wound healing and modern wound dressing as compared to traditional methods. Another major benefit of ES is that the synthetic, natural, and hybrid polymers can be chosen readily and electrospun by precisely tailoring the scaffold properties for the desired applications. The multifunctional NFs that generate active therapeutics can be preferred for more than one biomedical function for effective treatments. The researchers from various sectors such as biology, physics, mechanical engineering, material science, life science, chemistry, medicine, and biotechnology must focus on gaining a proper understanding of the ES process and its mechanism and more importantly use this technique to tap its immense potentiality, especially in biomedical applications.

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Biomedical Applications of Hydroxyapatite Nanocomposites

Mariappan Rajan and Murugan Sumathra

Abstract This book chapter details the recent and very recent work on biomedical applications of hydroxyapatite nanocomposites. Single component of hydroxyapatite has not fulfilled the all obligation of biomedical process. The hydroxyapatite-reinforced polymer nanocomposites imitate the inhabitant tissue microenvironment due to their porous and molecular structure. An emerging approach has been involved as the reinforced polymeric compounds and to include multiple functionalities. Wide ranges of nanocomposites such as carbon-based, polymeric, ceramic, and metallic nanomaterial can be integrated within the hydrogel network to obtain nanocomposites with superior properties and tailored functionality. Hydroxyapatite nanocomposites can be engineered to possess superior physical, chemical, electrical, and biological properties. Mainly this book chapter deals with the hydroxyapatite composites applied for various application specifically tissue engineering, drug delivery, gene carriers and photodynamic therapy are discussed.

Keywords Biomedical · Hydroxyapatite · Tissue regeneration

Abbreviations

ALG	Alginate
ALP	Alkaline phosphate activity
ARG	Arginine
AMX	Amoxillin-clavulanate
BMSCs	Bone marrow-derived mesenchymal stem cells
BSP	Bone sialoprotein
BMP-2	Bone Morphogenic Protein
β-TCP	Beta-Tri-calcium phosphate
CS	Chitosan
CMC	Carboxy Methyl Cellulose

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K. K. Sadasivuni et al. (eds.), *Polymer Nanocomposites in Biomedical Engineering*, Lecture Notes in Bioengineering,
https://doi.org/10.1007/978-3-030-04741-2_6

CMPs	Chitosan microspheres
CNT	Carbon Nanotube
5-FCil	5-Fluorouracil
nCHA	Nanocrystalline Carbonated Hydroxyapatite
COLL	Collagen
Dox	Doxorubicin
DEX/BSA	Dexamethasone–bovine serum albumin
ECM	Extracellular Matrix
GG	Gellan gum
GM	Gentamicin
HA	Hydroxyapatite
n-HA	Nano-Hydroxyapatite
HARV	High Perspective Proportion Vessel
MBG/HA	Mesoporus Bioactive glass
MSCs	Mesenchymal stem cells
hMSCs	Human mesenchymal stem cells
MC3T3-E1	osteoblast cell line separated from mus musculus calvaria
MMT	Montmorillonite
PCL	Polycaprolactone
PEG	Polyethylene Glycol
PEI	Polyethylen imine
PHB	Poly(hydroxybutyrate)
PLGA	Poly(lactic-co-glycolic acid)
PLLA	Poly-L-Lactic acid
PLEA	Poly (ethylene adipate-co-D,L-lactic acid)
PVA	Polyvinyl alcohol
mRNA	messenger Ribonucleic acid
SA	Sodium Alginate
SF	Silk
SBF	Stimulated Body Fluid
M-THPP	Tetrakis Hydroxy Phenyl Porphrin
XRD	X-ray diffraction
XPS	X-ray photoelectron spectroscopy

1 Introduction

The ideal characteristics of nanocomposites have focused in prominent investigate significance, particularly within bio-therapeutic applications attributable to their biophysical characteristics. The distinctive sorts of nanocomposites as natural inorganic, inorganic–inorganic, and bioinorganic nanocomposites have permitted their utilization in clinical areas, for example, malignancy rehabilitation, drug delivery,

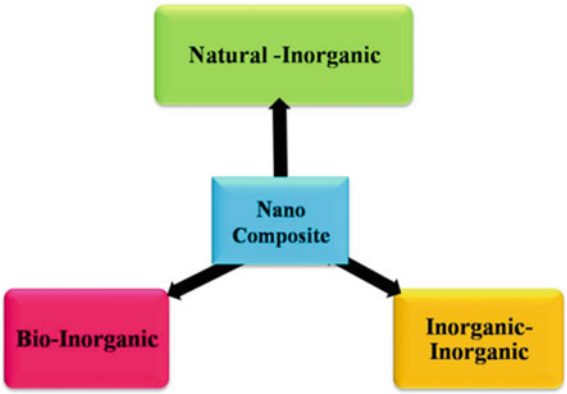

Fig. 1 Different types of nanocomposites formation

clinical imaging, and compound sensing (Zohaib et al. 2014; Muthu Vignesh et al. 2015). A nanocomposite is characterized while a numerous stages solid matter in which distinct of the stages has 1–3 dimensions less than 100 nm (Gaharwar et al. 2014; Wu et al. 2010). These substances might be both synthetically created or from the natural source. The objectives of this chapter are to concentrate on the primary uses of biocompatible hydroxyapatite (HA) nanocomposites, with specific concentrate on tissue revamp and rejuvenation (Govindaraj et al. 2017a; Govindaraj and Rajan 2018; Chung et al. 2016). Before to begin with this it is significant to establish the types of composites. Subsequently, the chapter will explore the significances identified with that particular territory of investigating (Fig. 1).

2 Established Hydroxyapatite Nanocomposite Information

Hydroxyapatite nanocomposites are a biocompatible substance and it appropriate for biomedical applications, because of the numerous physiological interfaces and physic-chemical performance at the nano-level. The terms tissue revamp also recovery can be utilized reciprocally, specifically while in orientation to injury recovering (Venkatesan and Kim 2014). On the other hand, in the right utilization, in renovate structure of tissue shapes the harmed tissue returning to normal functioning though in improvement undamaged tissues inside epithelia can renovate tissue to work as typical without wound formation (Samira and Khosro 2015; Pistone et al. 2014a).

The expressions for biocompatible fabrics can be a commitment to 1969, while Hench characterized the idea biocompatible fabrics as “one that evokes a particular physiological reaction at the interaction of the substance which brings about the arrangement of a bond among the tissues and the substance” (Hench et al. 1993). Hench gave an early criterion to the detail of biocompatible fabrics, which was

spent until 1994 when a different two-characterization framework was recommended (Arcos et al. 2002). Class (I) substances (bio-glass) are Osseo-prolific, they acquire a bio-compacts exterior, which can be co-culture via osseo-genic stem cells as a result of the substance suggesting both an intra and extracellular reactions. Class (II) is Osseo-conductive, affording a bioactive exterior for Osseo cells relocation. This substance nature, an instance of which is reproduction hydroxyapatite, encourages only physiological reactions starting the objective tissue (Fig. 2).

Biocompatible can also identify with tissue engineering substances through the objective to make frameworks that consolidate together bio-inductive with bioresorbable characters that can perform in vivo process of tissue rejuvenation, prompting encouragement for the physique to cure itself, furthermore which at that point prompts substitution of the composite through the rejuvenated tissue (Oh et al. 2006).

The interface experienced with a composite can be significantly more capable than possible among micro-or macro-morphology substitutes, by biocompatible nanocomposites frequently being employed in one of two situations, whichever as a thin bio-stimulative deposition or as a mass item (Sumathra et al. 2017a, 2018a). With regard to tissue engineering, nanocomposites all the more firmly copy the structure of characteristic normal tissues (bone), which can be characterized as a profoundly progressive nanocomposite including nano-HA powder and collagen. Nano-hydroxyapatite is the chief inorganic constituent of teeth and bone.

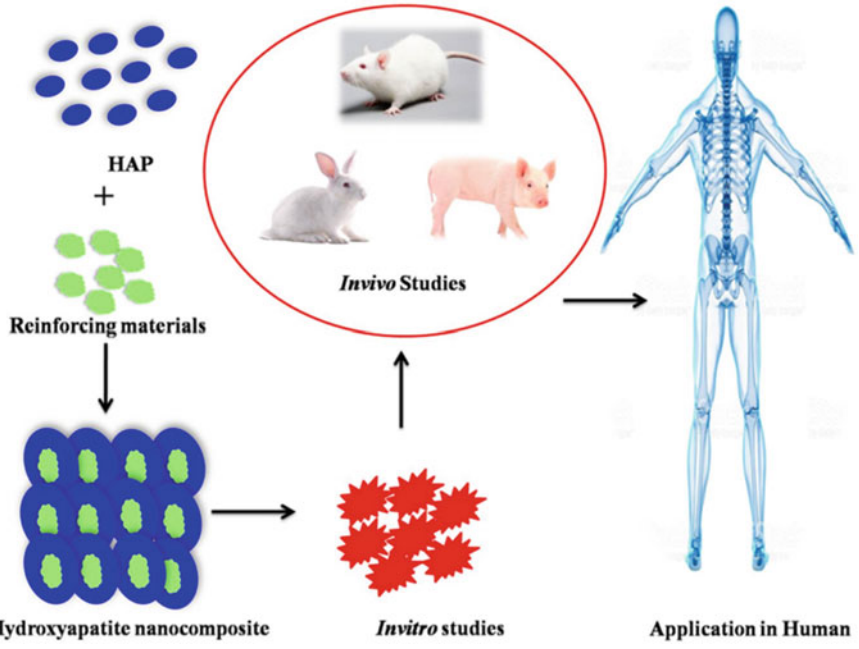

Fig. 2 Schematic representation for HA-based nanocomposites of biomedical evaluations

Chemically fabricated n-HA is cytocompatible and widely used for orthopedics and orthodontic implants and sustainable drug discharge (Sumathra et al. 2018a, c). The nanocomposites enclose n-HA with biophysical properties close to those of physiological bones. Cytocompatibility investigations on the n-HA demonstrated safe to mesenchymal stem cells (MSCs) (Benning et al. 2017).

A perfect contestant for orthopedic and orthodontic inserts is n-HA owing to its tremendous bioactivity and bone combination capability. The exercise of n-HA bio-ceramics in medical applications is restricted because of its poor mechanical potency, fragility, and weariness breakdown. Additionally, revamp of orthopedic and orthodontic imperfections over 30 mm using tissue engineering techniques is a hard biomedical problem. Consequently, reinforcing material/nHA-based nanocomposites will be capable advance to defeat the aforementioned anxieties (Govindaraj et al. 2015; Sumathra et al. 2017b).

3 Classification of HA Nanocomposite

In HA, nanocomposite investigates there is numeral of decision for the part that includes the composite. Traditionally, they are described into the classifications based on the polymer network: polymer, metallic, ceramic, and hybrids-based nanocomposites (Fig. 3). HA nanocomposites have favorable circumstances above their ordinary partners as expanded quality, hardness, and assimilation protection, accomplished by refining particles dimension alongside improving the flexibility, custom, and super flexible owing to the nano-phase (Govindaraj et al. 2017b).

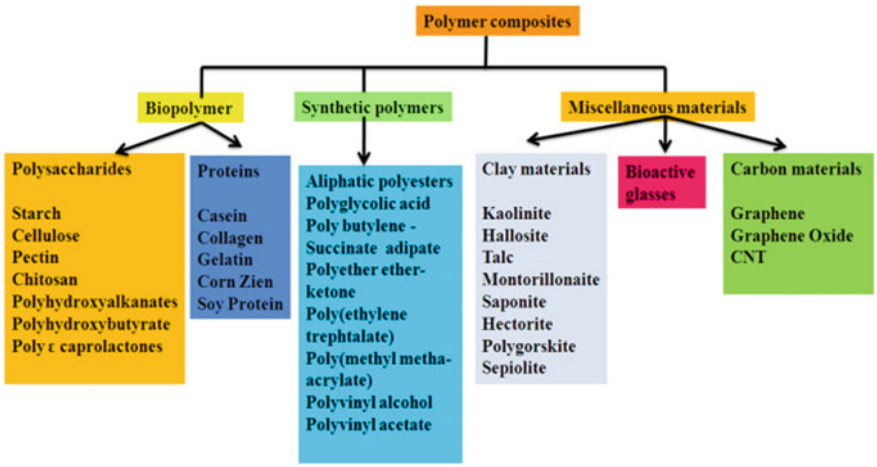

Fig. 3 Flowchart for HA nanocomposites

3.1 Polymer-Based Nanocomposites

As specified before, polymers are of extraordinary utilized in the biomedical field. The polymers employed in tissue rejuvenation can be also bio-decomposable or non-decomposable with can have a natural or synthetic origin. There are several researchers completed that macromolecules stimulated hard tissue construction in vivo animals models (Corcione et al. 2017; Roul et al. 2012). Mixtures of artificial and natural macromolecules have been experienced straight or in mixture with HA to imitate natural tissues and bone networks (Fig. 4).

3.1.1 Biopolymers Based HA Nanaocomposites

Polymers can fill as a framework having different characters with bio-decomposable (Corcione et al. 2017; Roul et al. 2012). Currently, biopolymer nanocomposites engaged with more consideration than artificial polymer nanocomposites for biomedical uses. This is frequently a result of the bioactive and bio-decomposable behavior of biopolymers. The biopolymer-based substances are natural macromolecules which comprise chitosan, starch, hyaluronic acid, fibrin, soy, silk, collagen, and gels with a reputable variety of bio-fibers (Zheng et al. 2015). Biopolymers frequently force very sorted out structures and may contain extracellular materials, called ligand which is important to tie with cell acceptors. Biopolymers often have extremely sorted out structures, which can manage cells to develop at different phases of advancement; they may reinforce an insusceptible reaction in the meantime (Mano et al. 2007). A few biopolymers-based HA nanocomposites have accounted for their uses in biomedical application.

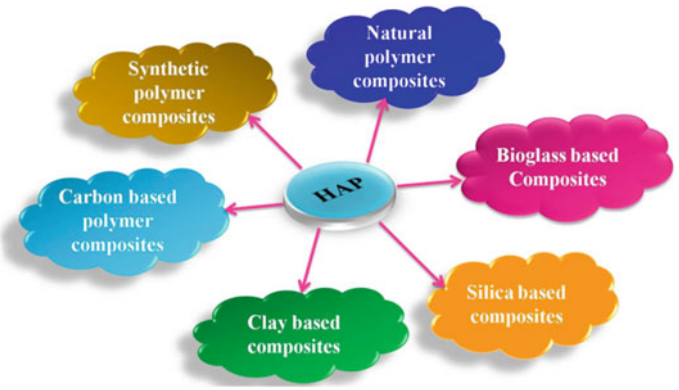

Fig. 4 Classification HA nanocomposites

3.1.2 Synthetic Polymers-Based HA Nanocomposites

Synthetic polymers have been employed in hard as well as soft tissue engineering owing to their improved mechanical strength and chemical constancy than natural macromolecules. Presently, synthetic polymers used for biomedical engineering are polyethylene, polypropylene, polytetrafluoroethylene, poly(vinyl chloride), polyamide, PMMA, poly(ethylene terephthalate), and PEEK among others. Synthetic polymer/HA nanocomposites are generally employed while tissue cannot be rejuvenated because of great sufferers or foraged patients with a fewer efficient self-curing capability of the tissue (Guo and Ma 2014).

3.1.3 Hybrids-Based HA Nanocomposites

Nanocomposites have recognized themselves as a capable class of hybrid substances derivative from biopolymer to artificial polymer also inorganic fillers. The natural polymer with synthetic polymer scaffolds, polymer with ceramic nanocomposites, and carbon-based nanocomposite combined with n-HA have been developed for bone graft substitute. All the fabricated nanocomposites demonstrated adequate pore range, increased mechanical strength, superior in cell adhesion and proliferation; sustain drugs and gene delivery, and ALP discharge with mineralization (Rao et al. 2017; McCarthy 2017; Reddy and Swamy 2005).

4 Applications of Hydroxyapatite Nanocomposites

The fabrication of nanocomposites will be discussed within each application. Each type of nanocomposite substances recommends its own advantages in imitating the association of natural tissue arrangement. An explanation of each application is subjected as follows.

4.1 Tissue Engineering Applications

Design and improvement of nanocomposites ready to replace the frame and capacity of local tissue and to advance recovery without rot/disfigure development is a present investigate theme. Nanocomposite substances can copy the regular topography of the extracellular matrix (ECM) that encompasses cells and thus might be perfect for recovery of tissue arrangements (Chen and Liu 2016). To this end, main qualities of the ECM ought to be considered: (A) a hybrid arrangement made out of bio-macromolecules and inorganic substance as well as (B) a polymer surface described by an excessive perspective proportion and a nanoscale size. These nanoscale substances can afford improved mechanical performance with permit appropriate transduction of the automatic stimulus toward the cellular stage.

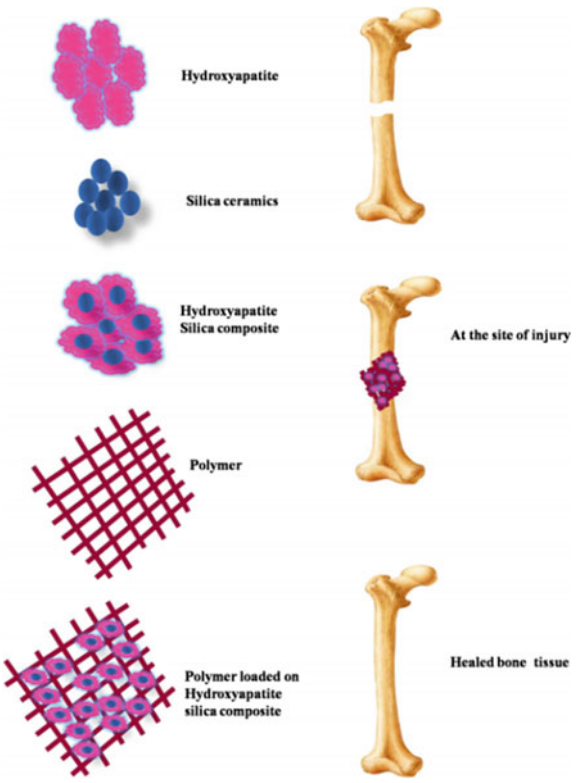

Fig. 5 Tissue regeneration on injured bone

Composites concerning natural and synthetic matrix and biocompatible reinforcement materials (nano-fillers) have been considered as a technique for tissue rejuvenation (Fig. 5). The reinforcement materials with nano-sized characteristics can seriously alter the physicochemical possessions of the bio-macromolecules matrixes, considering the designing of enhanced biomaterials that the entity materials cannot accomplish. The nanoparticles have an extensive surface region while contrasted with the regular micro-sized reinforcement materials, which can frame a stretched interaction by the macromere matrixes, contribution enhanced compressive characters, whereas keeping up the great osteo-conductivity as well as cytocompatibility of the reinforcement materials, accordingly impacting biomolecules adsorption, cells grip, expansion with integration for fresh tissue development (Bramhill 2017).

4.1.1 Biopolymer-Based HA Nanocomposites

Numerous natural polymeric substances have been examined for hard and soft tissue designing uses, despite the fact that the firm necessities for clinical requests

cannot be proficient via solitary polymers. Subsequently, the multi-segment framework turns into a feasible technique and particularly the presentation of n-HA into natural polymers is a standout among the most appealing options (Rao et al. 2017).

Chitosan (CS) and its compounds are extremely smart contenders for composites in biomedical applications owing to their non-toxicity, biodegradability, pore configuration actions, appropriateness for the cell enlargement also essential bactericidal properties. Additional benefits of CS composites are the development of extremely spongy materials with consistent pores, and the capability to develop bone configuration both in vitro cell colonization and ex vivo animal studies (Pina et al. 2015; Tanase et al. 2013). Fabricated chitosan/HA nano-fibrous nanocomposite by improved human hFOBs propagation for hard tissue engineering. The viability of CS/n-HA composites was assessed (Nguyen et al. 2013; Govindaraj et al. 2018a; Hunter and Ma 2013). It was revealed that the CS/HA nanocomposite mechanical potency is in the sort of trabecular cartilage, propagation as well as segregation of osteoblast cells on the nanocomposite. Likewise, MSCs co-colonization on CS/HA nanocomposite demonstrated enlarged propagation while contrasted to that co-colonization on pristine CS (Liao et al. 2010; Kim et al. 2013). The synthesized porous CS/HA nanocomposite with 3D dimensions illustrating an excessive amount of propagation of osteoblast cell, attachment as well as ALP movement (Peng et al. 2012; Zhang et al. 2014).

Alginate (ALG) has been broadly utilized for tissue designing frameworks for hard tissue, skin, and ligament. Such enthusiasm for ALG is credited to its compound morphology, which takes after glycosaminoglycan one of the significant segments of the usual ECM in the human being tissue (Jiaxzhen et al. 2014). ALG/HA nanocomposite fibrous scaffolds acquired utilizing electro-spinning and a biomimetic in situ fabrication has as of lately been proposed (Liu et al. 2012). This procedure brought about a uniform loading of nano-apatite on the nano-fibers, beating the serious cluster of composites handled via the ordinary mixing/electro-spinning strategy. The connection of rodent osseous cells on these ALG frameworks was steadier than bond on pristine ALG.

Additionally, MSCs encapsulating HA/alginate nanocomposite have revealed compressive strength coordinated the accounted rates of cancellous tissues, and the summarize cells continued feasible with osteo-inductivity, yielding high ALP, and gene appearances (Bartkowiak-Jowsa et al. 2011). Similarly, it was published that nanocomposite of HA/ALG composite encourages the development of the hard tissue-like network in vitro for the rejuvenation of bone-chondral crossing point tissue manufacturing (Hu and Yu 2013; Kang et al. 2012; Gong et al. 2012; Luo et al. 2013; Park et al. 2014; Nguyen and Lee 2012; Lee et al. 2011; Zhao et al. 2010; Khanarian et al. 2012). Also, GG-based hydrogels blended with gellan gum/HA nanocomposite hydrogels have been projected for cartilages and bone-chondral uses demonstrating better compressive with physiological properties in contrast to the micrometric composite (Bajaj et al. 2007). Besides, the addition of n-HA in hyaluronic acid networks has exposed high prospective for the healing of bone injury (Jansson et al. 1983; Correia et al. 2013; Kang and Veeder 1982).

The Coll/apatite composite showed superior compressive properties also the same high biochemical action as the Collagen control scaffold, exhibiting its potential as a hard tissue graft substitute in bone regenerative prescription. Gelatin/n-HA nanocomposite-based porous materials fabricated via freeze dehydrate (Cunniffe 2010; Curtin 2012; Villa 2015). The mechanical strength of the nanocomposites was very close to normal cartilage. In vitro investigations demonstrated superior adhesion and propagation of human MSCs on Coll/apatite composite (Sotome et al. 2004; Maehara et al. 2010). Gelatin/n-HA nanocomposite synthesized by a co-precipitation technique. This nanocomposite displayed a mechanical potency of 13,300 kPa and demonstrated a superior bioactive founded on cell adhesion, propagation, ALP formation, and mineralization investigations (Marino et al. 2016; Djagny et al. 2001; Gorgieva and Kokol 2011; Barbani et al. 2012; Baheiraei et al. 2015; Bakhtiari et al. 2010; Khan et al. 2012; Azami et al. 2010).

Silk (SF)-based nanocomposite materials with improved biophysical and biochemical properties have been established for hard tissue engineering (Li et al. 2006; Kim et al. 2005, 2008; Unger et al. 2004; Suganya et al. 2014). The addition of n-HA/SF nanocrystal into silk demonstrated a progressed porous morphology, osteogenic integrations, and in vivo cartilage formation (Liu et al. 2011; Niu et al. 2012). SF composites in mixture with mesenchymal stem cells for hard as well as ligament tissues production have been developed (Tanaka et al. 2007). The osseous cell integration of stem cells, L929 cells, and MG63 is fusion of SF composites (He et al. 2012).

Schemes-based on Collagen fibers as well as n-HA are the nanocomposite substances most considered because the indicated constituents are prearranged at the nanoscale in normal cartilages (Sotome et al. 2004). Electro-spinning is potentially the least demanding approach to join natural's polymers having a nano-fiber topography with biocompatible inorganic substances, for example, HA (Maehara et al. 2010). In addition, the produced nano-fibers may have suitable properties focused on bone recovery.

Little quantities of n-HA powder can be joined keen on the fiber mats strands in three distinctive methods to rely upon the virtual volume among substances and fibers. In this manner, surface connection, incomplete encapsulation, and the aggregate embodiment can be watched if the measurement of the mats is altogether littler, comparative, with bigger, separately than that of the n-HA. Fractional and sum loading of n-HA are normal for strands enclosing a lot of substances. Finished loading of nano-powder might be great while compressive strength is measured, though fractional nano-substances interface to the mats exterior ought to be high sufficient toward upgrade the biocompatibility of the spun mats.

Electro-spinning of polymer–filler nanocomposites may have intrinsic issues identified with the readiness of a uniform electrospinnable arrangement. Moreover, it has been accounted for that relying upon the dissolvable electro-spun regular biopolymers should prompt a denatured shape that free the common physiological properties got as of their morphology. For instance, the multiple helixes normal for Collagen atoms are gone in the wake of electro-spinning offering ascend to gelatin

(Hassan et al. 2014; Tetteh et al. 2014; Fadiran et al. 2018; Illa et al. 2018). However, cross-connected electro-spun Collagen is accepted to in any case have great prospective as a nano-fibrous substrate for bone rejuvenation.

Electro-spinning of n-HA specifically blended with a gelatin arrangement is difficult since more often than not prompt the development of inexhaustible beads. The issue can be proficiently comprehended by electro-spinning natural solutions of a formerly formed HA/gelatin precipitate. n-HA showed up for this situation very much dispersed in the gelatin framework showing a uniform nano-fibrous topography. Strangely, amino acids having a place with the natural polymer appear to be ready to balance the precipitation of n-HA (Junxing et al. 2006; Jianchao and Ping 2012).

4.1.2 Synthetic Polymer-Based HA Nanocomposite

Incredible endeavors are subsequently occupied in control of the uniform of the macromolecule/inorganic composite and to maintain a strategic distance from the disturbance of fiber texture, being the utilization of ultrafine n-HA powder a key instrument. The interfacial attachment has likewise been fortified by adjusting n-HA with surface-united macromere to enhance communications with the hydrophobic polyesters (Cunningham et al. 2011) (Fig. 6).

The 3D PLGA/HA nanocomposite has been produced while a prospective hard tissue engineering network appropriate for elevated perspective proportion container bio-responders uses. The mix of these frameworks with stem cells in bio-responders may take into consideration the production of designed hard tissue. Consequences have a biomedical importance because tissue engineering develops may give contrasting options to customary bone grafts (Jose et al. 2009). To enhance the bioactivity of n-HA/Poly (L-Lactide Acid), the polymerization of PLLA on n-HA exteriors by various exterior OH^- ions usefulness was achieved. The PLLA-g-HA nanocomposite could be steadily scattered in $CHCl_3$ and could be effectively electro-spun providing hard tissue directed recovery layers of potential intrigue (Lan et al. 2014; Wang et al. 2016).

Fine mixing of HA with water-soluble polymers, for example, the polyethylene glycol has additionally been shown viable toward enhancing properties because of the solid interfacial grip among HA and the hydrophilic polymer (Govindaraj et al. 2017c; Akhbar et al. 2017). Lamentably, hydrophilic PEG needs biodegradability and is not steady in watery conditions without fabrication cross-connecting, influencing un-modified polyethylene glycol inadmissible for manufacturing decomposable HA-polymer nanocomposites by spin coating. To defeat this test, triblock copolymer PELA was likewise assessed (Kutikov et al. 2013). HA-PELA nanocomposite was remarkably extensible, superhydrophilic, advanced osteochondral genetics responsibility of BMSCs cells, and reinforced osteogenic quality articulation upon induction. Results unmistakably maintain that consolidation of PEG shows up a powerful procedure to enhance the execution of degradable polymer/HA nanocomposites for hard tissue designing applications.

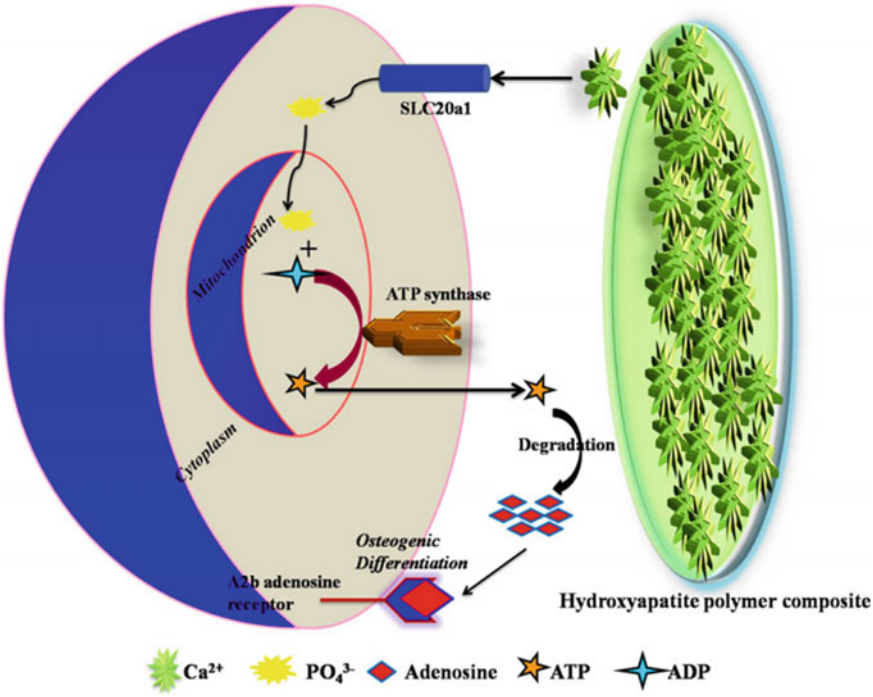

Fig. 6 Mechanism of osteogenic integration

HA nanocomposites with poly(L-Lactide Acid) or poly(lactic-co-glycolic acid) have good compressive strengths except may demonstrate poor effects produced via degradation results from this macromolecule on the nearby cells (Gentile et al. 2014). Subsequently, an expanding attention carries on to investigate the perspective utilization of further degradable macromolecule. Polyvinyl alcohol, an aqua-solvent as well as the degradable macromolecule, has been utilized broadly in the clinical area as a result of its cytocompatibility, demonstrated mechanical quality, and anabolic impact on hard tissues arrangement (Chen et al. 2017).

Furthermore, PVA has a self-crosslink capacity owing to the bottomless numeral of hydroxyl active groups originating from the monomer sequence. Though, nano-fibers have confinements, quick dissociation, and a biostatic character that damage the biomolecules and cell bond (Zafar et al. 2016). So as to enhance the properties of PVA nano-fibers, n-HA and collagen were joined by the electro-spinning procedure. These nanocomposites could associate with PVA particles expanding the hydrolytic protection and enhancing mechanical properties. These inorganic-natural nanocomposites were observed to be in vitro biodegradable and indicated an upgraded attachment and multiplication of murine osseous cells (Song et al. 2012).

As an elective approach for n-HA with PVA nano-fiber nanocomposites were synthesized via spinning-coating additionally after that calcium deposition was done for secure in a medium of calcium/phosphate toward nature an n-HA film. These deposited Ca particles in the fiber could leave about as nucleation locales with enhanced promote phase development amid secure treatment. Very permeable three-dimensional nano-fibrous HA/polymer nanocomposites were effectively given for prospective applications in hard tissue engineering (Antonio et al. 2016).

Electro-spun nanocomposites were likewise fabricated from n-HA to PLGA/PCL (Cai et al. 2017). It was demonstrated that the combination of n-HA could back off the biodegradation degree of PLGA-based substances in HA-subordinate way. Under pH 8, the n-HA may respond to balance acidic biodegradation results of poly (lactic-co-glycolic acid)as well as in this manner may maintain a strategic distance from their unfriendly impact on the hard tissue reaction as showed through bring down filtration of provocative cells subsequent to in vivo surgery (Cai et al. 2017).

Physiological characters, for example, cell multiplication, interaction, and ALP movement were established to increment the apatite deposition on the outer surface of fiber mats by means of interchange extinguish development as opposed to electro-spinning a macromere arrangement containing nanoparticles (Dongming et al. 2016). The n-HA deposition has additionally been performed over uniform CS nano-fibers by using SBF. After six days, SBF immersed the CS fiber mats were observed to be adequate to achieve the greatest mineralization. Besides, tissue feasibility and integration on these deposited nano-fibers was considerably higher than on non-deposited CS nano-fibers (Thien et al. 2015; Frohbergh et al. 2012). The amino and hydroxyl groups on CS went about as atomic conditions for the arrangement of n-HA in simulative body fluid action. Also, the expansion in the particular exterior territory of platforms expanded the powerful thickness of cores for n-HA development.

Electro-spinning was connected to manufacture PLLA layers that were grafted on their exterior with CS through aminolysis responses. The biocompatibility of the layer was shown by XRD, XPS subsequent to absorbing simulative body fluid. The stores had a calcium/phosphate proportion of 1.67, showing the n-HA arrangement on poly(lactic-co-glycolic acid)/CS film. Contrasted with an unadulterated PLLA electro-spun film that was relatively non-decomposable, the debasement degree of poly(lactic-co-glycolic acid)/CS nanocomposite was capable of 30% of every a month and a half while keeping up its fundamental engineering to continue supporting the recovered tissue (Chen et al. 2013a). Electrospraying of n-HA nanoparticles onto the exterior of macromere nano-fibers shows up likewise a capable system for upgrade attachments, multiplication, with an integration of stem cells. The capable outcome was particularly accomplished while n-HA were electro-sprayed on the exterior of PCL nano-fibers for hard and soft tissue engineering (Seyedjafari et al. 2010).

Injectable hydrogels with enhanced arrangement steadiness and upgraded hard tissue repair work were created by mixing triblock copolymers with n-HA. Furthermore, the joining of reinforcing nano-substances addicted to polymer framework prompted a sustainable reduction on basic gelation parameters to regard

to the pristine composite (Liu et al. 2017). n-HA/PLA fabricated via air-jet spinning as a new and simplistic nanocomposite preparation procedure. Advanced cell enlargement and propagation were experiential on n-HA-PLA nanocomposite contrasted to pure PLA with MC3T3 osseous cells (Kondiah et al. 2016). Poly-2-hydroxyethylmethacrylate, poly(hydroxyl butyrate-co-hydroxyvalerate), poly diisopropyl fumarate and poly-2-hydroxyethylmethacrylate nanocomposites were fabricated with n-HA-PCL as a choice for hard and soft tissue engineering. Poly(caprolactone fumarate)-N-vinyl pyrrolidone nanocomposites with n-HA were fabricated by solvent vanishing and electro-spinning technique. n-HA/Polymer nanocomposites could bolster the development of MSCs and guide their osteogenic separation. After refined hMSCs on nanocomposite nano-fibers, the joining of either HA to the polymer nano-fibers did not influence cell practicality, in the meantime, the nearness of the mineral stage builds the action of ALP, and mRNA articulation stages of the bone cell transmitted qualities, in all-out nonappearance of osseous-genic enhancements (Kondiah et al. 2016; Mousa et al. 2018).

4.1.3 Hybrids Polymer-Based HA Nanocomposite

Not withstanding characteristic bio-macromolecules like Coll, ALG, as well as CS, diverse bio-decomposable engineered macromolecules have likewise been assessed to acquire nanocomposites with biocompatible-reinforcing substances via utilizing the spin-coating procedure. Along these lines, PLA, PLGA, PCL, and PHB have been examined with various accomplishments because of the issues related to their hydrophobic character that formulates hard to get a uniform as well as the great scattering of the fillers stages. Indeed, nano-fillers tend to aggregate in the spin-coating arrangement also prompt the development of dabs. For instance, this issue has been as late abstained from utilizing surface active agent toward balance out the inter-stage among n-HA substance and the Poly(L-Lactide acid) (Bajaj et al. 2007; Liu et al. 2017; Kondiah et al. 2016; Hajiali et al. 2018). Determined nano-filament frameworks can advance osseous cell development and phenotype articulation on the larger amount than platforms in view of strands without the bioactive n-HA.

4.1.4 Miscellaneous Nanocomposites

Bio-clays, 45S5 Bio-glass, KGS Ceravital, 55S4 Bio-glass, A/W glass-ceramic, KGX ceravital, Al_2O_3-Si_3N_4, SWCNT, MWCNT, calcium sulfate, and graphene combined with n-HA have been developed for bone graft substitute. All the fabricated nanocomposites showed enough pore volume, increased mechanical strength, excellent in cell attachments, and improved cell propagation, ALP emission and mineralization (Mousa et al. 2018; Sumathra and Rajan 2017; Bellucci et al. 2017; Basirun et al. 2017; Zhijiang et al. 2018; Park et al. 2017; Hossein et al. 2017; Ponnamma et al. 2018; Meng et al. 2018).

4.2 *Applications of HA Nanocomposites as Drug Delivery Systems*

Enhancing human well-being is at present experiencing an explosion of consideration drove by the utilization of nanocomposites to convey drugs to cells. Such HA nanocomposites are designed with the goal that they are pulled in particularly to sick cells, which takes into account the immediate treatment of those cells, enhancing adequacy, diminishing reactions, and generally enhancing human well-being. This method diminishes the side effects of medications in the body. Though, in spite of the guarantee of nanomedicine over all problems, there are various burdens for utilizing these nano-drug conveyance vehicles, which ought not to be disregarded. Medications conveyed from nanoscale elements may act uniquely in contrast to when conveyed in an ordinary or customary frame (Goldberg et al. 2007) (Fig. 7).

4.2.1 Biopolymer-Based HA Nanocomposite

HA has high absorbability and restricting proclivity with an assortment of atoms and in this manner, constitutes a perfect composite to be utilized as medication conveyance framework, and furthermore in division, isolation, as well as refinement

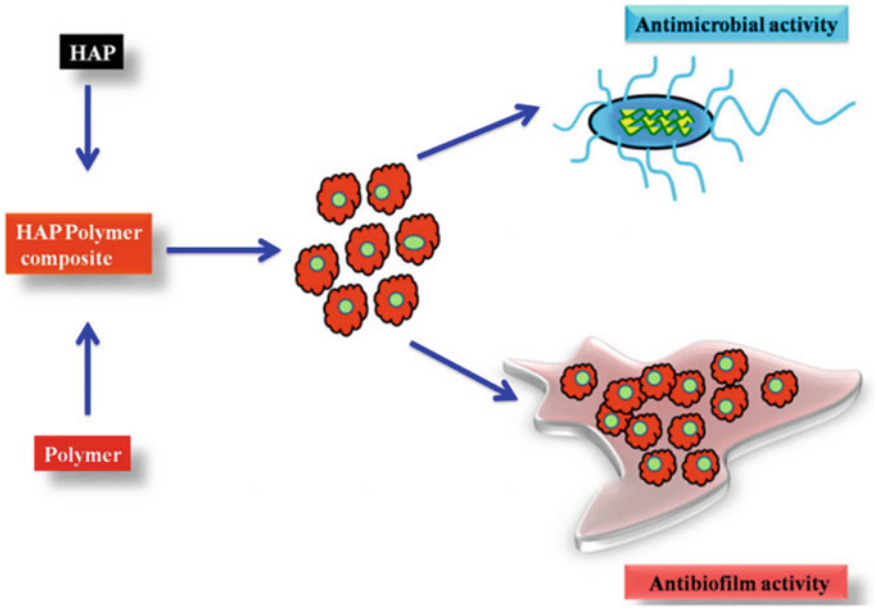

Fig. 7 Antibacterial properties of HA nanaocomposites

of biomolecules (Chung et al. 2016). HA substance can be effortlessly suspended down at low pH as clarified before; furthermore, they can without much stretch discharges the fused drug in proper situations. Nanocomposites intended for tissue designing applications are an unmistakable case of fascinating medication conveyance frameworks, since they can have an additional esteem when going about as stores for drugs. The sustained arrival of anti-infection agents, anticancer drugs, and development elements to dispose of disease and protect osseous cell integration is, for instance, a pertinent theme for the plan of porous implantable gadgets of osteogenisis (Govindaraj et al. 2018b; Venkatasubbu et al. 2011).

Bioactive particles can be fused into bioactive composites via physisorption. This straightforward strategy can accomplish neighborhood delivery, however, in addition a constrained fleeting control over discharge kinetics. On the other hand, development factor can be consolidated amid the framework arrangement, being conceivable for this situation to get a homogeneous circulation and a slower discharge. In any case, keeping in mind the end goal will not harming the bioactive particle of the scaffold fabrication step alerts must be fittingly considered. The adsorption and arrival of medications depend additionally on the surface of n-HA. As a rule, the examinations as of recently performed demonstrated that n-HA and medications can be chosen such that the biocompatible of the medicine-HA composite could be custom fitted for particular remedial uses. Several fascinating late efforts concentrated on the utilization of n-HA as medication delivery framework legitimacy to be remarked (Venkatesan and Kim 2014).

Minocycline, a semi-manufactured antibiotic medication anti-toxin that is additionally intriguing for upgrading bone development, diminish bridging tissue collapse, moreover reduce osseous resorption, was stacked in a bio-substance integrated utilizing a bio-imitating technique. The n-HA-gelatin-minocycline nanocomposite was gotten in the wake of maturing overnight and frizz drying. n-HA was observed to be all around circulated equally in the fibrils of gelatin. The medication was gradually discharged from the nanocomposite and advanced rodent bone marrow stromal cells attachment, expansion, and integration in vitro (Vekatesan and Kim 2014).

Alginate/HA nanocomposite circles were set up by adding n-HA powder to a watery alginate arrangement and consequent drops-wise expulsion of the framed glue into a Ca connecting arrangement. Round molded particles were promptly created by a volume that could be controlled by managing the expulsion stream speed. Powerful dosages of antimicrobials (i.e., erythromycin and amoxicillin) were beforehand stacked via drenching of n-HA in antimicrobial arrangement and consequent dehydrated. Osseous multiplied well on composites, being cell development improved within the sight of anti-infection agents with particularly erythromycin displayed the majority gainful impact. Consolidating the controlled antitoxin discharge with the osteo-inductive prospective used as injectable hard tissues filling substance are permeable nanocomposites, these frameworks gave a forward overlap advantageous impact (Dou et al. 2011).

Microwave light strategy was utilized to blend acid functionalized n-HA, and n-HA/CS–gelatin nanocomposite spheres were formed by the water/oil emulsion

technique joined with various emulsification mixture crosslink procedure. n-HA was extraordinarily inserted by CS-gelatin offering ascend to circular microspheres. Gentamicin could be viably stacked with a normal entanglement effectiveness of 49.20%. Nanocomposite could keep up restorative fixation inside 3 days (Govindaraj et al. 2017d).

Drug-loaded bioactive nanocomposite is utilized for the treatment of bone and teeth problems and remedial action of disease or provocative response after surgical implantation. An antimicrobial (amoxicillin-AMX) and anticancer (5-fluorouracil-5FCil) sedate loaded microwave-warmed n-HA/agarose nanocomposite gave a stretched out medication discharge when contrasted with the as-combined and the traditionally warmed specimens. The specimens were hemo-compatible and sedate loaded powders were firmly dynamic against the most widely recognized bacterial strains. Nanocomposite powder could be utilized for bone filling, medicate conveyance and for reconstructive surgery applications (Budiatin et al. 2014).

The nanocomposites are tremendously utilized for filling of voids in bone and as drug delivery carrier to keep the infection or burning response in the harmed tissues. Mesoporous, n-CHA/agarose nanocomposites with n-CHA exemplified by agarose were set up by solvothermal strategy at two distinct temperatures (120 and 150 °C). At 150 °C, prolonged nanorods of nanocomposites have formed. The nanocomposites demonstrated a controlled sedate (AMX, 5-FCil) discharge and the high antimicrobial movement against normal bacterial stain of E. coli, S. aureus, and S. epidermidis in complexity to calcined (n-HA) tests. The devise of porous nanocomposites showed an improved surface territory, bioactivity, managed sedate discharge, and high antimicrobial safe against gram-positive and gram-negative local microscopic organisms, empowering their void filling applications for bone and drug delivery framework. The calcined tests can be utilized for the fast arrival of the anti-toxin and against tumor medication to harmed tissues (Kolanthai et al. 2016).

Local antimicrobial delivery is favored for treating periodontitis because of the advantages of high neighborhood sedate fixation and insignificant symptoms. Conversely, marketable polymeric drug delivery frameworks need bioactivity and need extra hard tissue joining to treat the periodontal bone misfortune. Calcium inadequate HA (CDHA) consolidated gelatin–alginate (GA) films were created as anti-infection delivery bone substitutes for treating infra bony periodontal imperfections. CDHA were consolidated into GA polymer mix films arranged by salting out technique. GA/CDHA nanocomposite films equipped with supported antimicrobial delivery while all the while encouraging alveolar bone recovery was created (Isikli et al. 2012).

n-HA/Coll-ALG nanocomposites have been created as a cartilage filler as well as drug delivery cargo. In particular, development features that invigorated hard tissue arrangement were stacked in the nanocomposites (Madhumathi et al. 2018). Permeable HA/collagen frameworks are exceedingly effective for together cartilage and ligament recovery and have furthermore been composed as bearers for skin cell development feature (Amaro Martins and Goissis 2000). Ca-inadequate apatite

(CIA)/CS scaffolds have likewise been set up as medication stacked grids, as well as the sustain arrival of nutrients from such networks assessed (Kane et al. 2015). Furthermore, the part of macromolecule-reinforcing materials collaboration in the drug delivery was additionally assessed. It was discovered that both the measure of CDHA fused and the engineered procedure adjusted essentially the degree of the filler–polymer interface, which impacts clearly the distribution example and porous of CDHA/CS nanocomposites. Consequently, CDHA could simultaneously assume the parts as bioactive nano-filler and medication discharge controller (Bose and Tarafder 2012).

4.2.2 Synthetic Polymer-Based HA Nanocomposite

Electro-spun composite made out of PCL/Coll/HA was established to help more noteworthy stem cells grip, multiplication, also the initiation of integrin-connected flagging falls than platforms made out of PCL or collagen only. Likewise, these cartilage-imitating composites were demonstrated toward fill in as bearers for the conveyance of the platelet-inferred developed feature, which can intersect osseous chemo axis. This developed feature was adsorbed toward, moreover along these lines discharged from PCL/Coll/HA composite in a superior sum than utilizing ordinary polycaprolactam frameworks. The composite discharged was chemically dynamic, demonstrating that biocompatible was not decreased by sorption to the bio-substances (Liu et al. 2006).

Fresh polycaprolactam/polyvinyl alcohol composite mixed with together n-HA along with Collagen has been contemplated. DOX and dexamethasone were effectively consolidated into these coaxial nano-fibers for sustain discharge. These nano-fibers embodying medicines demonstrated incredible prospective in improving insert bone cell coordination also anticipating insert contamination (Phipps et al. 2012). Permeable triphasic nanocomposites for hard tissue designing and medication conveyance scaffold were additionally arranged from n-HA, bio-decomposable calcium connected polyvinyl alcohol with SA via the strategy for co-precipitation. It was exhibited that n-HA segment could scatter consistently in PVA/SA copolymer grid. Phenomenal solubility existed between the three stages as well as between otherwise intra-hydrogen holdings could be shaped with the three stages. The passage of polyvinyl alcohol network in the compound improved the compressive strength of the nanocomposite (Song et al. 2013).

Osteomyelitis is an extreme problem that generates dynamic hard tissue annihilation and the development of sequestra. A ceaseless spread of disease, hematogenous seeding, and coordinate immunization of microorganisms are conceivable causes that ought to be kept away from by utilizing, for instance, GM as an aminoglycoside anti-toxin. The GM-loaded composite was assessed toward broadening the medication discharge occasion for the action of constant osteomyelitis. The composites were set up an arrangement comprised of n-HA, CS, with GM-stacked EC composite. These composites were furnished by superb

medication discharge properties that help an extraordinary corrective impact on the behavior of endless osteomyelitis (Wang et al. 2010).

Healing impact of the tetra component framework comprised via PBH-PEG-GM/n-HA has been assessed as a neighborhood sedate delivery framework for osteomyelitis treatment. Staphylococcus aureus was infused into animal tibia toward deciding the impact of conveyed sedate. Consequences demonstrated that the gentamicin stacked platform could be embedded as essential unity keen on the staying contaminated deformity to adequately treat osteomielitis (Shi et al. 2010; Popelka et al. 2018).

4.2.3 Hybrids Polymer-Based HA Nanocomposite

Significant endeavors have been made to build up an appropriate biocompatible platform for hard and soft tissue designing. A permeable CS-PLLA-co-acrylamide/HA composite was combined via a several-step course as a bone embeds and a medication bearer. Celecoxib as a model medication was effectively stacked into the readied platforms due to the substantial particular surface territory. The in vitro arrival of the medication showed a biphasic design with a small starting rupture with a supported arrival of two weeks. The outcomes proposed that the cytocompatible nanocomposite frameworks may be effective embeds in bone tissue engineering (Zhang et al. 2011).

PCL-Gel composite nano-fibers arranged by electro-spinning method were utilized as the co-conveyance arrangement of Dox and n-HA. The co-conveyance arrangement of Dox and n-HA has a double helpful impact. To start with, the impacts of Dox/n-HA treatment on Caco-2, 4T1 and 431 tumor cells, and the outcomes demonstrate that the mix of the two operators advances higher cytotoxic impact in vitro contrasted with single-specialist treatment. Second, the blended treatment of the discharged Dox/n-HA from PCL/Gel is more proficient in its capacity to repress S. aureus and P. gingivalis microscopic organisms development in a static situation. Obviously, utilization of anti-infection agents as anticancer medication shapes an essential procedure for the treatment of early malignant injuries and progressed metastatic illness. In this regard, Dox/n-HA-stacked PCL/Gel composite nano-fibers are exceptionally appealing for biomedical applications, for example, postsurgical chemotherapeutic gadgets and additionally encouraging material in the field of periodontal recovery (Samaneh and Samandari 2017). Some common application of hydroxyapatite in drug delivery is illustrated in Fig. 8.

4.2.4 Miscellaneous Nanocomposites

Successful addition of the MBG particles to the nano-fibrillar (Nf) gelatin network give substance exceptional properties for its application in hard tissues treatment, for example, high antibiotic stacking limit and supported discharge capacity, solidness, swelling and debasement rate limitation and osteoprogenitor cells

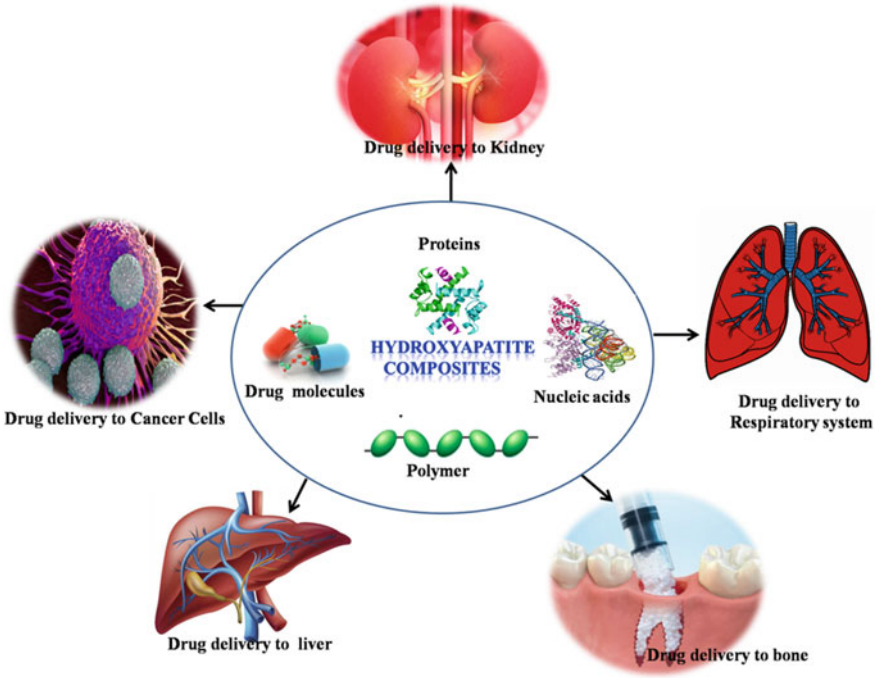

Fig. 8 Application of hydroxyapatite composites in drug delivery

biocompatibility. Industrial versatility potential regarding process dependability and nonappearance of dangerous substance specialists, low crude substance natural price, and immunogenicity are other vital favorable circumstances supporting MBG-Nf Gel as a prospective possibility to grow to assist for application as the local anti-infection gadget in hard tissues surgery and treatment (Ramirez-Agudelo et al. 2018). The manufactured HA/MWCNT/Fe_3O_4 nanocomposites indicated high cytocompatibility, and the clodronate-doped frameworks could discharge the medication in vitro, demonstrating a superior diminishment of the osteoclast development contrasted with the parent ones not including clodronate; specifically, the osteoclast restraint action for the attractive HA clodronate-substituted framework is equivalent to that applied by clodronate only. This composite can symbolize a multistage that could be utilized for hard and soft tissue designing functions (Pistone et al. 2014a).

Biocompatible inorganic substances are appealing for hard tissue recovery, and they are utilized as conveyance vehicles for pharmaceutical particles, segments for nanocomposites. The bioactive glass (BG) nanospheres that exhibited the ability to release the drug molecules. Permeable BG circles were stacked with ibuprofen (IBU); they displayed a supported discharge profile in reproduced body liquid (SBF). Meanwhile, the IBU-stacked BG nanospheres corrupted in SBF, and actuated apatite layer development at first glance because of their great bioactivity.

At the point when the BG nanospheres were utilized as composite filler to PCL, they were appeared to be successful at enhancing the in vitro bioactivity of PCL microspheres (Sara Borrego et al. 2018).

The DEX/BSA-stacked MBG/n-HA nanocomposites displayed and all the while maintained discharge conduct, and the DEX/BSA discharge speeds diminished with expanding the calcification time frame. Consequently, the calcification of bio-glass substances to shape the MBG/HA nanocomposites is a capable methodology to manage co-conveyance of remedial medications and biomolecules for cartilage recovery (Pistone et al. 2014b). Ibuprofen loaded into sodium montmorillonite, CS, and CS montmorillonite nanocomposites as a sustained release drug carrier. The consequences exposed that ibuprofen was released from MMT, CS, and Mod-CS/MMT progressively and was pH dependent (Wang and Li 2016).

4.3 Applications of HA Nanocomposites as Gene Carriers

In the area of tissue designing, the part of quality treatment in helping injury recuperating and care for different ailments/deformities has turned out to be progressively essential. The utilization of n-HA-based nanocomposite in quality conveyance has developed as a famous and essential conveyance vehicle for getting controlled quality conveyance (Zhu et al. 2014). The primary test for any fruitful little meddling RNA-based treatments is the innovative work of a proficient in vivo conveyance vehicle. Li et al. (Abdeen and Salahuddin 2013) recommended the productive conveyance by means of intravenous organization of RNA to a xenograft tumor display utilizing HA nanopowder with a normal width of around 60–80 nm covered through liposome. As indicated by the writers, the nanoparticle demonstrated high-quality hushing proficiency in refined pancreatic tumor cells without related cytotoxicity. Intravenously infused nanoparticles consolidating vascular endothelium development factor siRNA prompted huge lessening in tumor development. Right now, n-HA is a standout among the most alluring non-viral vectors being explored for the in vitro conveyance of plasmid DNA (pDNA) into refined cells because of elements, for example, the simplicity of dealing with, biodegradability, biocompatibility and known adsorption limit with regards to pDNA (Fig. 9).

4.3.1 Biopolymer-Based HA Nanocomposite

Non-viral quality treatment turns out to be these days a quickly developing system for the healing of both gained as well as acquired maladies. Non-viral vectors have clear favorable circumstances because of their low or no immunogenicity, generally basic arrangement methodology, minimal effort, and high adaptability to oblige the measure of the conveyed transgene (Li 1998).

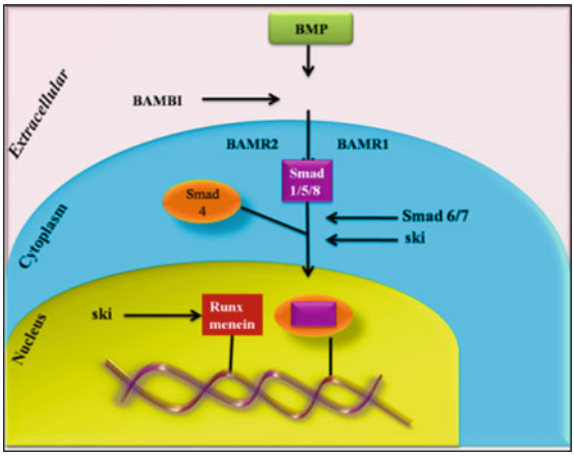

Fig. 9 Gene delivery profile

Awesome endeavors are engaged, for instance, in the advancement of quality conveyance frameworks that can secure pDNA and forces a prospective focusing on capacity. The benefits of HA substance lie in its common productivity for an extensive variety of soft tissue, straightforwardness, viability, and bio-decomposition. Combination of HA/DNA buildings can be executed through co-precipitation, embodiment, multi-orbital morphology arrangement, with cover. These edifices can be consolidated into the tissue via endocytosis through shaping ECMcargos, which converge with biomolecules. Top nanoparticles can be broken down still in low acidic support discharging gene. In this manner, the gene can be discharged in the endosomal section and in the long run enter the cores of cells to impact quality exchange and articulation (Qiu et al. 2007).

The take-up component of HA materials through tissue is still under scrutiny because the course of the section of HA furthermore their last intracellular confinement is unequivocal for a prospective use as quality conveyance specialist. For HA nanoparticles, a macro pinocytosis component appears to be supported as derived from contemplating completed utilizing particular inhibitors for the diverse take-up forms. A direct centralization of HA nanoparticles inside cells is wanted to keep away from cell apoptosis created when a high intracellular Cacontents achieved subsequent to the disintegration of HA (Sun et al. 2009).

Resulting atomistic subatomic elements reproductions permitted reasoning that the foundation of the DNA twofold helix can go about as at template for HA development (Sumathra et al. 2018b). Hypothetical estimations were additionally validated by the planning of nanocapsules and HA with DNA inside. These composite shows up very important for clinical purposes requiring the insurance of gene from forceful ecological circumstances.

Diverse pertinent works have been accounted for in the most recent decade to investigate the utilization of n-HA as exceedingly encouraging quality transporter vectors. HA/DNA nano-half and halves from lamellar-organized HA. Gel electrophoresis examination affirmed that the lamellar HA could shield gene from the

debasement of DNase I. The so-secured gene could be recuperated promptly under acidic circumstances and the honesty of discharged gene was affirmed by UV–vis spectra. EGFP-N1 pDNA on n-HA as well as in this way exhibited these buildings transfected in vitro the plasmid into disease SGC-7901 cells with proficiency ~80% (Neumann et al. 2009; Bertran et al. 2013).

Arginine (ARG)-adjusted nano-HA could shape quickly nanocomposite with gene by electrostatic collaboration. These nanoparticles could adequately tie and ensure gene and be measured as a prospective quality bearer (Chen et al. 2013b). DNAzymes are manufactured, single-stranded, synergist DNA that quandary also divide target mRNA in a grouping particular way. These have been investigated for geno-healings in spite of the fact that their application is genuinely blocked because of the absence of an effective conveyance framework. That all around n-HA can be using as a carrier. It was watched that in a rat cancer display, the ARG-n-HA composite was productively conveyed to cancer cells, down regulating articulation of dormant film biomolecules in nasopharyngeal carcinoma tissues and smothering cancer development (Nouri et al. 2012).

4.3.2 Synthetic Polymer-Based HA Nanocomposite

New ternary HA/biopolymer/engineered polymer composite networks—involving β-TCP as well as nHA, Coll, GAG, and PCL—were read utilizing cryogelation strategy. They got nanocomposite platform as a quality conveyance framework demonstrated that it can be proficiently stacked with polyplexes shaped between the non-viral vectors in light of PEI25 and a pDNA, and that this one can go about as a warehouse for the managed arrival of hereditary material, transgene articulation being seen at an abnormal state until 3 weeks. It was likewise discovered that the framework diminishes the harmfulness of cationic hyper expanded polymer PEI 25 while keeping up an expanded quality transfection for PEI25/pDNA framework relative to pDNA alone in HEK 293T cells. In this way, the cross-breed bio-substance could speak to a decent contender for the regenerative drug, as a framework or reasonable stage for quality conveyance (Raina et al. 2018).

A gelatin/n-HA platform was set up by glutaraldehyde synthetic crosslinking of a gelatin fluid arrangement with n-HA granules and after that BMP-2 stacked fibrin stick was consolidated. The readied half breed framework had a three-dimensional permeable morphology and could be utilized as a bone marrow protein-2 maintained discharge framework to enhance the regeneration in vivo of a basic volume sectional cartilage imperfection (Kaito et al. 2005).

4.3.3 Hybrids Polymer-Based HA Nanocomposites

CMPs typified with manufactured protein got from bone marrow protein-2 were arranged also joined on a framework comprising on n-HA, Coll, and PLLA (Wang et al. 2013). The composites showed up as a perfect conveyance framework for the

maintained arrival of bone marrow protein-2-inferred engineered protein and existing advancement for the conveyance of development features. The incredible bioactive of the CMPs/n-HA/PLLA nanocomposite was credited to both the CS part and the biocompatible engineered peptide embodied within.

CMPs containing adrenomedullin (ADM), a biocompatible administrative protein that influences relocation and expansion of assorted tissue, were likewise consolidated and all around scattered into a half-breed platform constituted through PLGA and n-HA. The expansion of CMPs expanded aqua assimilation and enhanced the compressive strength of the frameworks without influencing their elevated porosity. The articulation levels of osteogenic-related and angiogenic-related qualities were likewise enhanced the ADM conveyance frameworks, upgrading the enthusiasm of such for osseous tissue building. BMPs, particularly BMP-2, are the best in actuating complete bone morphogenesis. A sustained, limited conveyance framework is one of the most extreme significance in ensuring BMP-2 biocompatible and drawing out its quality at the imperfection site for powerful cartilage recovery (Seeherman and Wozney 2005).

4.3.4 Miscellaneous Nanocomposites

2D-layered materials show wanted functionalities while being utilized as quality conveyance materials. In this investigation, a novel quality vector, overlaid attractive hydroxyapatite, is blended through a template strategy in situ. The outcomes propose that the LM-HA is potential to be connected with focusing on quality conveyance and quality division (Zuo et al. 2012). A basic aqueous methodology was executed to get ready n-HA nanorods developed on graphene oxides (GO) sheet. The CD comes about were all around bolstered by enduring state and lifetime estimations, which too demonstrate that the instrument of unfurling and ensuing refolding is reversible in nature despite the fact that the protein does not recover its structure in totality. The fabricated HA/GO nanocomposites demonstrated no cytotoxicity impacts on A431 malignancy cell lines. Subsequently, HA/GO nanocomposites utilized as biocompatible possibility for a few biomedical applications (Ramadas et al. 2017) (Fig. 10).

4.4 Application of HA Nanocomposites for Photodynamic Therapy

Bioimaging and restorative release purposes are territories of clinical where nanocomposites have had a huge effect, yet the utilization of nanocomposites in these purposes can be restricted by its biophysical properties. HA nanocomposites are biocompatible and degradable and are subsequently viewed as the alluring contender for bioimaging and helpful medication conveyance applications.

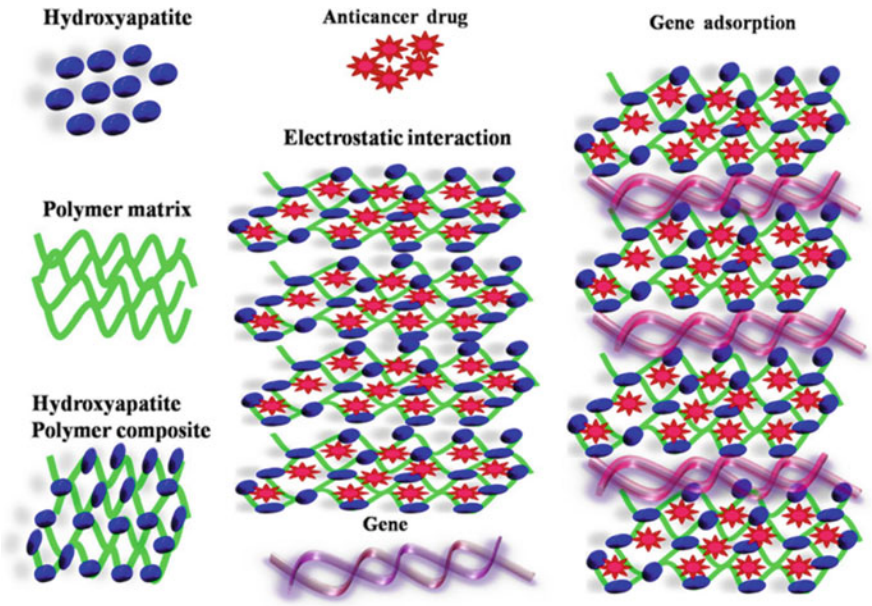

Fig. 10 Interaction of DNA on HA nanocomposites

Likewise, the pH-subordinate solvency profiles of n-HA substances make this class of nanocomposite particularly valuable for in vitro and in vivo conveyance of stains, oligonucleotides, and medicines. In this section, we discussed how HA nanocomposite satisfies a portion of the necessities regularly made for nanocomposites for clinical purposes. We also highlight current articles in bioimaging and restorative conveyance applications concentrating on how these investigations have tended to a portion of the difficulties related with utilizing these nanocomposites in bioimaging and release of therapeutics (Wu et al. 2015) (Fig. 11).

4.4.1 Biopolymer-Based HA Nanocomposite

The charge of nanocomposites impacts their capacity to go during the tissue film, and a positive charge ought to be valuable. The negative charge of calcium phosphate nanoparticles with an inward shell of CMC was switched by including an external shell of PEI into which the photoactive color mTHPP was stacked. They demonstrated a decent proficiency against HIG-82 and J774A.1 cells. A little measure of the nanocomposite is valuable for tissue endurance in light of the fact that the measure of possibly unsafe PEI and calcium is decreased. The unadulterated color must be regulated in an alcoholic arrangement which makes torment the patient. Moreover, aqua-dispersible nanocomposite opens the way for additionally

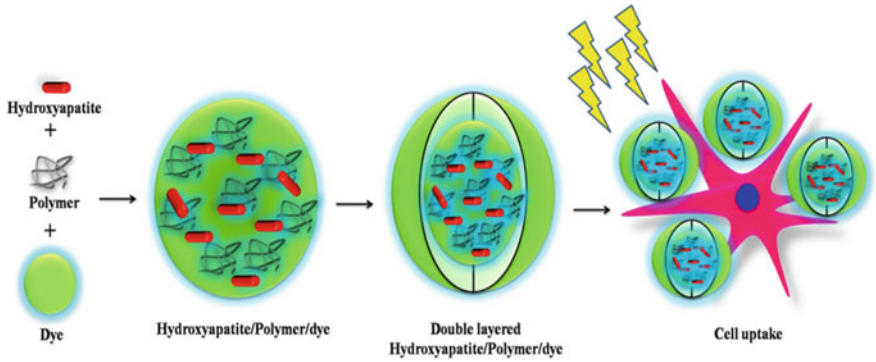

Fig. 11 Schematic representation of the photodynamic activity of HA nanocomposites

surface functionalization toward accomplishing a photodynamic activity coordinated to the particular tissue or microscopic organisms (Klesing et al. 2010).

4.4.2 Synthetic Polymer-Based HA Nanocomposite

n-HA fortified photosensitizer-stacked polymer composite has been produced for photodynamic treatment. Chlorin e6 (Ce6)-loaded core-shell-corona polymer micelles of poly(ethylene glycol)-b-poly(L-aspartic acid)-b-poly(L-phenylalanine) (PEG-PAsp-PPhe) were utilized as a layout nanoparticles for calcification with n-HA. The top affidavit was performed by the electrostatic restriction of Ca particles at the anionic PAsp center shells and the consequent expansion of PO_4^{3-} anions. n-HA strengthened nanoparticles showed upgraded dependability. The n-HA mineral layer viably hindered Ce6 discharge from the Ce6-stacked mineralized nanoparticles (Ce6-NP-HA) at physiological pH esteem. At an acidic endosomal pH estimation of 5.0, Ce6 discharge was improved, attributable to the quick disintegration of the n-HA minerals. An endless supply of Ce6-NP-HA treated MCF-7 bosom tumor cells, the phone feasibility significantly diminished with expanding light occasion. The phototoxicity of Ce6-NP-n-HA was considerably superior to that of free Ce6. Non-obtrusive optical picture comes about demonstrated that Ce6-NP-CaP showed improved cancer specificity contrasted and free Ce6 and Ce6-stacked non-mineralized polymer composite (Ce6-NP) (Lee et al. 2013).

4.4.3 Hybrids-Based HA Nanocomposites

The DOX-stacked center shell-crown micelles with CaP mineralized center shells (DOX- n-HA -PM) showed improved tumor aggregation and antitumor helpful efficacy contrasted and their non-mineralized partners (DOXNPM). DOX-n-HA-PM heartily kept up their morphology in serum with below micelle destabilization

circumstances (SDS). The testimony of pH-responsive minerals into the center shell of PEG-PAsp-PPhe micelles may meet the significant necessities of focused nanocarriers with high conveyance effectiveness and low poisonous quality: (i) high solidness in the circulatory system because of the stable mineralized shells; (ii) delayed blood course because of the PEG external crown; (iii) capacity to diminish medicate spillage before achieving target tissues; (iv) improved EPR impact; (v) encouraged medication discharge inside target cells by disintegration of the n-HA mineral; and (vi) discharge from the body as non-lethal PEG, amino acids, and calcium and phosphate particles. The shell-particular CaP mineralization inside the center shell-crown micelles may give a valuable apparatus to improving the antitumor viability of existing or recently created polymer micelles and nano-totals (Min et al. 2012).

The nano-carrier was developed by the basic blending of HA particles, PEG-PAsp, and Ce6 in the fluid arrangement, trailed by aqueous amalgamation. The n-HA-based nano-carrier stifled photochemical harm in the circulatory system, though its PDT viability was recouped in the focused on the tissue. This investigation was shown the pH receptive on/off switch of PDT viability utilizing n-HA. This endogenous jolts responsive switch will offer a promising way to deal with plan PS-stacked nano-cargos focusing on harmful cancer through the broken cancer-related vasculature with negligible photosensitivity (Nomoto et al. 2016).

The HA micelles hybridized with PEG-polyanion piece copolymers and consolidated with the clinical MRI differentiate specialist Gd-diethylene triamine penta acetic acid (Gd-DTPA/HA). The Gd-DTPA/HA were nontoxic to malignancy cells at the grouping of 100 μM in view of Gd-DTPA, while more than half of the tumor cells were murdered by warm neutron illumination at this fixation. In addition, the Gd-DTPA/HA demonstrated a drastically expanded amassing of Gd-DTPA in tumors, prompting the specific differentiation improvement on cancer tissues for exact tumor area by MRI (Mi et al. 2015). The upgraded cancer-to-blood conveyance proportion of Gd-DTPA/HA brought about the compelling concealment of tumor development exclusive of loss of body mass, demonstrating the capability of Gd-DTPA/HA for safe malignancy healing (Zhou et al. 2017).

The cross-connected HA-ss-HA prepared HA half and half nanoparticles are basic and smaller mixture nanocarriers that have various capacities, for example, redox responsiveness, endosomal escape, and tumor focusing, for quality conveyance in antitumor treatment. This framework has promising potential as a stage for quality conveyance in focused tumor treatment (Kopp et al. 2017). The autofluorescent protein R-phycoerythrin is effectively taken up by 4 diverse cell lines with the assistance of HA composite, yet not in broke down shape without composite. Outcomes feature the way that subsequent a fluorescent name connected to proteins isn't the same as following the protein itself. An effective composite-intervened take-up of a marked biomolecule does not really imply that the biomolecule is as yet practical. As the capacity of a biomolecule inside a cell is regularly hard to gauge and to evaluate, autofluorescent biomolecule offers a simple method to examine the proficiency of new transporter frameworks for protein.

Early identification is a vital component for the convenient conclusion and fruitful treatment of every single human growth yet is restricted by the affectability of current imaging philosophies. Combined and examined bioresorbable HA in which atoms of the close infrared (NIR) producing fluorophore, indocyanine green (ICG), are implanted. The ICG-CPNPs exhibit uncommon colloidal and optical qualities. Suspensions comprising of 16 nm normal measurement particles are colloidally steady in biological arrangements with carboxylate or PEG surface usefulness. ICG-doped HA display altogether more prominent force at the greatest outflow wavelength in respect to the free ingredient fluorophore, steady with the different atoms exemplified/molecule. The quantum productivity per particle of the ICG-HA is 200% more noteworthy at 0.0490.003 over the free fluorophore in PBS. Photostability in view of fluorescence half-existence of epitomized ICG in PBS is 500% longer under run of the mill clinical imaging conditions in respect to the free color. PEGylated ICG-CPNPs gather in strong, 5 mm breadth xenograft bosom adenocarcinoma tumors via enhanced maintenance and penetrability (EPR) inside 24 h after fundamental tail vein infusion in a bare mouse model. Exsitu tissue imaging further confirms the office of the ICGCHA for profound tissue imaging with NIR signals discernible from profundities up to 3 cm in the porcine muscle cell. Ex vivo and in vivo analyzes confirm the guarantee of the NIR CPHA for analytic imaging in the early recognition of strong cancers (Altinoglu et al. 2008).

Leukemia (LUK) is a standout among the most widely recognized and forceful grown-up growths, and additionally, the most pervasive youth tumor. LUK is a tumor of the hematological framework and can be isolated into an assorted variety of exceptional malignancies in light of the beginning of the illness and additionally the particular cell genealogies included. Growth immature microorganisms, including as of late distinguished leukemia undifferentiated organisms (LSCs), are speculated to be in charge of disease advancement, backslide, and protection from treatment and new therapeutics focusing on these cell populaces are critically required. Nontoxic and non aggregating HA characterized the near infrared fluoroprobe indocyanine green (ICG) was as of late produced for analytic imaging and medication conveyance and also PDT of strong tumors. Earlier examinations uncovered that particular focusing of HA considered improved amassing inside bosom growth tumors, by means of CD71 focusing on, or pancreatic disease cancers, via gastric accepter focusing on. The ICG loaded HA was assessed as photo sensitizers for PDT of LUK. Utilizing a fresh bio-conjugation way to deal with particularly target CD117 or CD96, surface highlights upgraded on LUK foundational microorganisms, in vitro ICG-HA-PDT of a murine LUK tissue and human LUK tests were drastically progressed. Besides, the in vivo adequacy of PDT was significantly upgraded in a murine leukemia display by using CD117-focused on ICG-CPSNPs, bringing about 29% infection free continued existence. Inside and out, this investigation exhibits that LUK-focused on ICG-stacked CPSNPs offer the guarantee to successfully treat backsliding and multidrug-safe LUK and to enhance the life of LUK patients (Barth et al. 2011).

4.4.4 Miscellaneous Nanocomposites

The hybridization of HA with CNTs and graphene nano-sheets not just enhanced the photothermal proficiency of CNTs-COOH-HAP and GR-HA yet, in addition, their photostability. This technique gives a multipronged way to deal with defeat from the non-bioactive PTE operators right now being used. Aside from PTT, the fantastic NIR assimilation capacity of CNTs-COOH-HAP and GR-HAP is favorable to other naturally significant purposes, for example, bio-sensing. Both CNTs-COOH-HAP and GRHAP could be promising multimodal stages to enhance current malignancy therapeutics inferable from their incredible bioactive as well as multi-functionality (Neelgund and Oki 2016).

5 Concluding Remarks

Nanocomposites containing hydroxyapatite are a successful field of biomedical research. The bioactivity of n-HA and its efficiency of being associated with a massive portion of materials also converted with numerous methods have supported the fabrication of a range of nanocomposites with superior properties and fascinating biomedical studies. Its outstanding physicochemical and biochemical properties are correlated to its crystalline phase and its chemical content. In addition, the complication of the structure is achieved with its efficiency of integrating various bioactive minerals and macromolecules that greatly influence the phase development with its biochemical properties.

All these past highlights turn into the reason for the nanocomposite investigatearea searching for improved properties while n-HA is associated with bioactive materials (polymers, bio-glass, ceramics, and clays ect). Hard tissues (bone and teeth) are shaped joining n-HA and collagen protein to acquire an astounding substance in regards to its mechanical strength and elasticity. Analysts have created distinctive methodologies with a specific end goal to consolidate both n-HA and bioactive reinforcing materials in order to investigate how some demanding medical circumstances can be overcome. Several encouraging methods have been connected to acquire the nanocomposites, as discussed expulsion, electro-spinning, freeze drying and solvent casting, however it can be effortlessly comprehended that novel method ready to blend, soften, or make more liquid without debasement n-HA and reinforcing materials, are prospective contender to be utilized for acquiring novel ages of nanocomposites with enhanced physicochemical properties. These nanocomposites can perform with improved quality, long-haul stability, superior compressive and modulus properties, or expanded cytocompatibility.

The significance for biomedical applications isn't just identified with the physicochemical properties of the nanocomposites. They are likewise referred to the biochemical aspects that represent conceivable to encapsulate distinct materials in the HA nanocomposites. Also, they can be utilized as nano-cargo to target particular cells or to manage the arrival of the medication in order to accomplish more

adequacies or sustain discharge. This methodology permits various blends with reinforcing materials that shield the nano-container from the physiological hit or postpones the arrival of the drug material sequentially to accomplish long-haul viability. The advances identified with co-precipitation, deposition, and emulsion, and so on, are significant to formulate the composite viable. They can acquire benefit of the components utilized via the tissue to disguise the composite, process them through suspend or decomposition. Concerning the impact of the physiological chemical features of HA nanocomposites, It has to be observed the case of apatite with the gene, wherever the natural composition permits the loading and sustained release of the gene and proteins into the targeted cell nucleus. HA nanocomposites continue as a recognized and harmless choice to be combined with novel methods as well as advances for enhanced genetic material treatment.

It is likewise significant to say that HA-based nanocomposites can be joined with bioactive reinforcing materials (polymers, ceramic, and clays) to shape composites with particular attributes of porosity and compressive and modulus properties while the live cells can move and recover the tissue meanwhile the composites is debased. Also, this technique for tissue rejuvenation open innovative inquiries regarding how the procedure can be restricted or enhanced as best in the class of operation strategies requires the finest approach for tissue rejuvenation.

Ultimately, the absolute most vital physiological responses in the living beings happen just an interface with the characteristic composites of hydroxyapatite. This reality demonstrates how vital the part of HA nanocomposites for supporting life. At the point when n-HA is mixed with characteristic or manufactured materials, as reinforcing materials, to acquire nanocomposites, the demand and prospects are significant. Toward the end, the nanocomposites put on a show to imitate or enhance what nature has created following million years of development. To investigate on the off chance that it is conceivable is the thing that makes so energizing the examination in this new area. Though, at the premise of the execution of these nanocomposites are intermingle between the synthetic or natural polymer and the hydroxyapatite filler, which can be adjusted and consummated to suit particular requires. We trust that further research into these connections will demonstrate important in thinking about the design of novel hydroxyapatite nanocomposites for biomedical applications.

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3D Printing Technology of Polymer Composites and Hydrogels for Artificial Skin Tissue Implementations

Jenifer Joseph, Kalim Deshmukh, Tran Tung, K. Chidambaram and S. K. Khadheer Pasha

Abstract Today, the need for tissue and organ transplant has occupied the centre stage in the field of biomedical engineering. The requirement and the replacement ratio increase drastically where the supply was not met by the demand due to the lack of donors, poor biocompatibility of tissues from donors that boycotts the transplant itself. On the other hand, from the advancement in technology, it is possible to replace natural tissues with some polymeric hydrogels whose mechanical behaviour and biocompatibility resembles the natural tissues. Additionally, hydrogels are one of the effective materials that offer an aqua environment with enriched oxygen and nutrition content that a biological cell needs. Further, three-dimensional (3D) printing, a manufacturing technique where the biomedical organs are fussed with materials such as plastic, ceramics, liquids, powder, living cell etc. in such a way that it provides a 3D object in the micron-scale resolution. Therefore, the combination of polymer composites, hydrogels and 3D printing has its application in skin bioprinting and tissue engineering. Thus, it contributes in acquiring a new, efficient, cost-effective and enhanced biocompatible biological organ.

Keywords 3D printing · Hydrogels · Polymer composites · Artificial skin · Biomedical field

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K. K. Sadasivuni et al. (eds.), *Polymer Nanocomposites in Biomedical Engineering*, Lecture Notes in Bioengineering,
https://doi.org/10.1007/978-3-030-04741-2_7

List of Abbreviations

3D printing	Three-dimensional printing
AM	Additive manufacturing
APS	Ammonium persulfate
CA	Cellulose acetate
$Ca2^{+}$	Calcium
CAD	Computer-aided design
CMC	Carboxymethylcellulose
dECM	Decellularized extracellular matrix
ECHs	Electro-conductive hydrogels
ECM	Extracellular matrix
FDM	Fused deposition modelling FDM
GelMA	Gelatin methacrylate
GO	Graphene oxide
HA	Hydroxyapatite
KPS	Potassium persulfate
LAB	Laser-assisted bioprinting
MgO	Magnesia
MWCNTs	Multiwall carbon nanotubes
PAN	Polyacrylonitrile
PANI	Polyaniline
PCL	Polycaprolactone
PE	Polyethylene
PEG	Poly ethylene glycol
PEGDA	Poly ethylene glycol diacrylate
PES	Polyethersulfone
PGA	Poly glycolic acid
PLA	Polylactic acid
PLGA	Poly lactic-*co*-glycolic acid
PNIPAAm	Poly *N*-isopropyl acrylamide
PPy	Polypyrrole
PSF	Polysulfone
PTFE	Poly (tetrafluoroethylene)
PU	Poly urethane
PVA	Poly vinyl alcohol
PVC	Poly vinyl chloride
PVDF	Polyvinylidene fluoride
PVME	Poly (viny1 methyl ether)
RP	Rapid prototyping
SFF	Solid-free form technology
STL	Stereolithography
SWCNTs	Single-wall carbon nanotubes

1 Evolution of 3D Printing

Three-dimensional (3D) printing is a mechanism in which 3D solid objects were designed from a digital file. The 3D printing is also known as additive manufacturing (AM)/rapid prototyping (RP)/solid-free forms technology (SFF) that was established by Charles Hull. In 1980s, Hull started working on the fabrication of plastic devices from photopolymers (Gross et al. 2014). The tedious fabrication process in addition to the high chances of design imperfection made him go for several iterations to get it done perfectly. This process triggered him to improve current methods in prototype development. In 1986, he rooted 3D system and promoted the stereo lithography (STL) that can finish the electronic 'handshake' from computer-aided design (CAD) programming and accordingly transmits records to print 3D objects (Jones et al. 2011). Hull developed the initial 3D printer named the 'Stereo lithography Apparatus' which is accessible to the general population, the SLA-250. In addition to Hull's efforts and the evolution of fused deposition modelling (FDM) by Scott Crump in 1990, 3D printing was ready to refashion not only research but also manufacturing areas. In 1993, the MIT teachers Michael Cima and Emanuel Sachs introduced the first device named '3D printer' after which many organizations have progresses 3D printers for commercial uses. 3D printing technology has also got its place in mechanical applications both in automotive and in aviation corporations for printing the models of auto and plane segments. The application of 3D imprinting in architecture includes the printing of structural models and in case of defence, 3D printing is used in gun prototyping. Thus, 3D printing emerged in almost all the areas (Gross et al. 2014; Jones et al. 2011).

2 Concept of 3D Organ-Printing Technology

The notion 3D printing has occupied the centre stage in vast regions including building, fabricating, art, education and drug (Murphy and Atala 2014). The concept of 3D printing in the field of medicine is given more interest considering the complications faced due to the lack of organs. Though there is an increase in the number of volunteer donors, the organ shortage surpasses the transplantation needs. In order to put an end to these serious problems, a long-term solution is needed. In the past three decades, tissue engineering has developed as one of the solutions where the biological organ that mimics the native tissue were created by seeding cells onto the scaffolds thus new cell generates. An extension of tissue engineering is 3D organ printing that has the potential to create de novo organs; the process includes the deposition of living cells along with the hydrogel base scaffolds and it is a computer-aided bio-additive process (Ozbolat and Yu 2013). Thus, in 3D bioprinting, the 3D structure of biological structures is made by arranging the organic samples and living cells explicitly (layer-by-layer) with spatial optimization and placement of functional units.

3 Methods in Bioprinting—A Brief Description

The 3D printing concept is the origin for the evolution of 3D bioprinting. For bioprinting, the bioink is built by biomaterials, living cells, etc. (Arslan-Yildiz et al. 2016; Stanton et al. 2015). If the bioink is prepared just by cells in suspension, then the pre-arranged hydrogel scaffold whereupon the bioink printed is turned to be a bio paper (Xu et al. 2006). Figure 1 shows the fabrication of the biomaterial based on bioprinting that has some successive stages such as designing of ink, computer-assisted designs of the scaffold complex, reading script using a computer program, final shaping done by depositing the specimen through hardware and specimen testing followed by culturing them in bioreactor (Pati et al. 2016; Gu et al. 2016; Włodarczyk-Biegun and del Campo 2017).

4 Approaches for 3D Bioprinting

In order to perform 3D bioprinting effectively, three central approaches are there such as biomimicry, autonomous self-assembly and mini-tissue as shown in Fig. 2.

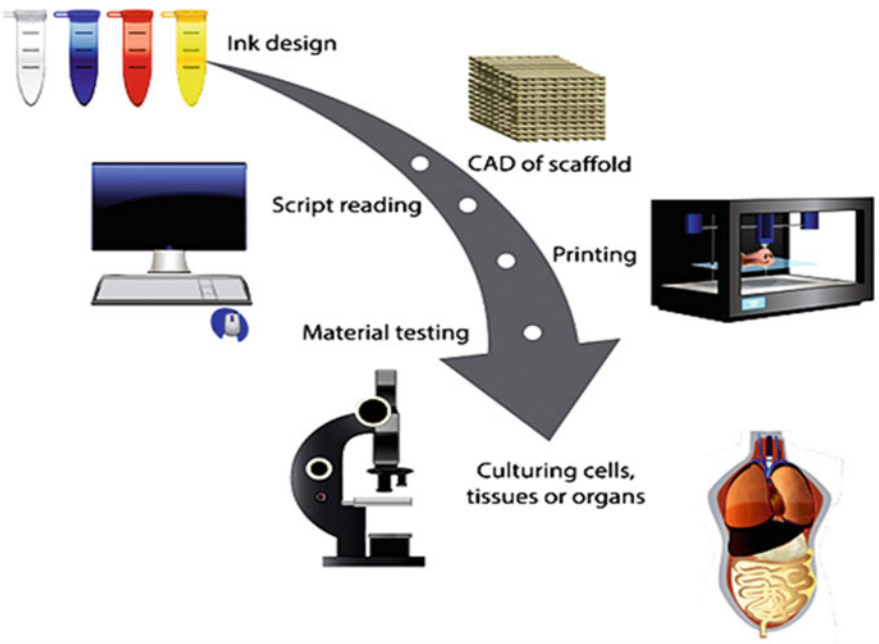

Fig. 1 The process of material printing (Włodarczyk-Biegun and del Campo 2017). Copyright 2017. Reproduced with permission from Elsevier Ltd.

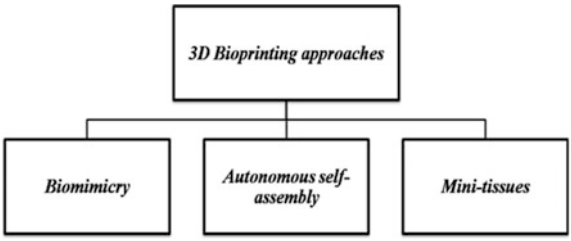

Fig. 2 Representation of the approaches in 3D bioprinting

4.1 Biomimicry

Biologically influenced engineering techniques have been implemented in various application areas to solve numerous technological issues such as materials research (Reed et al. 2009), cell-culture techniques and nanotechnology (Huh et al. 2012). The well engineered biological system has a great response in the case of 3D bioprinting applications such as manufacturing the identical reproductions of the cellular and tissue/organ's extracellular components (Ingber et al. 2006). This can be accomplished by the re-creation of definite cellular functional units of tissues like replicating the branching arrangements of the vascular tree or assembling physiologically precise biomaterial groups and gradients. This method is valid only when the biological tissue is on the micro-scale range. Thus, it is obvious to analyse the microenvironment, such as the distinct settlement of functional and aiding cell types, gradients of soluble/insoluble aspects, content of the extracellular matrix (ECM) and the quality of the biological strength within the microenvironment. These preliminary ideas will help in succeeding this technique (Murphy and Atala 2014).

4.2 Autonomous Self-assembly

Autonomous self-assembly is a 'scaffold-free' technique where the cellular organization mimics the evolving tissues and self-assembling cellular spheroids bear coalition. It depends upon the cell, as the elementary driver of histogenes is operating the content along with the localization, structural and functional properties of the tissue (Derby 2012; Kasza et al. 2007). It is necessary to have the knowledge of developed mechanisms of immature tissue genesis and organogenesis in order to drive undeveloped mechanism in bioprinted tissues (Murphy and Atala 2014).

4.3 Mini-Tissues

The approach can be related to both biomimicry and autonomous self-assembly techniques of 3D bioprinting. In this technique, organs and tissues amount to tinier,

functional building blocks are also called mini-tissues (Kelm et al. 2010). It tends to be characterized as the basic structural and functional unit of a tissue, like a kidney nephron. Mini-tissues are made and arranged into the bigger construct by logical model, either by self-assembly technique or by the combination of both methods (Murphy and Atala 2014).

5 Tissue Bioprinting Strategies

Figure 3 reveals the flow chart of different technologies used for printing of biological materials they were inkjet (Xu et al. 2013), micro-extrusion (Iwami et al. 2010) and laser-assisted printing (Guillotin et al. 2010), respectively. In addition to this, the schematic representations of these strategies are shown in Fig. 4 and their advantages and disadvantages were compared in Table 1.

5.1 Inkjet Bioprinting

Inkjet printers or drop-on-demand printers are the one of the widely utilized kinds of the printer in both non-natural and biological applications. In this type of printers, controlled amount of fluids are deposited into predefined regions. These printers are formed by modifying the monetarily accessible two dimensional (2D) ink-based printers (Xu et al. 2008) where the ink in the cartridge was altered by a biological material, and the paper was changed by an electronically guarded lift arrangement in order to afford the authority over *Z*-axis along with the two axes (X and Y) (Xu et al. 2008). At this point, the inkjet-based bioprinters are specially crafted and ready to deal with and print biological samples with enhanced resolution, accuracy and speed. This printer uses either thermal (Cui et al. 2012) or acoustic (Xu et al. 2008) forces to discharge the drops of fluid onto a substrate (Murphy and Atala 2014). Thus, the two sub-categories of inkjet bioprinters are thermal inkjet printers and piezoelectric inkjet printers.

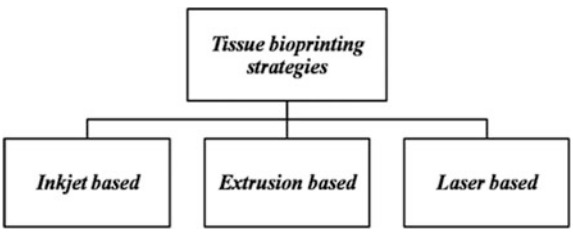

Fig. 3 Types of bioprinting strategies

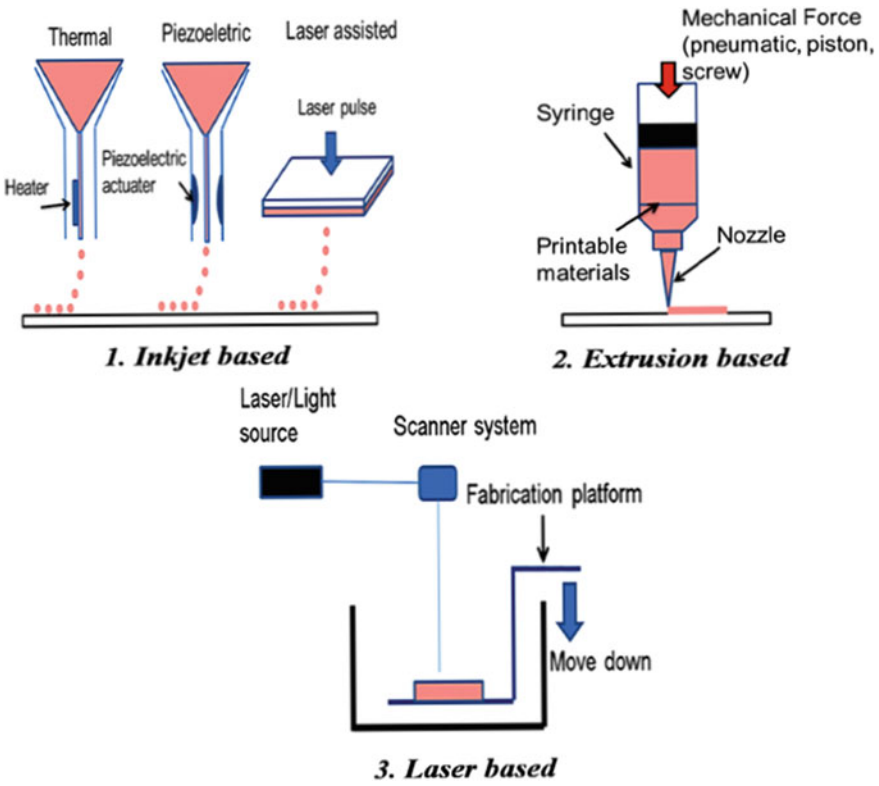

Fig. 4 Schematic representation of different bioprinting strategies (Duan 2017). Copyright 2017. Reproduced with permission from Springer

5.1.1 Thermal Inkjet Printers

In this case, the print head has been heated electrically in order to deliver pulses of pressure which pushes beads from the nozzle. Form the literature survey, it is clear that this confined heating that can vary between 200 and 300 °C will not have a massive effect on the strength of biological molecules (Okamoto et al. 2000) and the viability of mammalian cells (Murphy and Atala 2014; Xu et al. 2005).

5.1.2 Piezoelectric Inkjet Printers

Several inkjet printers consist of a piezoelectric crystal which generates an acoustic wave within the print head to crack the fluid into beads at customary interims (Murphy and Atala 2014). When the voltage is applied to a piezoelectric substance, a quick variation in the shape was induced that produces the pressure required to discharge droplets from the nozzle (Murphy and Atala 2014). Scarcely any inkjet

Table 1 Advantages and disadvantages of bioprinting strategies

Bioprinting strategies	Advantages	Disadvantages	References
Inkjet printers	It is low cost, high speed It has multimaterial capability	Posses moderate strength	Rengier et al. (2010)
Extrusion based	High resolution and accuracy, capability to produce high degree-of-freedom motion, the ability to dispense various biomaterials simultaneously, Is friendly, compact, sterilizability, affordability and versatility	Still more to be investigated to generate robust and viable end-products for applications such as pharmaceutics, transplantation and clinics	Ozbolat and Hospodiuk (2016), Dababneh and Ozbolat (2014), Ozbolat (2015)
Laser based	Is without nozzle, consequently issue of stopping up with cells or samples can be bypassed LAB is compatible with viscosities ranges from 1 to 300 mPa/s In LAB, the cells with density of up to 108 cells/ml with micro-scale resolution of a solitary cell can be deposited per each drop utilizing a laser pulse recurrence rate of 5 kHz, with acceleration up to 1600 mm/s	Less flow rate Synthesis of every individual ribbon is time consuming	Murphy and Atala (2014), Guillotin et al. (2010), Guillotin and Guillemot (2011)

printers' uses acoustic radiation constrains joined with an ultrasound field in order to discharge liquid beads from an air–liquid interface (Murphy and Atala 2014; Fang et al. 2012).

5.2 Micro-Extrusion Bioprinting

Micro-extrusion printers are one of the most familiar and economical non-biological 3D printers. It works by mechanically controlled extrusion of a substance that is collected onto a substrate by a micro-extrusion head. It provides uninterrupted beads of material instead of fluid droplets. A myriad of materials, for example, biocompatible copolymers, cell spheroids and hydrogels, were adaptable

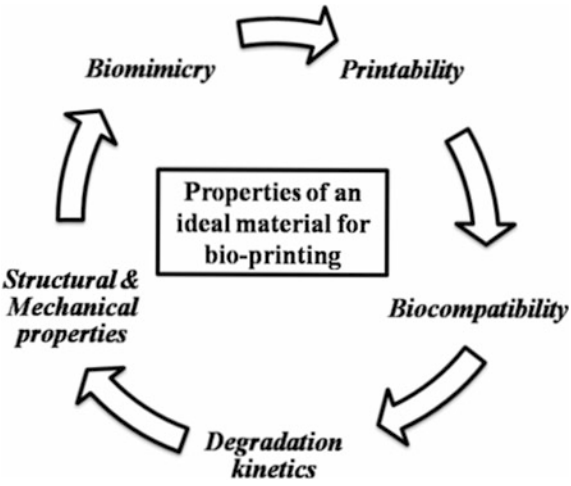

Fig. 5 Properties of an ideal bioprinting material

with the micro-extrusion printers (Peltola et al. 2008). Pneumatic (Chang et al. 2011) or mechanical cylinder or screw (Visser et al. 2013) administering frameworks are the well-known strategies to expel biological materials in 3D organ-printing applications. Also, the materials with viscosity vary from 30 mPa/s to $>6 \times 10^7$ mPa/s can be suitable for micro-extrusion bioprinters (Murphy and Atala 2014; Jones 2012).

5.3 Laser-Assisted Bioprinting

Laser-induced forward transfer is the principle behind the functioning of Laser-assisted bioprinting (LAB) (Barron et al. 2004). Laser-induced forward transfer technique was implemented effectively in biological components including cells, DNA and peptides (Colina et al. 2005; Dinca et al. 2008). Though LAB is not as familiar as inkjet or micro-extrusion bioprinting, its applications in engineering the organs and tissue have increased. A typical LAB device comprises of a pulsed laser shaft, a focusing framework, a 'ribbon' with a donor transit bolster (Murphy and Atala 2014). In order to replicate the biological systems, the bioprinting material should possess the characteristics as shown in Fig. 5.

6 Polymers with Biomedical Compatibility

Biopolymers such as Polycaprolactone (PCL), Polylactic acid (PLA) and poly lactic-*co*-glycolic acid (PLGA) were widely utilized as common materials for scaffolding. Biopolymers added with hydroxyapatite (HA) have shown outstanding

chemical and biological properties leading to bone tissues. To the biopolymers, some other additives were used in scaffolding (Poh et al. 2016; Tsai et al. 2017; Wong et al. 2014; Kim and Kim 2015). In recent days, research work has been done on numerous nanomaterials to understand their function as an additive with biopolymers. Few examples are magnesia (MgO) was added to PCL that shows a significant change in the regulation of signal transduction, stamina metabolism and cell multiplication that leads to the new bone arrangement (Roh et al. 2017). On the other hand, when PCL is added with magnetic nanoparticles like Fe_3O_4 or γ-Fe_2O_3 provides the scaffold with the potential of magnetic heating that triggers proliferation (Meng et al. 2013; Zhang et al. 2014). They are also research work based on nanomaterials including nanoclay, single-wall carbon nanotubes (SWCNTs), multiwall carbon nanotubes (MWCNTs), graphene and graphene oxide—GO with polymers (PCL/PLA) has been reported (Gonçalves et al. 2016; Aboutalebi Anaraki et al. 2015; Yang et al. 2016) in order to customize the thermal, electrical and mechanical properties of the base biopolymer (Wang et al. 2017). In particular, thermoplastic polymers have been commonly used to produce supporting frameworks in combination with other materials for engineering clinically relevant and mechanically robust tissues, such as bone and cartilage. A high viscosity thermoplastic polymer, such as PCL and PLGA, has their own unique properties, including good printability and high strength to maintain 3D shapes (Park et al. 2015, 2016; Lee et al. 2017; Shim et al. 2016; Jang et al. 2018).

Cheng et al. (2014) worked on making Heparin (an anti-coagulant/blood thicker) and heparin-like emulating polymer-functionalized biomedical membranes which has an exceptional demand in the biomedical applications, for example blood refinement and organ fabrications, etc. The heparin and heparin-like emulating polymer-functionalized membranes were outstanding materials for the medication of organ deterioration and blood-contacting areas. The widely used artificial membranes that are commercial were comprised of polymeric materials like cellulose acetate (CA), polyacrylonitrile (PAN), polyurethane (PU), polysulfone (PSF), polyvinylidene fluoride (PVDF), polyvinyl chloride (PVC), polyethylene (PE), polyethersulfone (PES), polytetrafluoroethylene (PTFE) and also various kinds of polyesters such as PLA, PCL and poly glycolic acid (PGA) (Zhu et al. 2013). The polymeric membranes have explored its properties in numerous expansive applications like fluid and gaseous separation, catalysis, biomaterials and lab-on-a-chip advances (Cheng et al. 2014; Ulbricht 2006).

7 Hydrogels

A 3D polymeric network hydrogels were produced using hydrophilic-natural or manufactured polymers. Thus, hydrogels/hydrophilic polymer networks have the potential to absorb a significant quantity of fluids from the neighbouring atmosphere (Ullah et al. 2015; Varaprasad et al. 2017).

7.1 Classification of Hydrogels

Hydrogels have been classified under two broad categories: one is the cross-linkage mechanism oriented and the other is based on the physical properties as shown in Fig. 6. They are explained under two divisions (i) physical cross-linkage or self-assembled hydrogel (ii) chemical cross-linkage hydrogel (Ullah et al. 2015; Varaprasad et al. 2017; Yue et al. 2015). Different cross-linking methods were depicted in Fig. 7, and various applications of physical and chemical cross-linking are summarized in Table 2.

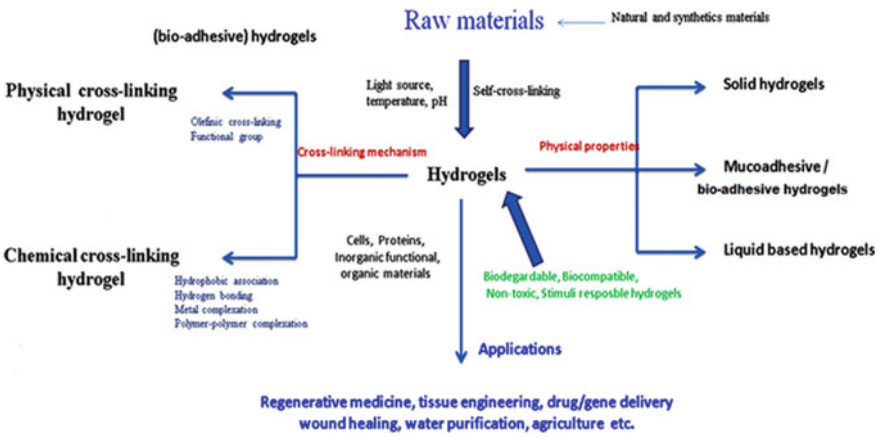

Fig. 6 Flow chart of classifications of hydrogels (Yue et al. 2015). Copyright 2015. Reproduced with permission from Elsevier Ltd.

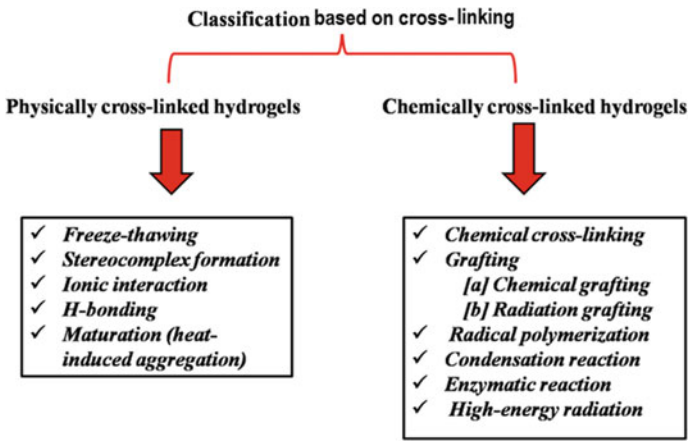

Fig. 7 Flow chart of various methods to obtain physical and chemical cross-linked hydrogels

Table 2 Various applications of physically and chemically cross-linked hydrogels (Varaprasad et al. 2017)

Cross-links	Method	Polymers	Application
Physically cross-linked hydrogel	Freeze-thawing technique	Poly vinyl alcohol (PVA), PVA/chitosan, PVA/starch, PVA/gelatine	Therapeutic applications, Tissue engineering (Varaprasad et al. 2017)
	Stereocomplex Formation technique	Dextran, PLA Poly ethylene glycol—PEG	Drug delivery Biomedical and pharmaceutical (Varaprasad et al. 2017)
	Ionic interaction technique	Cellulose microfibrils Chitosan	Drug delivery Antigen delivery (Varaprasad et al. 2017)
	H-bonding technique	Hyaluronic acid Cyclodextrin, polypseudorotaxane	Drug delivery Biomedical (Varaprasad et al. 2017)
	Maturation (heat-induced aggregation) technique	Alginate capsules Hyaluronic acid	Cartilage tissue Delicate tissue engineering, cell scaffold, advancing medicine and in also, ligament repair (Varaprasad et al. 2017)
Chemically cross-linked hydrogel	Chemical cross-linking technique	PEG	Biomedical
	Grafting		
	(a) Chemical grafting technique	Chitosan-cellulose, PCL, PEG	Agriculture and horticultural
	(b) Radiation grafting technique	Carboxymethyl cellulose, styrene sulphonate	Water purging (Varaprasad et al. 2017)
	Radical technique polymerization technique	Kolliphor Poly ethylene glycol methyl ether methacrylate	Antibacterial Antifouling (Varaprasad et al. 2017)
	Condensation reaction technique	B-Cyclodextrin	Restrained delivery (Varaprasad et al. 2017)
	Enzymatic reaction technique	PEG, methacrylate Chitosan	Tissue engineering and Bio catalysis Wound dressing (Varaprasad et al. 2017)
	High-energy radiation technique	Poly oligo propylene glycol methacrylate Polyvinyl methyl ether	Biomedical Biological (Varaprasad et al. 2017)

7.1.1 Physical Cross-Linkage Hydrogels

Physical cross-linkage hydrogels (also known as reversible gels) have picked up popularity because of their easy production and potential to be free from cross-linking agents during synthesis process (Varaprasad et al. 2017). The physical collaborations that take place between distinct polymer chains can stop the disintegration of physically cross-linked gels (Varaprasad et al. 2017; Slaughter et al. 2009). The election of hydrocolloid group relies upon the concentration and pH that develops a vast collection of gel textures and is presently drawing appreciable attention, in areas like nourishment, pharmaceutical and biomedical zones because of the usage of cross-linking materials being restricted (Varaprasad et al. 2017; Slaughter et al. 2009; Chung and Park 2009). On the basis of literature survey, different techniques for acquiring physical cross-linkage hydrogels were explained as follows.

(i) **Freeze-thawing**

Repetitive freeze-thaw cycles result in achieving physical cross-linking. In this technique, the microcrystal in the complex can be developed because of freezing and thawing (Varaprasad et al. 2017). One of the well-known examples is the preparation of PVA hydrogels by freeze-thawing. These hydrogels were attached by hydrogen bonds, exhibiting high porosity, sponginess, rubbery with improved elasticity than PVA hydrogels that are prepared by different techniques (Varaprasad et al. 2017; Jayaramudu et al. 2016a).

(ii) **Stereocomplex formation**

For drug delivery systems, the stereo complex formation-based hydrogels were developed in the recent times (Varaprasad et al. 2017). The hydrogels can be effectively assembled by liquefying every individual material in water and blending the solution, and this is one of the considerable advantages of this system. PLA is a standout among other cases that offer great stereo complex properties (Varaprasad et al. 2017).

(iii) **Ionic interaction**

This category contains the hydrogels of ionic polymers that are cross-linked with the inclusion of di-/tri-valent counter. The gelling of polyelectrolyte solution with multivalent ions of opposite charge is the principle under which this technique functions (Varaprasad et al. 2017). Some hydrogels that falls under this class were as follows: poly-[di(carboxylatophenoxy) phosphazene] calcium salt and chitosan-glycerol phosphate salt (Varaprasad et al. 2017; Zhao et al. 2009; Ebara et al. 2014).

(iv) **H-bonding**

The physical cross-linkage gel-like complexes were formed from hydrogen-bonding interactions (Varaprasad et al. 2017).

(v) **Maturation**

It involves a heat-instigated aggregation mechanism that outcomes in the arrangement of hydrogel with accurately complexed molecular dimensions. The heat-instigated gelation of gum arabic is one of the perfect examples of this hydrogel system (Varaprasad et al. 2017). This aspect is recognized because of the collection of proteinaceous segments exhibit in gum arabic, produced from thermal treatment. The mechanical properties along with the water binding ability of the hydrogel are enhanced as the molecular weight increases due to aggregation (Varaprasad et al. 2017; Aoki et al. 2007).

7.1.2 Chemical Cross-Linkage Hydrogels

(i) **Chemical cross-linking**

When covalent bonds occur amidst various polymer chains, there comes the evolution of chemically cross-linked hydrogels. Thus, chemically cross-linked hydrogels are stable and cannot be broken up in any solvents due to the presence of strong covalent cross-links (Varaprasad et al. 2017). In case of physically cross-linked hydrogel, there is a lack of flexibility as it faces difficulty to decouple the factors including, gelation time, pore size of the inner network, chemical functionalization and debasement time (Varaprasad et al. 2017; Slaughter et al. 2009), whereas in the case of chemical cross-linking, the networks are with comparatively increased mechanical stability and on the basis of the chemical bonds and the cross-links, the degradation period can also be extended (Varaprasad et al. 2017). The various techniques involved in getting chemically cross-linked hydrogels are listed as follows.

(ii) **Grafting**

Hydrogels can be prepared from grafting through the process of polymerization of a monomer. Depending on the activation initiator, grafting can be differentiated as, chemical or radiation grafting (Varaprasad et al. 2017).

(iii) **Chemical grafting**

In chemical grafting, the macromolecular backbones were stimulated with the response of chemical reagents (Varaprasad et al. 2017).

(iv) **Radiation grafting**

In radiation grafting, high-energy radiation such as gamma (γ) and electron beams initiates the grafting process (Varaprasad et al. 2017). An example of radiation grafting includes the grafting of carboxymethylcellulose (CMC) using acrylic acid with the existence of electron beam radiation in aqueous solvent. The free radical polymerization of acrylic acid on the backbone of CMC can be stimulated by utilizing electron beam (Varaprasad et al. 2017; Said et al. 2004).

(v) **Radical polymerization**

In this technique, chemically **c**ross-linked gels were derived from monomers (less-molecular-weight) in combination with a cross-linking agent. This efficient and extensively implemented method for preparing hydrogels and forming gels is quick even under gentle atmosphere (Varaprasad et al. 2017). Hydrogel prepared using free radical initiator: potassium persulfate (KPS)/ammonium persulfate (APS) is the best example of this method (Varaprasad et al. 2017; Jayaramudu et al. 2016b).

(vi) **Condensation reaction**

The formation of hydrogels by means of condensation reactions falls under this division. Usually, the hydrogels with hydroxyl groups and carboxylic acids or their subordinates are utilized for the development of these kinds of hydrogels. De Nooy et al. (1999, 2000) have given the perfect example of this condensation reaction by means of Passerini and Ugi condensation process.

(vii) **Enzymatic reaction**

It is a unique hydrogel approach, where hydrogels are formed from the enzymatic reaction. Sperinde et al. (Sperinde and Griffith 1997) proclaimed an intriguing technique where PEG-based hydrogels are fabricated from an enzyme.

(viii) **High-energy radiation**

To polymerize a compound that is unsaturated, a high-energy radiation (γ-electron beam radiations) can be applied. When polymers that are soluble in water exposed to γ-electron beam emission, they become derivatized with vinyl groups in order to produce radicals on the polymer chains by the homolytic scission (Varaprasad et al. 2017). In addition to this, micro-radicals are formed when a emission of high energy promotes water molecules to create hydroxyl groups which strike the polymeric chains. The covalent bonds, which offers a cross-linked complex, can be formed when micro-radicals combines with various chains (Varaprasad et al. 2017). A major benefit in this technique is that the procedure can be carried out in water under gentle conditions without the influence of any harmful cross-linking agents. But one of the disadvantages is that the irradiation creates C=C cross-links which results in the formation of non-biodegradable gels (Varaprasad et al. 2017; Hennink and van Nostrum 2012). Few cases that falls in this class were the evolutions of poly viny1 methyl ether (PVME) and poly N-isopropyl acrylamide (PNIPAAm) hydrogels which are obtained by applying high-energy γ-emission (Varaprasad et al. 2017; Kishi et al. 1993; Suzuki and Hirasa 1993).

7.2 *Hydrogels Classified Under Physical Properties*

Nowadays, due to the noteworthy physical properties, the evolved hydrogels have immense significance in biomedical applications because of their peculiar properties like swelling and dissemination (Varaprasad et al. 2017). Based on the physical properties, hydrogel has been categorized into three forms, solid, semi-solid and liquid as shown in Fig. 8.

7.2.1 Solid Hydrogels

It has the potential to mimic the most complex tissue architecture; also it replicates the organic tissues physical, chemical, electrical and biological properties (Varaprasad et al. 2017).

7.2.2 Semi-solid Hydrogels

They possess a durable adhesive interaction with interfacial forces like van der Waals, hydrogen bonds, electrostatic and delicate tissue networks which makes them applicable for the extended drug delivery and efficient dosage applications in biomedical areas including buccal, ocular, rectal, vaginal, nasal and sublingual routes (Varaprasad et al. 2017).

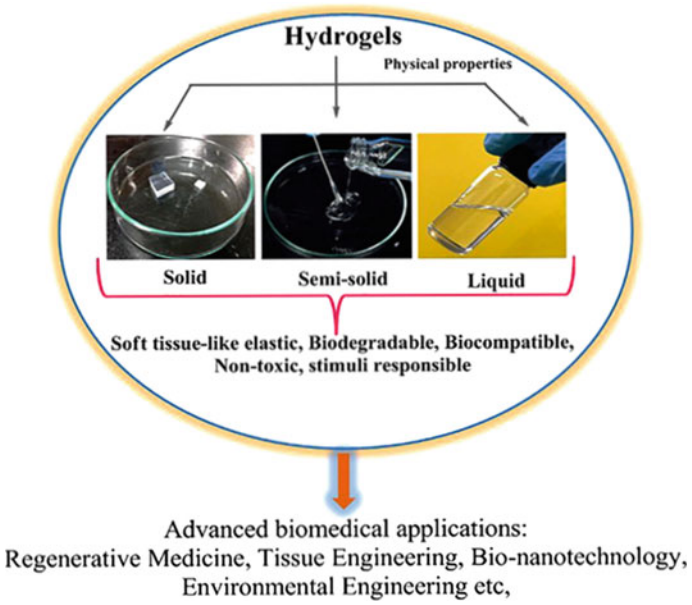

Fig. 8 Hydrogels with various physical forms (Varaprasad et al. 2017). Copyright 2017. Reproduced with permission from Elsevier Ltd.

7.2.3 Liquid Hydrogels

Hydrogels of these kinds are of great interest due to their flexible synthesis and the ability of self-alteration of their system as indicated by ecological conditions. The organic, inorganic, medication, proteins and cells can be fused effortlessly in the hydrogels with no surgeries which is the fundamental points of interest of this technique. Due to its highly hydrophilic properties, these drugs can be injected into the living systems (Varaprasad et al. 2017).

7.3 Role of Hydrogels in Biomedical Applications

As discussed, the properties of hydrogels make them applicable in many fields as illustrated in Fig. 9.

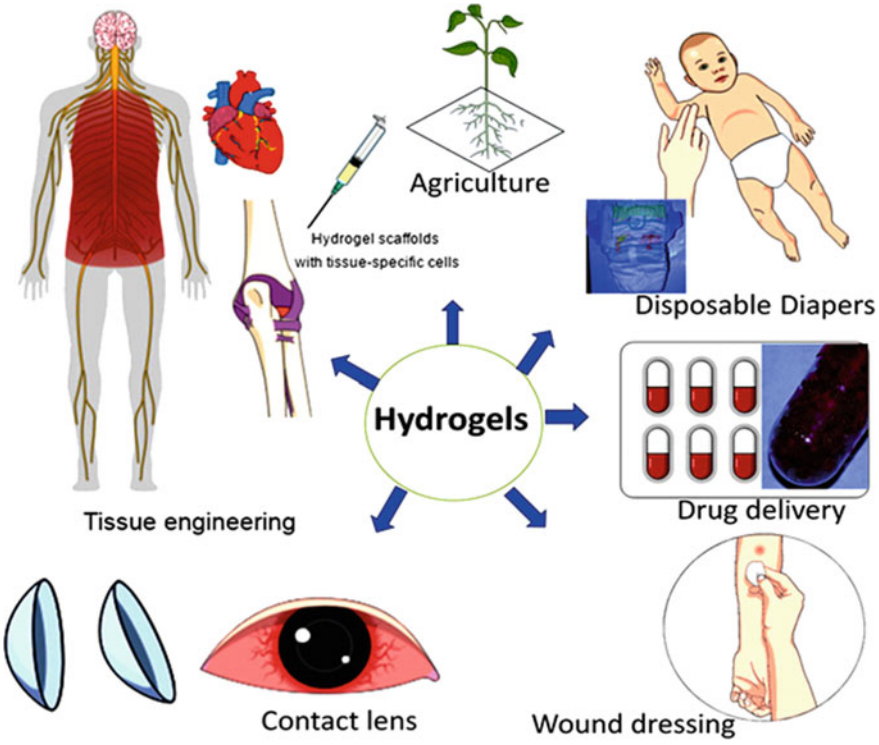

Fig. 9 Applications of hydrogel in their various fields (Yue et al. 2015). Copyright 2015. Reproduced with permission from Elsevier Ltd.

8 Need for Polymeric Hydrogels

Hydrogel plays a huge role in medical applications because of its closeness to its inherent ECM, in addition to its impressive biocompatibility, controllable mechanical and biochemical behaviour (Ullah et al. 2015; Yue et al. 2015). But, the main drawback of hydrogels is that they are non-conductive, that restricts their application as bioactive scaffolds for sensitive tissues, such as neural, cardiovascular and furthermore skeletal muscle tissues (Wu et al. 2016). But the electro-conductive behaviour of the hydrogels can be optimized by fusing it with other materials (nanomaterials or conducting polymers). Few examples for the materials added to hydrogels including carbon nanotubes, gold nanoparticles, GO and silver nanowires and conductive polymers such as polyaniline (PANI), polypyrrole (PPy), polythiophene (PT) to the hydrogel network (Wu et al. 2016; Lu et al. 2014; Kaith et al. 2015; Kaur et al. 2015; Shin et al. 2016). The utility of electro-conductive hydrogels (ECHs) and conductive polymers has increased in different biomedical applications, for example electrochemical biosensors, and electro-responsive medication conveyance systems because of their response with electrical stimulation (Noshadi et al. 2017). Mechanical stability of the material is also enriched when biodegradable polymers are added with hydrogel (Kang et al. 2016). On the other hand, synthetic thermoplastic materials are gaining popularity not only because of biodegradable polymers but also numerous different polymers can be combined to produce mechanically stable constructs. Though hard thermoplastic polymers are thoroughly applicable for musculoskeletal organs but for 3D printing it may not be ideal for soft tissue engineering (Radenkovic et al. 2016). Vandenhautea et al. (Vandenhaute et al. 2017) reported that the hydrogel degrades with the change in time and reveals its noticeable degradation while storing in dry and wet conditions both room temperature and at body temperature. From the results, it is confirmed that the application of hydrogels for self-healing concrete was obviously limited. However, biodegradation may be especially useful for various biomedical applications like drug delivery.

8.1 Polymeric Hydrogels in Biomedical Applications

In the earlier days, 3D printing mechanisms were designed in such a way that it will be applicable only for non-biological applications including thin film coating of metals, ceramics and polymers, etc., and with the presence of parameters like organic solvents, processing at elevated temperatures or cross-linking substance made them unsuitable with living cells and biological systems. Hence, the ultimate challenge here is to not only discover a material that is good with organic materials and the printing procedure yet in addition should offer the required mechanical and functional properties for tissue builds (Murphy and Atala 2014). Natural polymers such as gelatin, fibrin, collagen, chitosan, etc., and synthetic polymers such as PEG

play a major role in regenerative prescription for repair and recovery of tissues. The main benefits of using organic polymers for 3D organ-printing and other tissue-designing applications are their resemblance to human ECM, and their in-built bioactive property. Also, various natural polymers have high molecular weights that develops the gels with increased viscosities with lesser protein concentrations and decreasing obstruction for cells in comparison with the engineered biodegradable materials (Włodarczyk-Biegun and del Campo 2017). On the other hand, the convenience of using engineered polymers that the physical properties can be modified according to specific applications. The drawback of manufactured polymers incorporates poor biocompatibility, lethal debasement items and a lessening in mechanical properties during degradation. Still, engineered hydrogels that are hydrophilic and also retentive are desired candidate for 3D organ-printing and regenerative-medication applications because of its ability to control their physical properties while synthesizing (Murphy and Atala 2014).

8.2 Hydrogels for Skin Bioprinting

Tissue engineering-skin constructs technology has limited the problems faced due to the restricted number of donor skin, and this technology actually transformed an injury management done using traditional wound dressings into a bioactive cell-impregnated skin construct (Ng et al. 2016). Various biomaterials were suitable for organ-printing and tissue-building applications, such as metals, hydrogels and ceramics (Ng et al. 2016). But the factor that makes polymer hydrogels special because it has a 3D structure with cross-linkage that is enriched with an immense measure of water through hydrogen-bonding interactions, which results in high hydrophilicity. These remarkable hydrophilic qualities with cell non-harmfulness make polymer hydrogels a helpful tissue-building tools (Jeong et al. 2017). As we know, polymer-based hydrogels are known for their similarity to the structural ECM to advance cell proliferation with development. Thus, polymeric hydrogels have been taken into consideration when it comes to scaffolding such as burn injuries and cares for skin (Jeong et al. 2017). In Fig. 10, a skin biopsy is gathered from the patient and to get a desired measure of cells it is cultured in vitro. To make a bioprinted skin constructs, bioinks as cell suspensions, cell-epitomized hydrogels are utilized. Under immersed atmosphere followed by an air–liquid interface, the printed constructs are cultured to achieve a matured skin that is compatible with tissue transplantation (Ng et al. 2016).

8.3 Hydrogels in Tissue Regeneration

It is well-known that polymers occupy an important role in the 3D bioprinting especially as scaffolds in tissue engineering applications. Polymers which are used

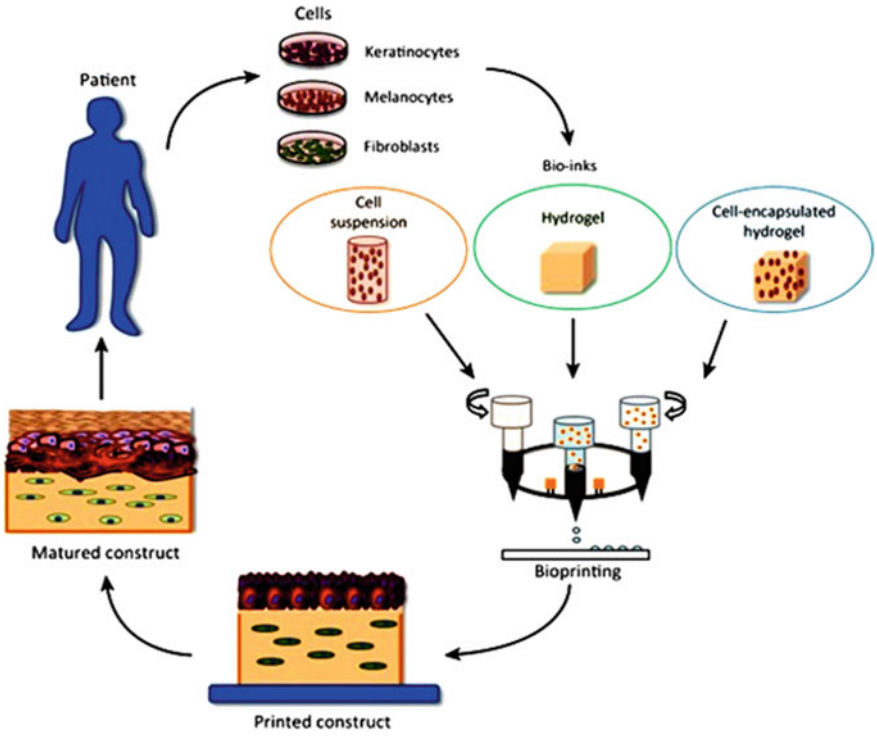

Fig. 10 Representation of bioprinting-skin tissue transplantation (Ng et al. 2016). Copyright 2016. Reproduced with permission from Elsevier Ltd.

in the formation of hydrogels include manufactured poly ethylene glycol diacrylate (PEGDA) and organic gelatine methacrylate (GelMA) (Billiet et al. 2014). Due to the attractive properties like biocompatibility, tuneable mechanical property and their capability to be hydrated and still being insoluble and not losing its 3D structure are remarkable which enables them to mimic biological tissues. The engineered polymers such as PLGA and PCL have certain advantages like minimal toxicity. The major drawback of using PLGA is that it results in inflammatory reaction while oligomers development (Intra et al. 2008). Infection has a serious impact on tissue recovery prompts poor functioning of tissue or even dismissal of the embedded scaffold. Hence, it is essential to control the height of inflammation. Research has been done already where 3D printed PLA and chitosan scaffolds were contrasted for their capacity to induce infection of their effect on tissue recovery (Almeida et al. 2014; Do et al. 2015).

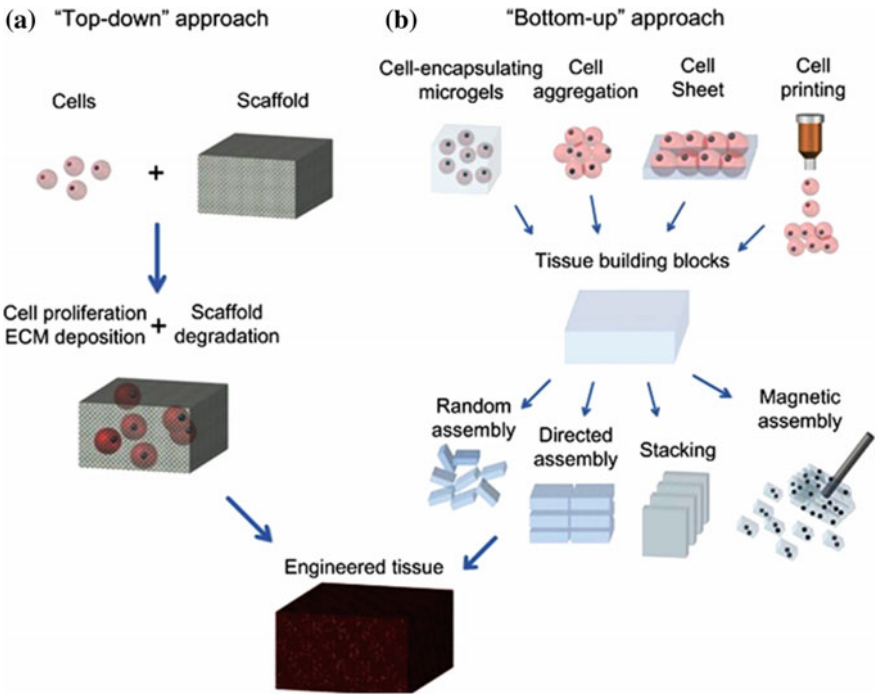

Fig. 11 Schematic representation of 'top-down' and 'bottom-up' approaches for tissue engineering (Lu et al. 2013). Copyright 2013. Reproduced with permission from Dove Medical Press Ltd.

9 Different Approaches for Tissue Engineering

Various tissue engineering techniques were produced to face the difficulties of reconstructing/reproducing very convoluted and functional tissues (Zhang et al. 2017). The traditional method for loading the cells is done by making use of scaffolds as matrices as shown in Fig. 11. The scaffolds are prepared either from intrinsically derived polymers such as gelatin, collagen, hyaluronic acid and alginate (Drury and Mooney 2003; Hoffman 2012) or engineered polymers such as PCL, PLA, PGA, and PLGA (Zhang et al. 2013, 2017). The scaffolds act as 3D templates which facilitate the cells to adhere, multiply and enlarge all through the integrated structure before they grow their own ECM, that at last prompts the production of developed cell-laden grafts with equal properties to their native counterparts. From analysis, it is clear that the phenotypes of seeded cells can be coordinated in the scaffolds by implementing a sequence of various organic and physical stimuli such as development factors (Tayalia and Mooney 2009) shear stress with electric and mechanical cues. But these traditional scaffold-based approaches have certain limitations such as the intrinsic inefficiency to mimic the complicated microstructures of biological tissues (Zhang et al. 2017).

10 Selection of Bioinks

A successful bioprinting begins with the selection of desired biomaterials as the bioink. Bioinks obtained from both organic and inorganic biomaterials has been used as they offer a wide range of properties including biocompatibility, printability and long-standing functionality. For example, the flexibility in deposition of free-standing structures depends on the viscosity of the bioink which is one of the vital rheological factors. Commonly used bioinks are shear thinning biomaterials including Pluronic, gelatin, PEG-based materials or their combinations with other hydrogels. These bioink can prevent the structure from collapsing as they acquire a liquid-like behaviour while experiencing extreme shear stress during the extrusion procedure, yet at that point rapidly recovers its gel state after bioprinted. In order to obtain more stabilized bioprinted structures, the bioprinted tissue constructs generally rely on a secondary cross-linking mechanism (Zhang et al. 2017). The cross-linking mechanisms are of two types: (i) Physical cross-linking and (ii) Chemical cross-linking.

Physical cross-linking are formed by means of non-covalent interactions for example, thermally actuated sol–gel transitions or ionic interactions while, chemical cross-linkage: such networks were developed due to the evolution of advanced covalent bonds (Zhang et al. 2017; Malda et al. 2013). For example, it is obvious that a solid physical hydrogel can be formed when alginate solutions which rapidly cross-link's with the presence of $Ca2^{+}$ ions (Christensen et al. 2015). Also, permanent 3D polymeric networks are developed when GelMA hydrogels are photo cross-linked with the existence of a photo-initiator upon light exposure (Yue et al. 2015). Due to the instability of physically cross-linked gels over a long time, they can be efficient outlaw formats where just fleeting dependability is required including making of conciliatory bioprinted constructs like the vasculature systems. On the other hand, chemically cross-linked gels are suited for helpful bioprinting to work as the biomimetic ECM as they acquire better long-term stability than physically cross-linked gels (Zhang et al. 2017).

As already discussed both natural biopolymers and synthetic polymers has been experimented to satisfy some required prerequisites for use as bioinks (Zhang et al. 2017). Though this bioinks from natural/synthetic polymer helps in the growth and enhances the activity of bioprinted living cells as they may fail to offer the support as sacrificial/constructive scaffolds. To overcome this drawback, recently a category of naturally derived composite biomaterials namely decellularized extracellular matrix (dECM). dECM contains a distinct advantage because it has the potential to administer materials from a similar tissue in the bioprinting procedure, which provides a very much coordinated compositional many sided quality with the engineering allegiance between the printed natural structures and the objective tissues as shown in Fig. 12. Nowadays dECM has occupied the centre stage for their application as bioinks (Murphy and Atala 2014; Zhang et al. 2017; Pati et al. 2014).

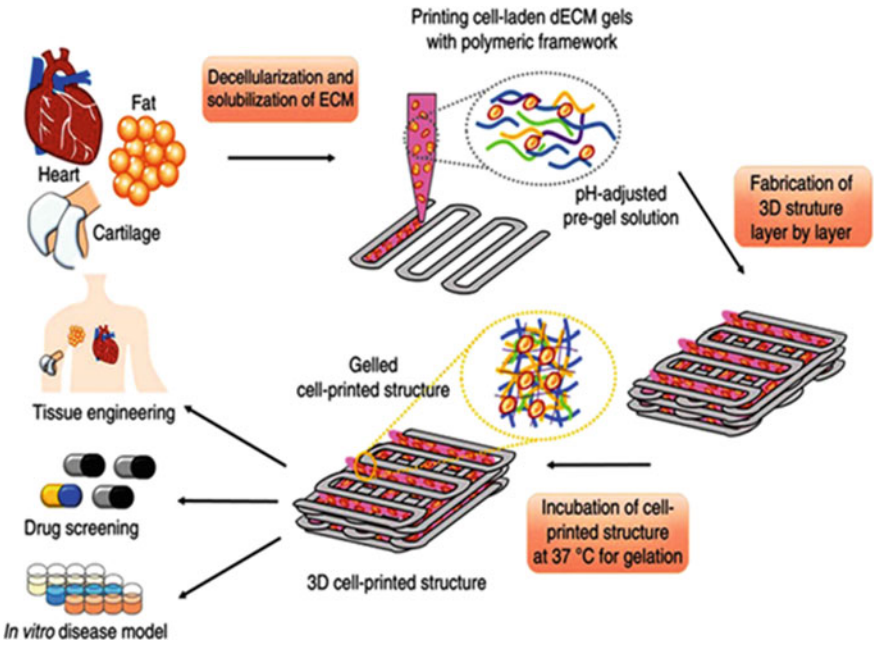

Fig. 12 Tissue printing process using dECM as bioink (Pati et al. 2014). Copyright 2014. Reproduced with permission from Nature Publishing Group

11 Advantage of 3D Printing Technology

- The main factor that showcases the difference between 2D and 3D printing technologies is that 3D printing does not follow the traditional manufacturing process. Also, it is a powerful technique for quickly creating patient-specific, high-constancy, medical hallucination at an economically profitable price.
- 3D-printed medical models gives the benefit of tactile criticism, explicit manipulation in addition to that it provides a clear understanding of a patients biological system.
- In comparison with other approaches, the 3D bioprinting technique enables to connect the dissimilarity between synthetically engineered tissue constructs and intrinsic tissues.
- 3D organ printing provides remarkable adaptability and the potential to distribute cells and biomaterials with definite authority over spatial circulation.
- In most of the cases, 3D-printed medical phantoms helps in assisting the surgeries; thus, it reduces the duration of medical procedures (Schubert et al. 2014).

- 3D-printed neuroanatomical models are used to carry out the surgical planning by neurosurgeons that reveals the physical portrayal of some difficult structures in the human body. Thus, the surgeon can visualize and understand the complications among sensitive parts like connections between cranial nerves, vessels, cerebral structures and skull design that are not possible in 2D technologies (Ventola 2014).
- Thus, errors in the surgery can be reduced by optimizing the medical procedure after visualizing the image (Wang et al. 2017).

12 Conclusions

The development of 3D printing technology in these recent days is commendable. This technology has offered numerous platforms in various fields, but a lot more in the field of biomedicine has been explained in this chapter. The contribution of polymeric hydrogels is enormous, and it helps in satisfying the patients requirement for repair and regeneration in the field of organ and tissue replacement, even polymeric scaffolds are used for tissue engineering. When there is a drastic increase in the number of organs needed, on the other hand, there is paucity in the number of donors and poor biocompatibility tends to immune rejection. Thus, scientist has found an alternate in scaffolds that can be used for transplantation. These scaffolds can mimic the ECM by granting structural support and contributes in yielding desired tissues and organs which is the ultimate aim. By applying 3D printing techniques, ECM-like scaffolds can be generated with a high precision, also it is possible to obtained fine informations even at a microscopic regime. Thus, these 3D printing technologies enables to take care of the demand of the patients for tissues and organs immediately without any delay or wait from the contributors for transplantation.

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Polymer Composite Strategies in Cancer Therapy, Augment Stem Cell Osteogenesis, Diagnostics in the Central Nervous System, and Drug Delivery

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Abstract This chapter covers the wide knowledge about polymer composite strategies in cancer therapy, augment stem cell osteogenesis, diagnostics in the central nervous system, and drug delivery. Many polymer composites were applied for the diagnosis and curing of cancer diseases. These areas include different types of polymer composites, their degradation, drug release mechanism from the polymer composites, and their needfulness for cancer therapy. In addition, this chapter explores the augmentation stem cell osteogenesis including morphology, environment, and polymer nanocomposites for osteogenesis. In the end, we focus on the drug delivery system for central nervous system.

Keywords Cancer · Central nervous system · Drug delivery system · Osteogenesis · Polymer composites

1 Introduction

In the current past, there has been an improvement in the best treatments using biopharmaceuticals and biological macromolecules including nucleic acids, peptides, proteins, as theranostics for identifying the disease. These innovative drugs have needed a purified drug releases framework which can be utilized to enhance absorption, distribution, metabolism, excretion and moreover additionally upgraded cell/tissue specificity and biocompatibility. In such manner, the improvement of novel drug release frameworks and instruments to limit them is required which has stimulated the advance in the up and coming phase of drug delivery systems (DDSs) (Vogelson 2001). The improvement of the medical research field has been impacted by the design and development of the DDS for more controlled and

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K. K. Sadasivuni et al. (eds.), *Polymer Nanocomposites in Biomedical Engineering*, Lecture Notes in Bioengineering,
https://doi.org/10.1007/978-3-030-04741-2_8

target-based therapeutic use. The cutting-edge DDS is one of the quickly creating areas of the pharmaceutical wholesale place (Shahani 2009).

In recent years, controlled DDS has turned out to be a standout among the most requesting and quick-advancing logical zones. It can give more important properties by the by shapes, excellent absorption, biocompatibility, the tissue, and cells, is focusing the bioactive compounds, soundness of the medicine against degradation by proteolytic catalysts, and the limited drug has been stable in the human body at a very long time, within the supportive limited (Grund et al. 2011). In the many cases, the most reassuring plausibility for controlled drug delivery is given by natural and synthetic polymers, respectively, due to their ideal, adaptable qualities, which can be effectively created at modern size and excellent for extra modification (Tiwari et al. 2012).

The necessary part of the drug release from the polymer carrier is suggested improvement measurements, the arrival of the both natures (hydrophilic and hydrophobic), the consistent arrival way at the very long time. Polymeric composite therapeutics incorporate straight otherwise extended polymeric composite long chain works have bioactive molecules. Ex. polymer medication or on the other hand as the latent transporter to which a medication cannot non-covalent attached Ex. synthetic polymer, polymer-counter acting agent conjugates, DNA grafted polymers, amphiphilic micelle, dendrimers, polymeric nanocarrier, different functionalized polymer (Amarnath Praphakar et al. 2018a). The polymers for medicate conveyance are legitimately grouped in view of the accompanying qualities: (I) Initial of the polymer can be technology aspects (II) Synthetic nature can be different functional of the polymer as well as natural polymers based and so forth (III) Backbone security the polymer can be biocompatibility nature. (IV) The soluble in polymers have been two natures: polar and than non-polar charter (Pradeepkumar et al. 2018; Amarnath Praphakar et al. 2018b). In any case, all the previously mentioned highlights have their own impediments, for example, common polymers, albeit most copious and good soluble, which are hard to repeat and purge. Design and development of polymers have very large immunogenicity, which is kept their long uses. Some polymers which are not good soluble in solvent medium should be removed by surgery after they discharge the medication at the focused in the vicinity. The general trademark includes the potential polymers that make protected, adequacy, hydrophobicity, non-appearance of immunogenicity, organic idleness, adequate pharmacokinetics, the synthetic polymer is useful gathering nearby medication, targeted moieties, and the arrangement of synthetic copolymers (Mehnath et al. 2017a). There are a few important points polymer is going about a vain transporter to which may be attached to the medication, for example the enhanced polymers applicable for pharmacokinetic and pharmacodynamic character biopharmaceuticals through different routes such as increase the plasma half-life, reduce the immunogenicity, support solidness of biopharmaceuticals, increase the solubility of the low molecular weights, and in the conveyance, medication has been focused (Ponnamma et al. 2018; Hobel and Aigner 2010; Kodaira et al. 2004). The functionalized polymers have focused on different

sicknesses, likewise rheumatoid joint inflammation and some human disease such as diabetes (Cooper 1993).

The functionalized polymer-related medication conveyance framework is separated into different classifications: dissemination controlled, artificially controlled (biodegradable), remotely activated frameworks, for example, pH, temperature (Rajan et al. 2017a), dissolvable initiated (Mrlik et al. 2000), and polymeric nanocarrier-related conveyance frameworks that execute three primary advancements (Amarnath Praphakar et al. 2017a): (I) PEGylation (Howard et al. 2008; Knop et al. 2010), (II) dynamic cell and organ particular focusing on (Bae and Kataoka 2009; Marcucci and Lefoulon 2004; Torchilin 2010), and (III) inactive focusing by utilization of the enhanced permeability and retention (EPR) impact (Torchilin 2010; Bhadra et al. 2002). The polymeric nanoparticles incorporate covered nanoparticles, enzyme, hydrogels, and SL nanoparticles. Other than this, promote the functionalized polymer medication conveyance frameworks is being imagined as a different functionalized of the broad framework which will give immediately excellent pharmacokinetics, reduced poisonous, sped up focusing on, and modified materials are discharged by medication. Also, more convincing treatment could be offered through mix treatment including conveyance of at least two medications/diagnostics specialists at the same time (Lammers et al. 2010; Ahmed et al. 2006a, b).

Moreover that case, there are some difficulties, it is used to polymers as medication conveyance vehicle that is should tend to. For instance, different types of polymers have a few points of heterogeneity. Every polymer-sedate conjugate particle contrasts with respect to atomic weight, medicate stacking, and resulting adaptation. Additionally, the complexities in combination and portrayal increments as the conjugates turn out to be more minds boggling, i.e., different functionalized nanobiomedicine. From now on, it is significant that the variations properties such as that are very limited to satisfy the stringent administrative principle. To overcome this problem, the polymeric grafted must be joined reproducibly. The approved techniques for physio-chemical portrayal should likewise be set up to guarantee the nature of the reproducible item. The measure of medication discharge is specifically corresponding to the adequacy and well-being of polymer-tranquilize conjugates; in this way, novel methodologies, for example, the arrangement of better linker sciences, will be valuable in empowering the further difference in polymer conjugates (Rajan et al. 2017b). In this chapter, we discussed the polymeric composite strategies for the drug delivery systems in cancer therapy, augment stem cell osteogenesis, and diagnostics in the central nervous system treatments.

2 Cancer

Cancer is a complicated disease that represents imperative reason for death in developing and developed countries (Emal et al. 2011; Al-Dimassi et al. 2014). Even though, the enormous of chemotherapeutic cancer drugs have been successfully accomplished in a medicinal point of view; it has been effectively utilized as a part of

a clinical perspective. But, there is no development in chemotherapeutic cancer treatment due to opposed to cancer cells (Pradeepkumar et al. 2017; Bildstein et al. 2011; He et al. 2014). In addition to that, the metal complex, metal organic framework (MOF), catalyst, heterocyclic compounds, inorganic material, and organic compounds resistance of cancer cells and these are used in limited anticancer treatment (Rajan and Raj 2013a; Ibrahim et al. 2017; Torshina et al. 2010; Martins et al. 2015a, b). Therefore, to overcome these problems, polymer composite, lipids, dendrimers, and carbon-based materials have been utilized as carrier part in cancer therapies (Ramakrishna et al. 2001; You et al. 2016; Gillies and Frechet 2005; Lee et al. 2006). Recently, nanotechnology was used in cancer therapies (Rajan and Raj 2013b). In fact, that few nanosized polymeric particles conveyance transporters have been affirmed for FDA (Food and Drug Administration). Moreover, nanotechnologies will probably constitute a developing of the cancer treatment. In recent years, lot of peoples cured in cancer therapies. Since remarkable fulfilments have been supported in the field of the cancer therapies drug delivery system. These nanoparticles can be lot of advantages in cancer therapies, the possibility to encapsulated different anticancer drugs, and protect therapeutic molecules. Further, the surface modification with target ligands (Biotin, folic acid, and peptides) enhances the effectiveness of the in vitro biological aspect and controlled release of the target anticancer drug delivery system (DDS) (Rajan and Raj 2013c; Sulistio et al. 2011). As we know that the lot of nanocarrier used in anticancer drug delivery system (ADDS) as well as these nanocarrier can be easily removed by the cancer cells of the reticuloendothelial system (RES), the present work has been focused on polymer composite of the nanocarrier. These nanocarriers used to cancer cells due to the invisible. Functionalized natural polymers such as starch, carbohydrates etc. Also, functionalized synthetic polymers such as PLA, PGA, PCL, PAA, Poly (amino acids). Polymethacrylate, Polymethyl methacrylate is commonly used to modify polymer composite of the nanoparticle which can bestow protection from protein adsorption (Saheb and Jog 1999; Rajan et al. 2013). These focal points make nanoparticles a potential method of treatment better than customary cancer therapies.

2.1 Polymer Composite for Drug Delivery System

Polymer composite has been used widely in the advancement of the DDS. The sustainable structure of polymer composite accepts for tunable characters (Fadiran et al. 2018). It is extensively used for drug delivery system.

2.2 Polymer Composite Properties

Polymer composite that displays diverse properties is broadly investigated as potential drug delivery system. Different polymer composites have been utilized for

drug delivery system. This polymeric system can be the release of the anticancer drug in the target sites. Moreover, theses manner have lot of advantage and reduced side effects (Rajan and Hari Balakrishanan 2015). Undoubted variety of polymer composite goods uses full properties such as biodegradability, biocompatibility, water solubility, and amphiphilic nature. Moreover, the modification of polymer composite nanoparticles can enhance colloidal stability with natural and synthetic polymer composite. In addition, the modified polymer composite may be used for nanoparticles. This polymer nanocomposite can form multifunctional drug delivery systems because these properties are unique character (Oh and Park 2011; Jeyaraj et al. 2016). The biodegradation of the particular polymer has some critical factors because of the controlled discharge of drugs. The polymeric nanoparticles were controlled by environmental pollution. By adjusting amphiphilic polymer composite, drug loading can be prolonged to largely undervalued drugs such as proteins, peptides, and further natural large molecules. The surface-modified polymer composite nanoparticles with different moiety can enormously enhance the cooperation among nanoparticles and psychology conditions. These results are a greater cell uptake and a more attractive biodistribution technique Specifically, bio-degradable polymeric nanocomposite particles appears to cancer targeted cancer cells and sustainable delivery of anticancer chemotherapeutic drugs which would some way released from the human body. The bio-degradable polymer composite utilized for drug delivery system still now have been used as a part of the type of nanoparticle frameworks which needs for critical methods using by organic solvents. Basically an organic solvent is pollution, toxicity, and so far. The introduce innovative methods have some issues likewise low stability, in-vitro, in-vivo, and cellular uptake nature; very limited drug release of bio-degradable polymeric nanocomposites could to a grerat extent enhance specificity and cell viability (Rajan et al. 2016).

2.3 Polymeric Composite Degradation

The more important role of polymer nanocomposite particles used to in-vitro and in-vivo applications (Amarnath Praphakar et al. 2016). There is a different type of polymeric composite degradation mechanism that is one of the properties of physic chemo method. The determined highly degradation pathway had given for biomedical applications; it is more important; while choosing the suitable polymer composite for a given application (Nagaraj et al. 2018). Thermal and photodegradation is a perfect application for drug delivery system (DDS). Another one, mechanical degradation of a polymeric composite, is an extremely durability nature. Ultimately, the polymeric composite bonds are broken by chemical degradation method. The chemical degradation processes was used for biomedical applications. The hydrolysis of chemical bond can be water medicated and enzyme catalyst. The last impact is frequently referred to as biodegradation; the degradation is well soluble in biological environment conditions.

The chemical degradation of the polymeric composite is minor intricate process (Popelka et al. 2018). Polymer composite enters in water molecules; later then, this might be joined by swelling nature. Afterwards, this water easily penetrates with polymer composite to hydrolysis process, and promoting the making of oligomers and monomers. The degradation of the polymer composites changed the surface morphology, through which oligomers and monomers are discharged. Generally, polymer composite at covalent bond degradation properties has two principal statements such as (A) hydrolysis reaction and (B) enzymatic reaction. Some factors affecting the rate of the reaction, phys chem bond nature's, different polymer composition, potential of hydrogen solution, and the most important for water uptake process. The polymer composite changed the physochemo potential of hydrogen solution and phase properties. The improvement of biodegradable polymeric composites during the most recent two decades has expanded exponentially. Particularly, these polymeric composites have been utilized for DDS due to the good biocompatibility more than biodegradation natures.

2.4 DDRM of Polymer Composites

Generally, consider how a drug molecule migrates from a beginning point in a polymer composite framework to the polymer composite's external surface and at last how it is discharged into the encompassing condition. The techniques of drug delivery incorporate extracellular infiltration, intracellular drug release, and cell uptake. The efficiency of anticancer drugs loaded polymeric nanocomposite would be decreased enter the tumor tissues. Generally, because of the defective tumor vasculatures and the impaired lymphatic system, the nanoparticles can passively target the tumor sites through the enhanced permeability and retention effect (EPR effect) (Mehnath et al. 2017b). Extracellular penetration can be reached by the fixed polymeric carrier of morphology tumor penetration biology molecules and various strategies, for example, the use of ultrasound. The tumor cell take-up can be encouraged by receptor-interceded endocytosis and tumor pH-activated non-particular endocytosis or TAT-intervened transduction. Drug release from pH-responsive polymer nanocomposite by intracellular cells. It is well know about, Extracellular, endo/lysosomal cellular pHs corresponding to 6.5–7.2, and 5.0–6.5. These tumors have been different pH solutions released by anticancer drugs in cancer cells and targeted drug delivery. Moreover, the incidence of hypoxia inside tumor cells also provides the acidic pHs. For example, a similar research group established a pH-sensitive polymer composite nanoparticle are used to some cancer drugs such as curcumin, paclitaxel, doxorubicin, cisplatin, chlorambucil, and 5-fluorouracil, a natural anticancer agent, for the treatment of various cancer studies such as breast cancer, prostate cancer, colon cancer, lung cancer, and leukemia cancer. The results exposed that the cancer drugs loaded polymeric nanocomposite is soluble in cancer cell pHs it is easily released to cancer cells (Fig. 1).

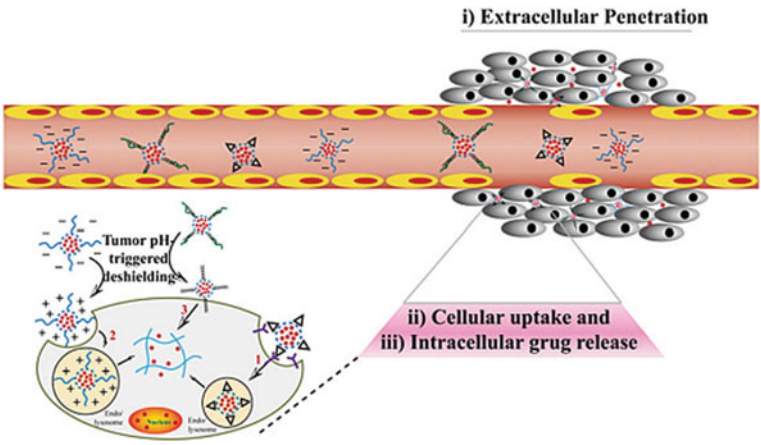

Fig. 1 Strategies of drug release (Xinru 2016)

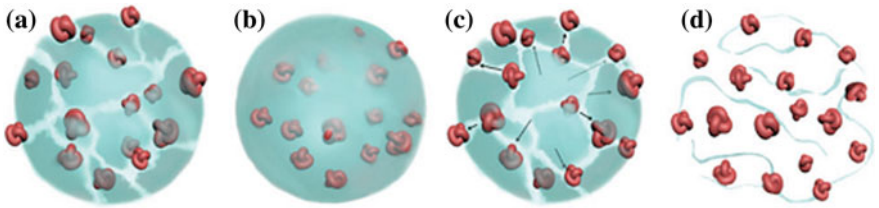

Fig. 2 Drug discharge system (mechanism) from polymeric composite nanoparticles; **a** drug spread way to water condition, **b** polymeric composite, **c** osmotic pumping, and **d** ich (Xinru 2016)

Until the principle, drug release tool could be compressed as four procedures. 1) Drug spread to water condition, 2) polymer composite 3) through drug spread water 4) osmotic pumping, and 5) erosion (Fig. 2). These drug release mechanisms would be able to the same time in the human body (Krishnan et al. 2017). This mechanism view, different polymer composite useful; the design and development DDS have been prepared to reducing time and matched dosing carrier.

3 Polymeric Nanocarrier for Cancer Chemotherapy

3.1 Designing Material

Cancer is a sickness originating from the epithelial cells covering the cancer cells parts of the place tract as previously mentioned. In the beginning period of cancer cells, surgical treatment is a reduced tumor (Wang et al. 2012). Another treatment is chemotherapy that utilizations against cancer growth. It can likewise be utilized

before surgery to shrivel the tumor and limit chance (Fredenberg et al. 2011). Chemotherapeutic anticancer drugs such as 5-fluorouracil, cisplatin, DOX, and PTX have been used for one type of the colon cancer therapy (Meyerhardt and Mayer 2005; Tol et al. 2009a, b). More, these therapies used to colon cancer contain radiation therapy (Bosset et al. 2006), stem cell transplant (Todaro et al. 2010), and immunotherapy (Koido et al. 2013).

Tumor tissues show an acidic condition and additionally a broken vasculature. The treatment of cancer usually depends upon the tumor estimate, the limited pH condition, and the scope of cancer metastasis (Anitha et al. 2016). Thinking about these physiological highlights, drug-loaded polymer nanocomposite can be an attractive biologic barrier. While treating specific cancer cells, the drug-loaded polymer nanocomposite can be easily penetrated with tumor sites. Moreover, the active agents should be therapeutic efficiency and reducing side effects.

The therapeutic efficiency, the nanoparticles surface morphology, and size of the ligand are a most vital role. There ought to be a profound thought of the synthesis technique to accomplish the desired nanostructure and the preparation of natural nanopolymers; these polymers grafted targeted ligands. The surface-modified polymer composite has shown that hydrophilic surfaces enhance circulation time and more can improve cell take-up. Polymer frameworks may offer incredible flexibility in the customization and optimization of nanoparticles to deliver capable agents and upgrade their movement to clinical practice; however, with such a significant number of parameters equipped for optimization, a thoughtful system design is required to reach the ideal.

3.2 Drugs for Cancer Therapy

Up to now, the number of drug delivery system for the treatment of cancer was developed which focuses on cancer affected patients. Chemotherapy is a cancer therapy after other treatments, Table 1.

Some chemotherapeutic compounds are used in cancer treatment such as cisplatin, carboplatin, camptothecin, doxorubicin, and paclitaxel, Table 2.

3.3 Polymer Composite Needs for Cancer Therapies

A usual nanoparticle plan is opsonized and cleared quickly by the mononuclear phagocytic system (MPS) because of the numerous factor influences, similar to insightful size, surface, and state of the properties, which are mainly determined by polymer composite properties. The utilization of biodegradable polymer composite nanoparticles (PCNPs) for delivery the medicinal drugs and bioactive molecules has demonstrated huge helpful therapeutic value with the recent finding for the effects of nanoparticles (Egusquiaguirre et al. 2012). The nanoparticle size is 10–100 nm.

Table 1 Polymer composite used anticancer drugs for cancer therapies

Polymer composite	Anticancer drugs	Cancer cell line
PLGA-PEG-PLGA	Salidroside	Breast cancer, pancreatic cancer
Hyaluronic acid ceramide (HACE)	Ginsenoside Rg3	Lung cancer
2-Hydroxyethyl methacrylate + choline formate ionic liquid	Curcumin	Breast cancer (MCF-7 cells)
PLGA	Doxorubicin, combretastatin A4	Lewis lung carcinoma, melanoma
HPESO	Doxorubicin, elacridar (GG918)	MDR breast cancer (MDA435/LCC6/ MDRI)
PLA-PEG-PLA	TGF-β receptor-I inhibitor (SB505124), IL-2	Melanoma (B16-F10 cells)
PLGA	PTX-loaded nanocrystals; sorafenib, and Cy7 NIR dye in lipid shell	Colon cancer cell (LS174 T)
PLA	Mitomycin C	(Lung cancer, A549, H22 cells)
PLGA	Paclitaxel, combretastatin A4, doxorubicin, pEGFP	Breast cancers (MCF-7, MDA-MB-231)
PLGA	10-Hydroxycamptothecin	MCF-7 and MDA-MB-435s cells)

Table 2 List of drug used for the treatment of cancer

Types of cancer	Drugs used
Brain cancer	Cyclophosphamide, everolimus, cisplatin, carmustine
Breast cancer	Paclitaxel, doxorubicin, capecitabine
Colon cancer	Cisplatin, cyclophosphamide
Cervical cancer	Hycamtin, topotecan
Lung cancer	Abraxane
Stomach cancer	Doxorubicin, fluorouracil
Skin cancer	Fluorouracil

The polymer composite properties can be utilized by broken veins and specially collected from the tumor by means of the EPR effect. The polymer composite utilized for the generation of these nanoparticles might be both of synthetic and natural origin. This polymer composite nanoparticle can enhance medication bioavailability, increase drug releasing time, and reduce side effect. Furthermore, the functionalized polymeric composite nanoparticles are capable of targeting specific tissue sites and enhancing the intracellular penetration of the drugs into the

tumor site. The excellent property of biodegradable polymeric nanocomposite are used to targeted and controlled drug delivery for cancer therapeutics.

We used several polymer composites such as hydroxyapatite (HA)/polyethylene (PE), carbon/polyethylene, silica/silicone rubber (SR), carbon fiber (CF)/epoxy, CF/polyetheretherketone (PEEK) which have been designed for delivery of therapeutic agents through passive or active manner (Sun et al. 2014). In general, a biodegradable polymer nanocomposite materials are used to drug delivery applications due to the hydrolysis of the human body which is a prompts metabolite monomers. Since, these monomers are easily metabolized by the cancer human body. This polymeric composite used to bio-medical applications due to the biologically active and sustained release manner and biocompatible natures.

In current studies, different types of polymer nanocomposite have been constructed mostly as controlled release biological active molecules in specific sites in the cancer therapies treatment. From the previous study of Monika datta et al., have composed a 5-FU loaded MMT based PLGA nanocomposite used to treating cancer therapies. The results demonstrated that this NP was able to significantly improve the therapeutic efficacy of 5-FU as well as induce tumor cell apoptosis, hence reducing systemic toxicity (Haley and Frenkel 2008). This drug delivery system showed a significant cell growth inhibition in cancer cell tumor compared to free 5-FU drugs at the same dose, which indicates an improvement of anticancer efficacy for 5-FU in cancer therapeutics. The usage of anticancer drugs is limited by their low bioavailability because of rapid metabolism. Hence, the polymeric drug delivery system plays a vital role in drug delivery system for cancer therapy to increase the bioavailability of the drug and enhance therapeutic effects.

3.4 Important Requirement of Nanostructured Drug Delivery System

For improving a highly efficient therapeutics, there are numerous issues that should be considered. To this overcome problem, the biological aspects. The arrangement of polymer nanocomposite should be able biological barriers, distinguish the tumor tissues from the normal cells, and biologically active molecules release from carrier to reach targeted sites. For that reason, the nanostructure is applicable for drug delivery system has exhibited huge promise to determine in previously issues (Prabhu et al. 2015). The nanostructures have a lot of advantages used to drug delivery system because of their flexibility sizes, surface charges. The molecular mechanism of different cancer cells and joining the therapeutic nanostructures are the importance for the effectiveness of the treatment of cancer and improved cancer patients (Xiao et al. 2015a). A sequence of polymeric composite nanostructures, such as polymer composite nanoparticles, self-assemble polymers, polymer composite hybrid systems, and Protein-drug formulation (Fig. 3), have current used for the developed for site specific drug delivery.

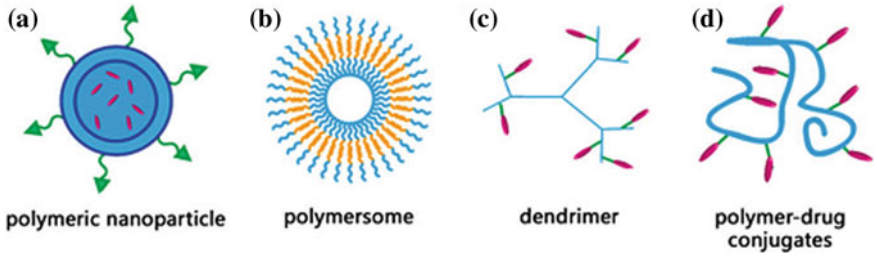

Fig. 3 Structure of various polymeric nanoparticle used in anticancer therapy: **a** polymeric nanoparticle, **b** polymersome, **c** dendrimer, and **d** polymer-drug conjugate (Xinru 2016)

The polymer nanocomposite particles have been an exact structure with well-defined carrier formation through self-assembly approach to the creation of spherical shape, capsules based on the assembling of the polymers. In nanoparticles, the stacking drugs (specialists) are disintegrated and scattered all through the polymer network, while the compound embodied in nanocapsules are restricted in a shell-like divider made by a lonely polymer membrane (Venkataraman et al. 2011). As beforehand talked about, there are numerous kinds of polymeric composite nanoparticles utilized as a part of the treatment of different various tumor therapies. A 5-fluorouracil (5-FU) enteric-covered polymeric composite nanoparticle has been created. This restricted the 5-FU to the malignancy cell region and delayed the concentration of drug in the tumor tissues in a controlled manner. This molecule conduct considered a huge diminishment in the tumor estimate contrasted with the free 5-FU control (Elsabahy et al. 2015).

Micelle polymeric composite have different nanostructures; it is utilized for carrier. They can be planned by amphiphilic square copolymers to self-amass into a core–shell structure. To be more specific, the center is framed by hydrophobic squares to convey the therapeutics with a high encapsulation/entrapment efficacy, while the shell is made out of the hydrophilic squares to balance out the center and give steric connection defense to the polymeric composite micelles (Rao and Geckeler 2011). This imaginative structure makes for drug release because, of course, the firmness of the natural conditions, ensuring the therapeutic compounds (Tummala et al. 2015). To treat growth patients, have been combined ZnO@polymer composite to form micelle (isotretinoin (ISO)) which had a mean size of around 50 ± 2 nm compared with free ISO; this micelle exhibited a managed and sustained release in vitro beside upgraded cytotoxicity and cell take-up way (Cabral and Kataoka 2014).

Polymer composites are a class of self-assembled polymer vehicle which can be utilized to embody and secure particles, for example, drugs, compounds, RNA and DNA molecules. Despite the fact that they have an equivalent structure of liposomes, the polymer composites display upgraded soundness and higher stacking productivity. Lorenza Gardella et al. have manufactured PLLA/porphyrin films biodegradable polymer composite for proficient and particular conveyance of

5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrin (THPP) to human tumor cells. The outcomes demonstrated that this drug releasing framework can diminish symptoms and expand the dissemination time. These nanostructures produced for growth treatment demonstrate a broad potential to enhance the restorative viability of malignancy (Oerlemans et al. 2010).

Polymer composite-therapeutic compound conjugates are tranquilized particles held up in water-dissolvable (solvent) polymeric composite. This structure can make them more proficient for a tumor targeting through the EPR impact and enable endocytic get at the cell level (Wei et al. 2017). Maybe a couple polymer composite conjugated anticancer drugs such as poly(3,4-ethylenedioxythiophene), triterpenoid have been effectively used to anticancer treatments (Lorenza et al. 2016) and settled excellent restorative potential at tumor cancer therapeutics.

3.5 Site-Specific Release of Anticancer Drug

Polymeric composite nanoparticles have an extensive measure of inclinations as a drug carrier in light of their biocompatibility, low poisonous quality, and controlled discharge properties. In any case, the most vital properties can be effortlessly adjusted and particularly drug releases is focused on tumor tissues; which can in a general sense enhance the remedial adequacy of the anticancer medications and diminish the manifestation (Duncan 2006). Typically, the site-specific delivery of polymeric carrier in the treatment of disease treatment can be isolated into latent and dynamic focusing on.

The pathophysiologic in tumor vessel are one of kind properties and nanoparticle carrier are fit for passive delivering because of the quick duplication of endothelial cells and tumor tissues are described by their flawed microvasculature (Pasut and Veronese 2007) additionally, tumor tissues generally need successful lymphatic elimination. From this subsequent, the vessels combined with lymphatic carrier and can encourage the extravasation of macromolecules and nanoparticles to the tumor tissue through the generally detailed “enhanced permeation and retention (EPR) impact.” As of now, it is an imperative on play of the components which influence the EPR impact so as to plan a tumor-target carrier. Be that as it may, the pathophysiological heterogeneity of expansive tumors and the absence of EPR impact in the focal districts of the metastatic tumor both lower the amassing of nanoparticles all through tumors (Kim et al. 2012). On-going years, all the more much consideration has been centered around polymer composite nanoparticle with focusing on ligand fuctionlized drug carrier, which empowers dynamic focusing in different tumor cells.

It is broadly detailed that dynamic focusing on can be refined by the change of polymer composite nanoparticles with focusing on ligands, for example, antibodies and their parts, nucleic acid, peptides, and smidgen atoms (Heinemann et al. 2013a). These focusing on ligands can overhaul official to the receptors which are overexpressed on the tumor surface cell, improving the maintenance impact and cell

take-up of polymeric composite nanoparticles. At the point when contrasted, untargeted polymeric nanocomposite, tumor therapeutic activity which is becoming effectively is focused on nanoparticles for drug releases; the ligands biocompatibility, cell specificity, restricting liking and also the ligand surface thickness and organization must be painstakingly considered to acquire the ideal impact. In any case, with indications of advance in the improvement of ligands and nanoparticles effectively site specific drug of polymeric carriers can be an attractive correlative methodology for uninvolved focusing on, additionally enhances the viability of tumor treatment (Byrne et al. 2008).

In the treatment of a variety of expansion therapeutics, equally active and inactive is focusing on assumes a critical part in releasing helpful of polymer nanocomposite particles of specific tumor sites. Small interfering RNA (siRNA) is extensively used to vascular endothelial growth factor (VEGF) and inhibiting angiogenesis to achieve therapeutic efficacy in the various cancer cell. siRNA are short double-stranded RNA fragments, It can be silence a target mRNA in a sequence of specific manner (Bertrand et al. 2014). As past detail, explained, polyvinylidene fluoride(PVDF) has been developed nanocarrier to carry SN-38 and small interfering RNA that can be targeted to the vascular endothelial growth factor (VEGF) for cancer therapy. The results showed that these polymer nanocomposites can passively target tumor regions and synergistically enhance VEGF chemotherapy, thus significantly suppressing the tumor growth (Heinemann et al. 2013b). Hyaluronic acid (HA) is polysaccharide which has been used as a tumor cell-targeting ligand due to its high affinity for the CD44 receptor. These receptors have only one chain of the glycoprotein has been found to different cancer cells such as lung, colon, ovarian, brain, and breast cell line (Rychahou et al. 2015). Recently, HA were modified polymeric nanocomposite for cancer targeted therapeutics (Lee et al. 2016). These fabricated HA modified polymeric composite nanoparticles which contain different contains anticancer drugs such as camptothecin/curcumin). These results are used to HA as a targeted ligand in cancer cells; it is a cell uptake compared with non-targeted polymer composite nanoparticles. In addition, these targeted polymeric composite nanoparticles have suggested the cell membrane and enhancing nanoparticle endocytosis via the folate receptors which are shown in cancer cells (Ponta et al. 2003). Several excellent targeted drug deliveries for cancer therapy are shown in Table 3.

Table 3 Targeted compounds based therapeutics in cancer cell line

Ligand	Target
Folic acid	Folate receptor
Antibody	Carcinoembryonic antigen (CEA)
Antibody	Death receptor 5 (DR-5)
Peptide GE 11	Epidermal growth factor receptor
Hyaluronic acid	Hyaluronic acid receptor
Hyaluronic acid	CD44 receptor
Transferrin	Cancer cells that over expressed the transferring receptor

4 Osteogenesis

Osteogenesis is the process laying down a new bone formation by cells called osteoblasts. In worldwide every year, billions of people were suffered from bone defects and thereby orthopedics became a multibillion-dollar industry (Levi et al. 2011). After six weeks in embryos, the bone appears and the growth continues till about 25 years old. There is a critical need for bone renovation, not only for fractures, but also for trauma, tumor resections, skeletal diseases, and bone malformations (Wang et al. 2014). In bone construction, marrow stromal fibroblastic stem cell termed as mesenchymal stem cell is responsible for the major source (Richard et al. 2005). To improve the remedial properties of conventional bone marrow transplantation with mesenchymal cells affected by genetic disorders, treatment with mesenchymal cells has the promising potential for patients (Horwitz et al. 2002). Recently, polymer-based stem cell osteogenesis in the nanorange has involved considerable interest as biologically active scaffolds to encourage the discrimination of various stem cells to definite lineages (Lee et al. 2015).

4.1 Types of Ossification

Intramembranous ossification: bone developed from mesenchyme or fibrous connective tissue.

Endochondral ossification: bone development occurred from the pre-existing cartilage model.

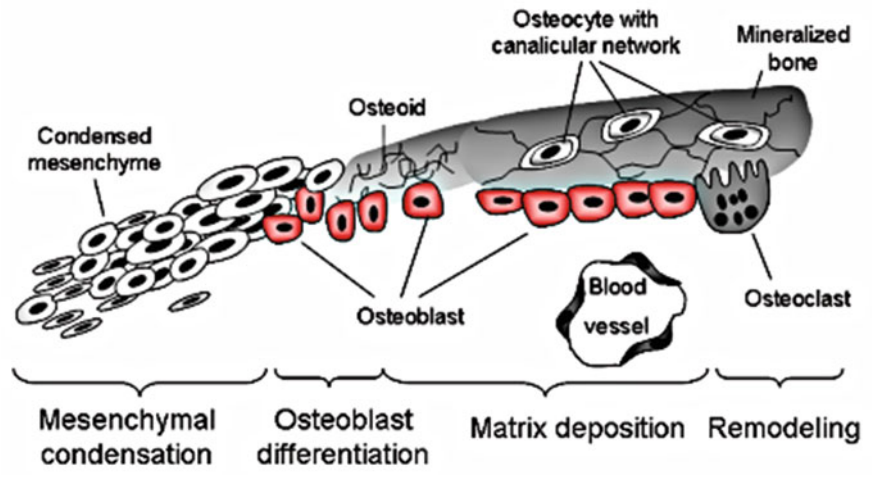

Fig.4 Process of intramembranous ossification (Eyckmans 2006)

4.2 Intramembranous Ossification Process

Mesenchymal cells migrate and aggregate in some specific areas known as ossification center. Then, the aggregated cells differentiate into osteoblasts. The developed osteoblasts create bone matrix, which response for calcification. The encased osteoblasts into bone matrix are called as osteocytes (Hall 1998; Ducy et al. 1997). Linear extensions of bone formation from ossification center are called as spicules. Then, the bone tissue was supported by the blood vessels around the spicules. As a result, the enlarged spicules in the trabecular network (spongy nature) were formed at ossification centers. Further, the reconstruction fabricated the spongy bone, marrow cavities, and characteristic of mature bone (Otto et al. 1997). The overall process of intramembranous ossification was given in Fig. 4.

4.3 Endochondral Ossification Process

Endochondral ossification arises in bone cartilage model of developing embryo. The cartilage model planned the bone shape and growth (interstitial and appositional growth) (Horton 1997; Cserjesi et al. 1995). The center of the cartilage model chondrocytes grows to be larger, and the nearby matrix becomes calcified. These chondrocytes perform planned death leaving behind cavities in cartilage matrix (Sosic et al. 1997). The osteogenic layer formed by the perichondrium of the cartilage model becomes altered into a periosteum. Finally, a bone thin collar around cartilage was produced by the periosteum (Safadi et al. 2009). The overall process of endochodral ossification was given in Fig. 5.

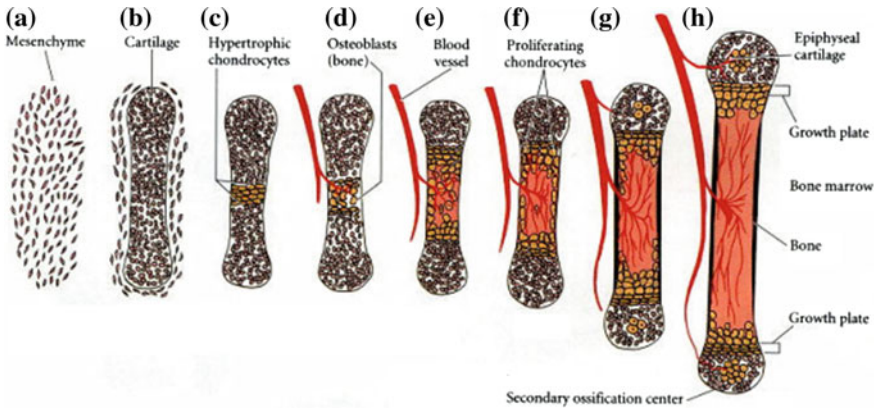

Fig. 5 Process of endochondral ossification (Safadi et al. 2018)

4.4 Stem Cells for Osteogenesis

Various types of stem cells were listed below.

Types of cells	Uses
Bone marrow mesenchymal stem cells (BM-MSCs)	High osteogenic potential (Potten 1997)
Embryonic stem cells (ESCs)	Pluripotency, able to differentiate all cell types in bone (Baldwin et al. 2017; Shrivats et al. 2014)
Umbilical cord blood mesenchymal stem cells (CB-MSCs)	Broad differentiation and proliferation potential, higher in vivo safety than embryonic stem cells (Rao et al. 2012)
Amniotic fluid derived stem cells (AFSC)	Pluripotency, able to differentiate all cell types in bone (Ko et al. 2013)
Adipose derived stem cells (ASCs)	Similar osteogenic characteristics as BM-MSCs

4.5 Morphology of Stem Cells

The different morphologies of stem cells are represented in Fig. 6.

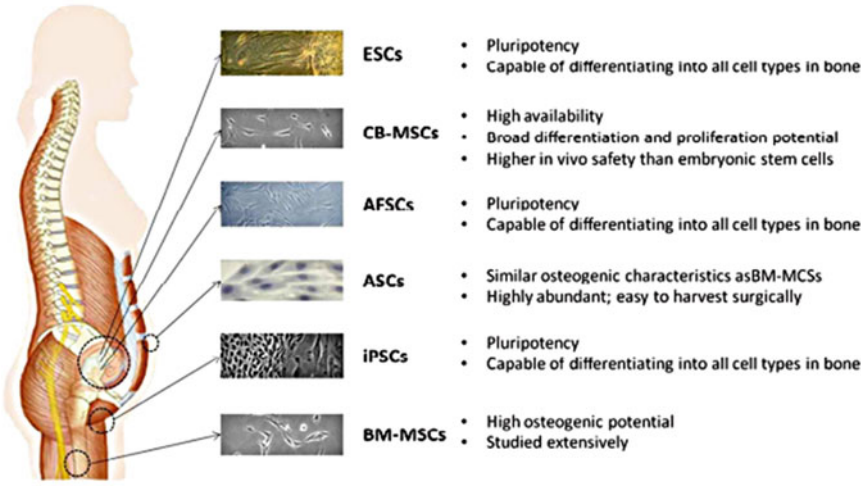

Fig. 6 Different stem cells

4.6 Environment for Osteogenesis

The proper micropore arrangement fulfills perfect osteogenesis effect for the porous scaffolds. Pore size, porosity, connectivity, surface area, and the degree of distortion are the characteristics of micropore structure (Bara et al. 2014; Liu et al. 2013). For growth of cell and reproduction, the scaffolds of bone tissue engineering build the microenvironment. In scaffold, no inflammation or toxicity occurred when a smooth cell growth is observed (Loh and Choong 2013; Forbes and Rosenthal 2014). The good biocompatibility of scaffold offers the high-quality microenvironment for cells (Lane et al. 2014).

4.7 Polymer Composites for Osteogenesis: An Overview

Currently, a sequence of biomedical materials including inorganic substances, polymers, and their composites has been improved into scaffolds for bone tissue engineering to explore their importance on osteogenesis (Weissman et al. 1991). Hydroxyapatite (HAp) and β-Triphosphate calcium (β-TCP) are the extremely used ceramic material and had been utilized in animal models to support the remedial of numerous kinds of crucial sized imperfections.

Polymers are alginate, cellulose, chitosan, collagen, gelatin, PLGA, PCL, silk fibroin, PEG, which posses the required properties of good biocompatibility, predictable degradation rates, tunable mechanical properties and good elasticity, osteoconductivity properties which make them outstanding materials for biomedical application. The various properties of organic polymer materials can be further considered; hence, these materials occupy significant position as the materials for extracellular matrix (Govindaraj and Rajan 2018; Srinivasan et al. 2012; Teh et al. 2018; Wang et al. 2006; Rottensteiner et al. 2014; Newman and McBurney 2004).

4.8 Polymer Composite for Stem Cell Augmentation

Recently, mesocellular silica foam (MCF)—481 embedded gelatin was designed for the delivery of dentin matrix protein 1 (DMP1). DMP1 was chosen due to the biological importance and the significance of biomimetic nature in scaffolding preparation for tissue renovation; we planned MCF as a delivery device for DMP1 and then embedded DMP1/MCF into a gelatin to form a new customized scheme for craniofacial bone renovation. This scheme shows a multilevelled porous structure including mesopores (MCF) and macropores (gelatin) to imitate the natural bone ECM porous structural design (Govindaraj et al. 2018). In osteogenesis and biomineralization, DMP1 is a well-known protein that plays a crucial function. The simultaneous release of Si ion and DMP1 from the hybrid system and the bone marker level of BMSCs suggested that a promising effect was observed between

DMP1 and Si ion. Consequently, to improve the activity of DMP1 with better application and effectiveness, it is required to extend its release throughout bone regeneration. In this work, the DMP1/MCF/gel was successfully prepared and reveals a prolonged release compared to other systems. Compared with other systems, this hybrid system shows an accelerated osteoinduction and osteogenesis during bone regeneration. The in vitro results confirm that this hybrid system encouraged separation and mineralization of BMSC. The in vivo calvarial defect study designated that the system reinforced more bone with superior quality after 8 weeks. These observations verified that all osteoinductive, regenerative, and biomineralization regulative properties were appreciably enhanced in our biomimetic DMP1/MCF/gel system, signifying that this system is a promising potential system for recovering bone regeneration (Sumathra et al. 2017).

As shown in Fig. 7, preparation scheme was investigated to design a coating of GEL/HAP hybrid on PLTGA terpolymer scaffolds. The PLTGA terpolymer was prepared via ring-opening polymerization with definite monomer supply (Lin et al. 2018; Yuan et al. 2015; Dong et al. 2014). Then, results show that the hybrid system coating could develop the hydrophilic properties and raise the surface roughness and improve other properties such as cell adhesion, proliferation, and osteogenesis. Therefore, MC3T3-E1 cells in vitro study show that the hybrid coating not only encourages cell adhesion and proliferation but also increases favorable properties. Overall, the coating system improves the PLTGA scaffolds behavior in osteogenesis (Munusamy et al. 2017).

Due to the cell endocytosis effect, nanomedicines posses attracting applications in regulation of cell biological behaviors. To improve the bone marrow mesenchymal stromal cell osteogenic differentiation, simvastatin (SIM)-tagged polyphosphazene-based nanoparticles (NPs) were prepared. In addition to that, polyphosphazene is further grafted with tryptophan ethyl ester and glycine ethyl ester. The NPs were prepared through precipitation technique. Finally, the resulting system shows the effective features in BMSCs. From the observation, the current study recommended an amazing biomaterial for bioactive components as a flexible and functional vehicle was reported by Amarnath Praphakar et al. (2017b).

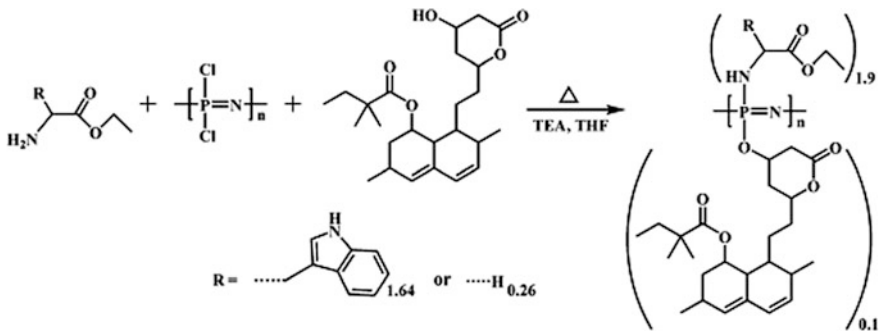

Fig. 7 Poly(simvastatin)$_{0.10}$–CO–(ethyl tryptophanato)$_{1.64}$–CO–(ethyl glycinato)$_{0.26}$phosphazene (PTGP-SIM) preparation (Huang et al. 2017)

Nanocomposites consisting of hydroxyapatite NPs coated with carboxyl-terminated PLGA through an ionic colloidal molding method conferred homogeneous dispersion and uniformity of the particles in the fabricated biomimetic scaffolds. HA-NPs with average diameters about 45 nm were produced. The carboxylate-modified PLGA (PLGA–COOH) was prepared by dissolving PLGA, succinic anhydride, and 4-(dimethylamino) pyridine (DMAP) in dichloromethane. The PLGA–COOH was achieved by precipitation method. Briefly, based on CMC, CTAB was used to control the size of HA-NPs. Calcium acetate hydrate solution and potassium phosphate tribasic monohydrate solution with the same molarity (0.15 m) were blended in the presence of CTAB. Recently, carboxyl-functionalized synthetic polymers have been shown to mimic the carboxyl-rich surface motifs of non-collagenous proteins in stabilizing hydroxyapatite and directing intrafibrillar mineralization in vitro. Based on this biomimetic approach, it is herein demonstrated that carboxyl functionalization of poly(lactic-co-glycolic acid) can achieve great material homogeneity in nanocomposites. This ionic colloidal molding method stabilizes hydroxyapatite precursors to confer even nanodopant packing, improving therapeutic outcomes in bone repair by remarkably improving mechanical properties of nanocomposites and optimizing controlled drug release, resulting in better cell in-growth and osteogenic differentiation using MC3T3-E1, a mouse calvaria-derived osteoblastic cell line, evolved by Huang et al. (2017).

Compared with other polymers used in scaffold preparation, gelatin has gained much attention for 3D porous scaffold fabrication in tissue engineering owing to its availability, low immunogenicity, easy handling and that it is inexpensive. Furthermore, the nature of gelatin-based scaffolds can be further improved by cross-linking and combining with inorganic compounds, thereby making it possible for them to become appropriate constructs for bone regeneration. Moreover, MSNs have been incorporated into polymer materials to increase their mechanical properties, improve cell adhesion and proliferation, and enhance the osteogenic differentiation of osteoblasts. In this study, Xiaojun Zhou et al. fabricated a composite scaffold based on vancomycin (Van) loaded mesoporous silica nanoparticles (Van@MSNs) and a gelatin matrix. The microscopic structure of the gelatin-based composite scaffolds was characterized as highly porous. By the addition of MSNs, an enhancement in the compression property of MSNs-incorporated composite scaffolds was observed. The drug-loaded composite scaffold showed no unfavorable effects on the proliferation and differentiation of bone mesenchymal stem cells (BMSCs), confirming good biocompatibility. Moreover, in vivo results demonstrated that promoting bone healing. Thus, results suggest that the fabricated Van@MSNs/Gelatin composite scaffold with a localized and sustained release of antibiotics is a promising biomaterial for treating infected bone defects (Govindaraj et al. 2017).

Later, graphene-based polymer nanocomposite was investigated in tissue regeneration field. Graphene was incorporated into the soft polymers to improve the soft polymers mechanical strength for wide applications in hard tissue engineering (Kumar et al. 2015). Polymer nanomaterials composed with graphene show better cell adhesion, proliferation, and differentiation due to its flexibility and adaptability (Zhang et al. 2012). Due to its noncovalent binding capability, graphene plays a

critical part in targeting the unmodified stem cells to osteogenic lineage (Lee et al. 2011). The strong interaction of polymer matrix with nanoparticles is believed to exhibit mechanically strong. The best way to achieve strong interaction was carried through surface modifications (Ramanathan et al. 2008). The introduction of functional groups (–OH and $–NH_2$) onto the surface of the NPs shows good response biologically (Chen et al. 2012; Wang et al. 2003). Owing to their several advantages, polyesters are a broadly favoured class of polymers for biomedical applications (Depan et al. 2011). Due to their unmodified structure such as surface erosion mechanism, thermoset polymers have widely applied in biomedical applications (Girase et al. 2012). Previously, nanocomposites of GO-based polymer had been considered for bone renovation (Wang et al. 2011; Natarajan et al. 2017). These results conclude the importance of graphene to improve the stem cell differentiation to osteogenic lineage. Extreme level toxicity was observed for high dose, whereas for a low and medium level, no toxicity was observed for GO. One more polymer poly(galactitol adipate) is also prepared through esterification in which water molecule was eliminated. From the osteogenic differentiation analysis, poly(galactitol adipate) has proved an excellent one (Stichel and Wernermueller 1998).

5 Central Nervous System Drug Delivery

Permanent neurological deficits and widespread functional losses may occur when adult mammalian central nervous system (CNS) suffered by injury (Tosi et al. 2008). Over the past few decades, several studies are performed to investigate the new medical treatments for various CNS disorders. Thus, this research field represents one of the most inspiring challenges for the medical world, as a result of the narrow quantity of therapeutics capable of reaching the most "secret and sacred" system of the body as the CNS (Pardridge 2003). The blood–brain barrier (BBB) and blood-cerebrospinal fluid barrier are responsible for the control and protection of CNS (Fig. 8). Owing to their molecular or physio-chemical properties, only small amount of drugs (2%) are capable to reach the blood–brain barrier, whereas large amount of drugs (98%) are unable to reach the BBB (Kroll et al. 1996). There are two possible approaches to rectifying the problem of drugs to reach the BBB. Invasive techniques of neurosurgery and direct distribution of drug at the target site are the first one (Patel et al. 2012). But this method incurs neurosurgical costs and increases the risk of infections, in addition to a low patient compliance. Second approach to drug delivery to the CNS is the noninvasive method. In the noninvasive drug delivery method, the polymeric nanosystems were designed and developed, which could be either natural or synthetic. The main advantage of nanocarriers are to improve effective delivery, drug kinetics, reduce off-target effects, and allow release of various therapeutic agents (Missirlis et al. 2005). For prolonged circulation without any degradation, the carriers should have enough tensile strength (Kasinathan et al. 2015). It involves the delivering of drug as control and target site binding delivery with the binding of CNS receptors.

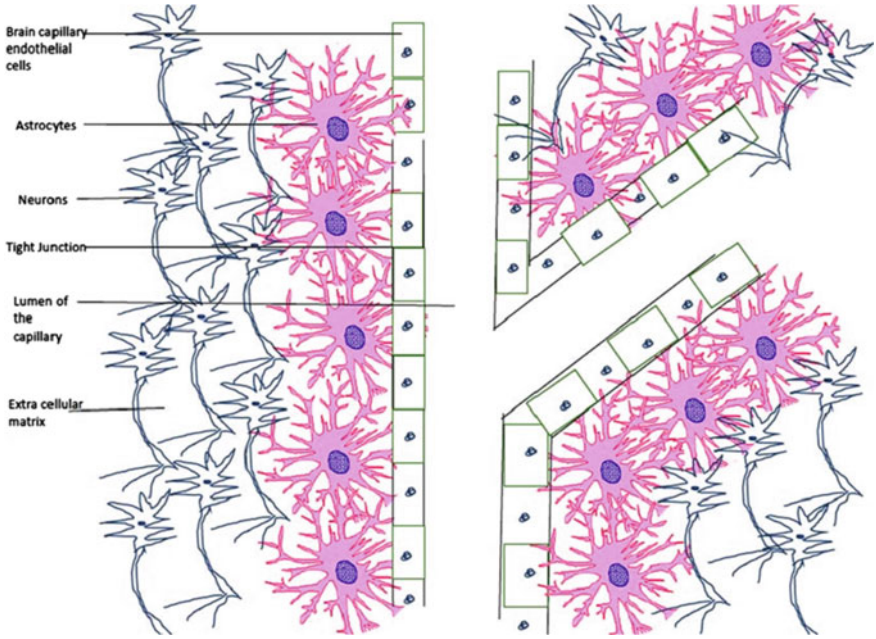

Fig. 8 Blood brain barrier (BBB) (Goyal et al. 2014)

5.1 Receptor-Mediated Transcytosis

In polymeric nanocarrier system, the receptor-mediated transcytosis mechanism was involved for the molecule transportation (Fig. 9) (Calvo et al. 2001). Receptor-mediated transcytosis mechanism is predominantly important in brain capillaries endothelial cells. In receptor-mediated transcytosis, the macromolecule ligand of macromolecule bind with the surface receptor of cell (luminal membrane) and internalized into endocytic vesicles with cell membrane. Transcytosis is achieved if the endocytic vesicle containing the macromolecule reaches the other end of the cell (basal membrane) without fusing with the lysosome, which may degrade the contents of endocytic vesicle. The macromolecules are finally exocytosed and released into the brain. In adsorptive-mediated transcytosis, the cationic macromolecule ligand interacts with negatively charged cell surface and enhances endocytosis and subsequent transcytosis.

5.2 The Role of Other Barriers

In spite of desires, there are locales of the CNS that really advantage from introduction to a more tolerant hindrance, for example, the ventricular and circumventricular regions. Four cavities are the reason for the formation of ventricular

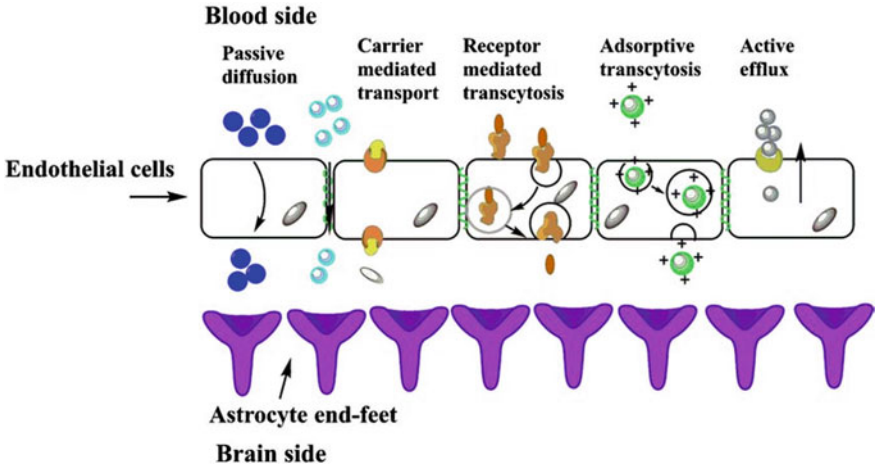

Fig. 9 Schematic representation of receptor-mediated transcytosis mechanism of bioactive compound delivery (Liu et al. 2016)

framework: two parallel and the remaining ventricles (3&4) whose choroid plexus and vessels are in charge of the formation of CSF. Vascularized structures have frail astrocytic contact that permits an immediate trade among the circulation system and the parenchyma. These regions divide a typical characteristic, a defective BBB, which invests them with a more prominent capacity to see harm and to participate in brain repair. Strikingly, late examinations have demonstrated that intravenous infusion of nanoparticles (NPs), freely of their payload and instrument of transport over the BBB, aggregates at abnormal states in these flawed areas. The brain regions which depend on a defective BBB may give an elective course to NP entrance into the brain and, significantly, balance the regenerative capacity of neural stem/progenitor cells. In any case, it ought to be noticed that these brain regions may stand different types of hindrance to helpful medications, by having expanded enzymatic action (i.e., enzymatic hindrance) in CVO.

5.3 Nanoparticles Based Drug Delivery

Nanoparticles for CNS delivery, many polymers such as poly(ethylenimines), poly(alkylcyanoacrylates), poly(methylidenemalonates), polysaccharides, proteins, amino acids, and polyesters are widely used. Commonly, the option of polymer is determined by the remedial goals of the nanoparticle system. Calvo et al. developed 130–150 nm range polycyanoacrylate nanoparticles for CNS delivery. The PEGylated nanoparticles with the size of 137 nm were the most efficient ones to reach the brain (Koziara et al. 2004). Koziara et al. developed polysorbate nanoparticles with size less than 100 nm for brain delivery (Gao and Jiang 2006). The similar results were reproduced by Gao et al., which firmly established that the

particle size for brain delivery should be less than 100 nm (Nance et al. 2012). They developed polysorbate 80 coated polybutylcyanoacrylate nanoparticles to deliver methotrexate across the BBB. In a similar research, which elucidated the effect of size on effective brain delivery, it was confirmed that the polysorbate 80 nanoparticles coated with PEG-COOH in between the size range of 40-100 nm diffused to the brain tissue rapidly (Oppenhiem 1981).

Gelatin is a smart polymer having anionic and cationic charge in addition with hydrophilic group. In preparative techniques, desolvation or coacervation techniques (Zambaux et al. 1999) or emulsion method (Li et al. 1998) was used to prepare gelatin NPs to deliver peptide sequence (Aymard et al. 2001). Hyaluronic acid is another one found in the brain extracellular matrix (ECM) and is also used in CNS drug delivery. It encourages prolonged circulation, which is important to improve sustained drug release. The delivering bioactive compounds on CNS systems were employed various systems like polymeric nanoparticles, polymeric micelles, lipid-based, cationic liposomes, solid lipid, nanoemulsions, polymer-based, liposomes, magnetic and magneto electric nanoparticles. This chapter deals with stimuli-responsive drug carrier systems with triggered drug releasing of drug on the CNS system. The natural response behavior of NPs was investigated to acquire the coveted and elevated therapeutic activity. At the point when presented to external stimuli, NPs property changes support the arrival of a drug at the objective site. These external stimuli might be a light, temperature, magnetic field and ultrasound, pH, ionic strength, redox potential, and enzymic activity. Significant endeavors are as of now being applied to grow more proficient and safe DDS that give remedial levels of drug in particular site.

5.4 Stimuli-Responsive Nanocarriers

Stimuli-responsive nanocarriers are classified into three categories based on the type of responsive factor: intrinsic stimuli-responsive nanocarriers, external stimuli-responsive nanocarriers, and multifunctionally responsive nanocarriers

5.4.1 Intrinsic Stimuli-Responsive Nanocarriers

Stimuli-responsive system responded to intrinsic factors like pH, redox level, or the concentrations of enzymes in CNS. Predictable solutions which by and large achieved their specific place by a prompt or dynamic bioactive compounds flooding of the body are no longer legitimate for the vast majority of the rising engineered and biotechnological bioactive compounds, as a result of their unpredictability what's more, toxicity issues or the issues of achieving the exact structure from the systemic circulation.

5.4.2 pH-Responsive Nanocarriers

In many CNS disorders, pH is a key of a target site. Few reports were reported for pH-responsive nanocarriers overcoming BBB and enter into the brain. Monteiro and Airoldi (1999) synthesized TAT-modified, PEGylated AuNPs (TAT-AuNPs) in which TAT induces the capability of nanocarriers to cross BBB. When compared to the normal system, pH-responsive carrier posses some advantages. First, it reduces the biodegradation of polymeric carrier at normal site. Second, it improves the accumulation of drug at the required site.

5.4.3 Enzyme-Responsive Nanocarriers

In metabolic processes, enzymes play a vital role. In various sites, enzyme level and activity varied, which mean that enzymes have specificity in nature. In several diseases, some enzymes activity and levels are altered when compared with their level in normal physiological conditions (Calvo et al. 1997; Kim et al. 2010; Gialeli et al. 2011; Park et al. 2012). Gao et al. developed angiopep-2 and an activatable cell-penetrating peptide (ACPP), a dual targeting ligand core (Gao et al. 2014). Furthermore, enzyme activity changes the drug active, inactive or changes over it in a nontherapeutic midway molecule.

5.4.4 Redox-Responsive Nanocarriers

The GSH level is too low in CNS tumor compared with the level of glutathione (GSH) results in the low level of redox potential in between tumor cells surrounding. In particularly, GSH cleaved the disulfide bonds easily and provided redox sensitivity. This information helps to design redox-responsive micelles. Jiang et al. synthesized polymeric micelles with redox response by using functionalized poly-PLAA block copolymers (Musumeci et al. 2006).

5.5 External Stimuli-Responsive Nanocarriers

External stimuli-responsive nanocarrier system is also used in the CNS treatment. They are magnetically responsive nanocarriers and light-responsive nanocarriers.

5.5.1 Magnetically Responsive Nanocarriers

In this type, the carrier system is constructed with a stable compound with magnetic behavior in normal conditions (Torchilin 2009). Cui et al. (2013) synthesized DOX- and PTX-loaded magnetic silica poly(lactic-co-glycolic acid) (PLGA) nanoparticles modified with transferrin (Tf) to enable their anti-proliferative effect. Fang et al. (2014)

developed PVA- and PAA-based iron oxide nanoparticles/lactoferrin nanocapsules (Lf-MDCs).

5.5.2 Light-Responsive Nanocarriers

Owing to the non-invasiveness of light, these type carriers are the most amazing one among all (Knezevic et al. 2011; Gu et al. 2010). Yoo et al. prepared GNRs coated by cetyltrimethylammoniumbromide (CTAB) (Yoo et al. 2014). The neural activity inhibition by the use of light-responsive nanocarrier offers a dominant remedial device to control the functions of cell.

5.5.3 Multifunctionally Responsive Nanocarriers

In recent years, multifunctional responsive nanocarriers have some attractions due to their multirole in the CNS microenvironments. An extensive range of nanocarriers exists dual or multiresponse (Zhu et al. 2014; Zhao et al. 2014; Xiao et al. 2015b; Wu et al. 2013; Hakeem et al. 2014; Fu et al. 2013; Baeza et al. 2015) to deliver drugs to CNS sites. Joosten et al. (1995) constructed a dual response carrier. They improved the dual response system by triggering the pH and MMP2 enzyme.

5.6 Polymer Micelles

The main objective of introducing polymeric micelles in CNS environment is due to the interaction between cell and polymer. Previous different polymeric micelle reports show that the interaction between micelles and drug provides a size controlled and stable drug delivery system. Block copolymers are normally used in the micelles preparation, which self-assembles to form a corona layer with hydrophilic inner and hydrophobic outer core.

5.7 Injectable Hydrogels

However, polymeric NPs are effective in CNS environment; they need invasive technique for sustainable drug delivery. Hence, injectable gelling hydrogels are an alternative approach. Agarose is a polysaccharide which converts its nature to gel when temperature is decreased and thus used widely in pharmaceutical field. (Lampe et al. 2011). Chitosan with TPP is also used as a hydrogel (Cheng et al. 2014) or cross-linked with glutaraldehyde (Jhaveri et al. 2014). Ellagic acid was delivered to brain cancer by using cross-linked chitosan with beta-glycerophosphate (Kessenbrock et al. 2010). Due to the thermogel properties, collagen also is used as a delivery candidate (Huang et al. 2013). PLA is a synthetic polymer which can be

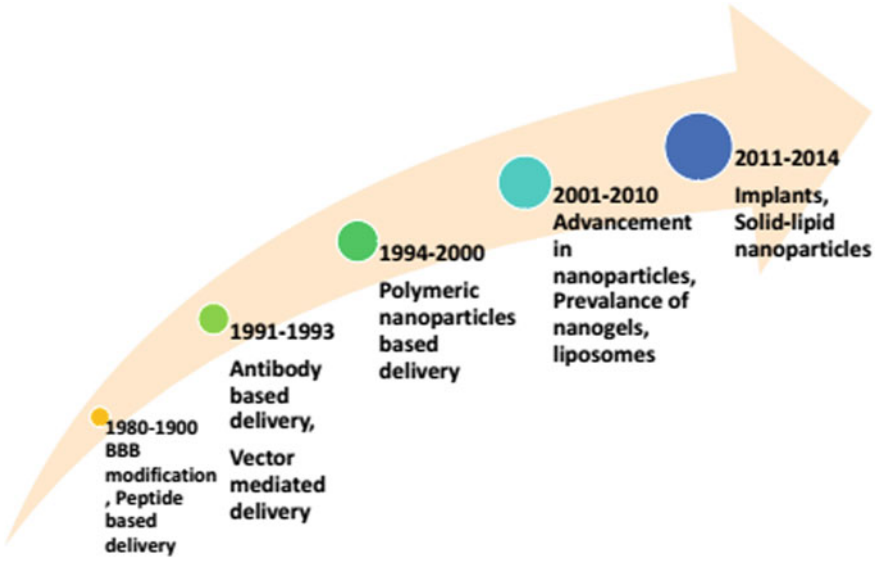

Fig. 10 Highlights of the major developments in the field of CNS drug delivery since 1980 (Goyal et al. 2014)

used to design micro-/nanoparticles. In rat models, the delivery of NT-3/PLA-PEG-PLA toward the spinal cord was analyzed. The synthetic polymer PLA-based gel also shows an interesting effect to deliver GDNF and BDNF to brain (Hillaireau and Couvreur 2009) (Fig. 10).

5.8 General Strategies for Crossing the BBB Through Polymeric NanoParticles

The activation of polymeric system is strictly associated with surface charge, hydrophobicity, and size of the nanoparticles. By the endocytosis-mediated transport mechanism, nanocarriers below 200 nm are easily taken up. Due to the positive surface charge, nanocarriers can quickly interact with negative surface of the cell (Albanese et al. 2012). Among all surface properties, the nanocarriers with small size and negative charges endorse the interaction between carrier and cell. The following are the important factors for polymer strategies in CNS drug delivery.

5.8.1 Role of Surface Charge

The surface of BBB was constructed with glycoproteins, and lipids confer a negative charge on the surface of the BBB. Thus, the nanocarriers with negative surface are not able to reach the BBB by electrostatic repulsion. Receptor mediated

endocytosis only the way to enter the nanocarriers to the BBB. At the same time, the nanocarriers with positive charge could be preferred to enhance the accumulation in CNS. However, a nanocarrier with positive charge causes transient disruption. In addition to that, in vivo system can easily eliminate positive carriers when compared to negative surface carriers (Nagpal et al. 2010). Previously several reports have been proposed to cross BBB with high-density positive charge on its surface. Chitosan, a natural biodegradable polymer, has the tendency to form nanoparticles with a high positive charge (Kumar et al. 2007). For effective CNS delivery, the pH < 6, the chitosan is easily protonated due to the amine group and the polymer is then covered with positive charge. In addition to that, cationic poly (ethylenimines) (PEIs) polymers that are well-suited for delivery of nucleic acid. Recently, systemically delivered, disulfide-linked PEI nanoparticles have been shown to deliver microRNAs to the CNS (Kumar et al. 2007; Hwang et al. 2011).

5.8.2 Role of Size

The size of nanocarriers also plays a vital role in transportation. Nanocarriers with size less than 100 nm can enter into the BBB irrespective to their surface charge. After entering into the BBB, the surrounding of nanocarriers was coated with plasma proteins. This concept was called as plasma protein corona formation, and this depends on the size of the carrier (Tenzer et al. 2011). For the small-sized nanocarriers, the surface and energy will be higher. Based on this at higher energy, the corona formation with plasma proteins will be more stable and favoured.

5.8.3 Role of Surface Modification

After drug loading, the surface of polymeric carrier should modify with some suitable polymers or ligands to enhance the prolonged circulation and minor elimination rate (Schoenmakers et al. 2004). Without any surface modification, the system can rapidly clear from the blood by spleen and liver. Previously, the surface modification with PEG promotes the circulation time when compared to the unmodified one. Coating with polysorbate 80 is also found to enhance the endocytosis process (Wohlfart et al. 2012).

6 Conclusion

Concepts such as polymeric drug delivery and injectable polymeric hydrogel systems may be designed based on their individual specifications to deliver drugs for cancer, CNS disease, and osteogenesis. The analysis of polymeric carrier design in various drug delivery applications and the interaction of functional groups toward cell are necessary for better and sustained release of drugs. The role of carrier in various drug delivery applications was briefly analyzed in this chapter. Especially,

the role of charge, size, and surface modification improves the release of drugs with high potential. In particular, this work was designed to discuss the essential concepts in the polymeric strategies of injectable hydrogels and polymeric drug delivery, focusing on the nanocarriers system. Overall, this chapter explains the strategies of polymeric composites in cancer, CNS, and osteogenesis.

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Photopolymerization of Polymeric Composites in Drug Delivery, Tissue Engineering, and Other Biomedical Applications

Husam M. Younes

Abstract Photopolymerization of polymeric composites has been widely used in several biomedical applications including, drug delivery, tissue engineering, and cell encapsulation as it combines the properties of both the photopolymerizable precursors and the photo-cross-linked polymeric networks. Nowadays, photopolymerization technology has expanded to show promising applications and uses in protein and gene delivery as well as other drug delivery designs and technologies. The present chapter aimed at providing an in-depth discussion on the latest advances in the utilization of photopolymerization technology in the drug delivery and tissue engineering fields with emphasis on the principles of photoirradiation and photopolymerization technology, common precursors, compatibility of photoinitiators, and their potential pharmaceutical and biomedical applications.

Keywords Photopolymerization · Photocuring · Photoinitiator · Ultraviolet light · Visible light · Composite polymers · Elastomers · Drug delivery · Hydrogels · Elastomers · Tissue engineering

1 Introduction

The history of photopolymerization or photocuring of resins and polymeric composites can be traced 4000 years ago when utilized by ancient Egyptians in the mummification process (Christian 2001). The mummies were wrapped in cloths which were soaked in a mix of resins and oils that were later dried and photopolymerized into a protective polymer once exposed to sunlight (Benson et al. 1978). Since then, the use of photopolymerization technology has significantly expanded into many industrial and biomedical applications as it offered a rapid conversion of liquid precursors to gels or solid cross-linked polymeric networks.

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K. K. Sadasivuni et al. (eds.), *Polymer Nanocomposites in Biomedical Engineering*, Lecture Notes in Bioengineering,
https://doi.org/10.1007/978-3-030-04741-2_9

Consequently, the research in this field has attracted significant attention for its wide uses and applications in the engineering of soft tissue and drug delivery systems (Baroli 2006; Challa 1993; Lu and Anseth 1999; Nguyen and West 2002; Schmedlen et al. 2002; Seymour and Carraher Jr 1993; Bose and Bogner 2010a, b; Liu et al. 2010; Hakala et al. 2011; Elvin et al. 2010; Di Biase et al. 2011; Matsuda and Magoshi 2002; Park et al. 2013; Sando et al. 2010; Vuocolo et al. 2012; Mishra et al. 2012). In fact, a significant number of current strategies to control drug delivery and tissue engineering applications are based on the design and fabrication of synthesized biodegradable photopolymerizable devices. The polymer composites have occupied a central status in fabrication of implantable systems since they can meet several criteria such as biocompatibility, reproducibility, and slow degradability thus allowing the successful design of controlled release drug systems and medical device (Nguyen and West 2002; Schmedlen et al. 2002).

Photopolymerization is a flexible polymerization process and possesses numerous advantages over conventional thermal and solution polymerization techniques (Table 1). First, precise control over the polymerization process can be easily achieved by controlling the exposure area and the time of light incidence. Second, photopolymerization can take place very rapidly at room temperature, in a matter of few seconds to minutes. Third, polymerization process can be conducted at a temperature and pH that resemble the physiological ranges during fabrication which can allow easy and rapid production of various complex matrix devices (Baroli 2006; Lu and Anseth 1999; Nguyen and West 2002). Fourth, photopolymerizable formulations can be typically solvent-free hence minimizing volatile

Table 1 Summary of advantages and disadvantages of thermal versus photopolymerization ($\surd$ = advantage, $\times$ = disadvantage, $\pm$ = intermediate)

Parameter	Thermal polymerization	Photopolymerization
Scientific		
Chemical Resistance	$\times$	$\surd$
Variety in formulation	$\surd$	$\pm$
No substrate damage	$\pm$	$\surd$
Low cure temperature	$\times$	$\pm$
Commercial		
Operational cost	$\times$	$\surd$
Formulation cost	$\surd$	$\times$
Capital cost	$\times$	$\surd$
Cure rate	$\times$	$\surd$
Skill level required	$\surd$	$\pm$
Environmental		
Non-solvent releasing	$\times$	$\surd$
Energy consumption	$\times$	$\surd$
Health and safety		
Radiation hazard	$\surd$	$\pm$
Fire hazard	$\times$	$\surd$

organic omissions and possible toxicities. In addition to the aforementioned, the biomaterials can be created in situ in a minimally invasive manner. In situ fabrication of polymers is attractive for a variety of biomedical applications as it can allow one to form complex shapes and designs that adhere and conform to tissue structures. It is not surprising then that the utilization of photo-polymerized polymer networks has been suggested in many drug delivery system and other biomedical application (Nguyen and West 2002; Elisseeff et al. 1999). Table 1 lists and compares advantages and disadvantages of traditional thermal versus ultraviolet (UV) photopolymerization.

This chapter aims at providing an in-depth discussion on the latest advances in the utilization of photocuring technology in the drug delivery, tissue engineering, and other biomedical fields with emphasis on the principles of photoirradiation and photopolymerization technology, common precursors used, compatibility of photoinitiators, and the potential use of photopolymerization in the targeted, controlled, and sustained drug delivery systems.

2 Photoinitiators: Modes of Action and Classifications

The photopolymerization process is mainly dependent on the availability of three main components which are: the photoenergy/light curing source (LCS), photoinitiators (PIs), and the photoreactive precursor which traditionally known as the photoreactive prepolymer (PRP). Frequently used sources of electromagnetic radiation comprise electron beam radiation, UV light (200–400 nm), and γ-radiation. Increasing use is being made of deep UV light (<200 nm), visible light (VL) (400–700 nm), near infrared (700–2500 nm) radiation, and microwaves (Kade and Tirrell 2013). Generally speaking, VL is considered the most benign light source and is more readily available than other light sources. This allows wide applications for drug delivery and tissue engineering (Zhou and Ito 2014).

The photopolymerization process takes place when PRP is exposed to irradiation from the LCS at the proper wavelength while the PI in the prepolymer composite or resin absorbs the incoming photons from the LCS and the monomers in the molecular structure become excited and in that active state change from monomers into a cross-linked polymeric network takes place. It is important to mention here that the success of this process strongly depends on having the light emission of the LCS matches with the requirements of the PI system to convert the monomers into a polymeric network. Knowing that different PIs absorb light at different wavelengths necessitates that PI maximum wavelength matches that of the LCS. As such, the choice of the photoinitiator moiety is a critical step in securing success to the photopolymerization process. It is common to use one or combination of PIs in achieving a successful photopolymerization process. PIs blends offer the advantages of absorbing light at a wider range of wavelengths to increase photopolymerization efficiency by making use of available light energy and avoid interference from other moieties.

2.1 Classes of Photoinitiators

There are three classes of PIs according to the reactive species: anionic, cationic, and radical. Anionic and cationic photoinitiators act upon molecules containing epoxies with cycloaliphatic epoxies being the most commonly used under this category. This type of photoinitiator is usually not compatible with biological systems as its reactivity is diminished by water and hence will not be dealt with further in this chapter. Radical photoinitiators on the other hand are water compatible and act on molecules containing an acrylate or styrene group with double bonds. The range of wavelengths for their utilization is typically near UV (300–400 nm) (Kade and Tirrell 2013).

According to their mechanism of action, radical photoinitiators can be categorized into two categories. The first category (Type I) undergoes a uni-molecular bond cleavage upon exposure to radiations to generate free radicals. The majority of these types include aromatic carbonyl compounds containing suitable groups which facilitate direct photo-fragmentation (Fouassier 1995). Whereas the second category (Type II) is subjected to bimolecular reaction, where the excited photoinitiator interacts with photosensitizer to generate free radicals. The polymerization pathways of this type II are two: hydrogen abstraction, which absorbs light and abstracts hydrogen from another molecule and photo-induced electron transfer, followed by fragmentation (Fouassier 1995). It is important to mention that UV photoinitiators of both types I and II are available. However, VL photoinitiators belong almost exclusively to the type II class of photoinitiators.

Photoinitiators have also been categorized according to the type of light used to induce photoinitiation process into UV, visible, and laser photoinitiators (Allen 1996). The only difference between them is the difference in light energy absorption capacity at the appropriate wavelength. The UV photoinitiators in turn include various classes, and over the last decade, most of them have been reported to be used for drug delivery purposes. As stated earlier, the system is exposed to appropriate light intensity and wavelength, the photosensitizers, which can be regarded as photocatalysts, absorb the energy and transfer it to the photoinitiators and/or act with photoinitiators, which then cause the photoinitiator to break into primary reactive species, usually free radicals. Reactive species then generate the polymerization in subsequent steps. Some photopolymerization system can be irradiated without using photoinitiators such as inulin-methacrylic anhydride which can be photo-cross-linked by long wave UV irradiation (Tripodo et al. 2005). Figure 1a shows a schematic representation of a typical free radical photopolymerization reaction which takes place through the initiation, propagation, and finally termination steps to form the photo-cross-linked polymeric network. Also, as illustrated in Fig. 1b, photoinitiation utilizes photoinitiators which are molecules responsible for initiating the polymerization reaction upon generating reactive species when exposed to light energy (Baroli 2006; Nguyen and West 2002).

Over the last two decades, various PIs have been investigated for the purpose of photopolymerization (Table 2). Since photoinitiators are reactive molecules, that

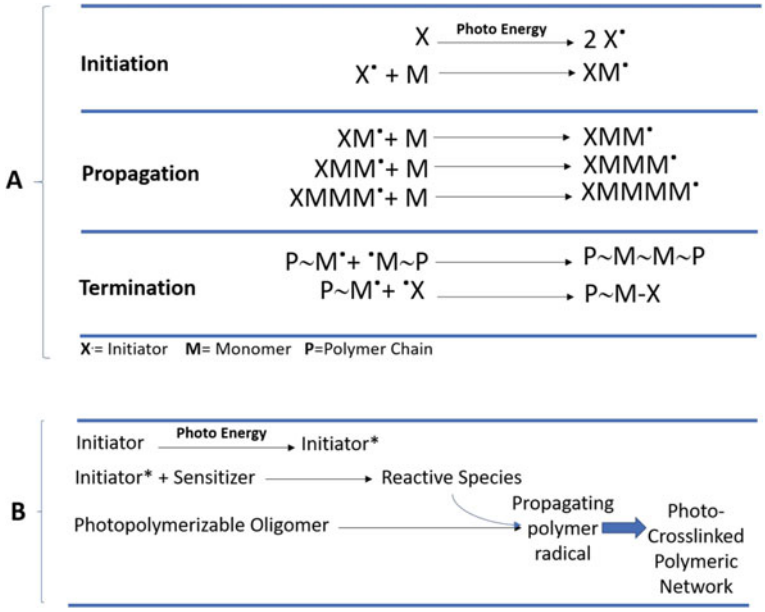

Fig. 1 Schematic representation of the photoinitiated polymerization. **a** Stages of a typical photopolymerization reaction and **b** the role of photoinitiator in the photopolymerization process

may even in trace amounts cause damage to human tissues and cells, only those photoinitiators with stringent characteristics and criteria with accepted biocompatibility can be utilized for drug delivery, tissue engineering, and other biomedical applications (Baroli 2006; Quick and Anseth 2003; Reiner 1987). First, photoinitiators should be completely stable and when dissolved in reactive monomers should not initiate spontaneous or random polymerization. Second, when irradiated, photoinitiators should undergo photolysis with high quantum efficiency and without liberation of biproducts that inhibit polymerization or compromise the quality of the final product. Third, photoinitiators should have as low toxicity as possible, both locally and systemically. Fourth, photoinitiators should be biocompatible with cells or other molecules loaded within the forming polymers, and also with cells and tissues in the vicinity of implantation or injection site. Finally, the synthesis of the prospective photoinitiators should be reasonably straightforward and inexpensive. Apart from for the above criteria, the final choice of initiators is frequently based upon similarly reported systems in the literature or prior experience (Fisher et al. 2001).

One of the most important groups of UV photoinitiators used in various biomedical applications includes *ketones* as functional groups. The reactive radicals in this group can be formed through a photo-cleavage of a bond to the carbonyl group. Different kinds of ketones photoinitiators with different reactive side chains were reported such as α-hydroxy ketone, α-amino ketone, and amino aryl ketone.

Table 2 Selected examples of commonly used classes of photoinitiators

Type	Class	Photoinitiator	Chemical name	λ_{max} (nm)	References
UV photoinitiators	α-hydroxyketone	Irgacure 184	1-Hydroxycyclohexyl-1-phenyl ketone	246, 280, 333	Bryant et al. (2000)
		Irgacure 2959	1-[4-(2-Hydroxyethoxy)-phenyl]-2-hydroxy-2-methyl-1-propane-1-one	276	Bahney et al. (2011)
		Darocur 1173	2-Hydroxy-2-methyl-1-phenyl-1-propanone	245, 280, 331	Li et al. (2016)
	α-aminoketone	Irgacure 369	2-Benzyl-2-dimethylamino-1-(4-morpholinophenyl)-butanone-1	233, 324	Elomaa et al. (2011)
		Irgacure 907	2-Methyl-1-[4-(methylthio) phenyl]-2-(4-morpholinyl)-1-propanone	230, 304	Elomaa et al. (2011)
	Acetophenones	Irgacure 651	2,2-dimethoxy-2-phenyl acetophenone (DMPA)	340	Bryant et al. (2000)
		Caccure 907	2-methyl-4′-(methylthio)-2-Morpholinopropiophenone (MMMP)	351	Frick et al. (2014)
	Phosphines	Irgacure 819	Phosphine oxide, phenyl bis (2,4,6-trimethyl benzoyl)	295, 370	Luo et al. (2016)
		Lucirin TPO	Diphenyl (2,4,6-trimethylbenzoyl)-phosphine oxide	295, 368, 380, 393	Ronca et al. (2017)
	Iodonium salt	Irgacure 250	Iodonium, (4-methylphenyl) [4-(2-methylpropyl) phenyl] hexafluorophosphate (1-)	242	Xu et al. (2015)
		DPIC	Diphenyliodonium chloride (DPIC)	350	Xu et al. (2015)
VL photoinitiators	α-diketones	Camphorquinone	4,7,7-trimethylbicyclo [2.2.1] heptane-2,3-dione	475	Zhou and Ito (2014)
		Dion	1-phenyl-1,2-propanedione		Zhou and Ito (2014)
	Dyes	Eosin Y	2′,4′,5′,7′-Tetrabromofluorescein	510	Bahney et al. (2011)
	Metallocene	Irgacure 784	bis (eta 5-2-4-cyclopentadien-1-yl) bis [2,6-difluoro-3-(1H-pyrrol-1-yl) phenyl] titanium	398, 475	Lin et al. (2013)

Irgacure 2959 (2-hydroxy-1-[4-(hydroxyl ethoxy) phenyl]-2-methyl-1-propanone) and Irgacure 184 (1-hydroxycyclohexyl-1-phenyl ketone) are the most commonly used ketone photoinitiators in tissue engineering (Schmedlen et al. 2002; Quick and Anseth 2003; Reiner 1987; Kim and Park 2002; Williams et al. 2005). Also, it has been invested for cross-linking of pH-sensitive glycol-polymers for oral drug delivery systems (Burkoth and Anseth 2000). *Acetophenone derivatives* of 4-Benzoylbenzyl-trimethylammonium chloride (BTC) are another group of UV photoinitiators used in drug delivery and biomedical applications. The 2, 2-dimethoxy-2-phenyl acetophenone (DMPA) is an example of acetophenones that has been significantly used as photoinitiators for photopolymerization of PEG to form hydrogels for use in biomaterial studies (Nguyen and West 2002; Hill-West et al. 1994; Hill-West and Chowdhury 1994; West and Hubbell 1998). Irgacure 6512 (2-dimethoxy-2-phenyl acetophenone) was also used to form hydrogels from PEG derivatives in several other studies (Baroli 2006; West and Hubbell 1998; Oudshoorn et al. 2006). Also, *Phosphine oxide* such as monoacylphosphine (Lucirin TPO), bisacylphosphine (Irgacure 819), as well as iodonium salt derivatives such as diphenyl iodonium hexafluorophosphate have also been used in photopolymerized biomaterial studies (Luo et al. 2016).

Photoinitiators having absorption capabilities in the VL energy range are based on dyes, quinines, diketones, and heterocyclic chemical structures. *Camphor compounds* such as camphorquinone (CQ), camphor and amine compounds such as triethylamine and triethanolamine (Baroli 2006; Poshusta 2001) and compounds such as Isopropyl thioxanthone (ITX) and ethyl 4-*N*, *N*-dimethylamino-benzoate (EDMAB) have also found used as photoinitiators for tissue engineering, drug delivery, and cell capsulation. Also, metallocene compounds such as Irgacure 784 have been used in drug delivery (Baroli 2006; Burdick et al. 2001; Davis et al. 2003). In addition, eosin Y belonging to the UV and IR light energy range has a broad biomedical use such as interfacial photopolymerization of PEG diacrylate and photo-cross-linked Pluronic hydrogel for plasmid DNA release (Chun et al. 2005; Cruise et al. 1998; Elbert and Hubbell 2001).

3 Biocompatibility of Photoinitiation System

One of the major requirements for advancing any tested polymeric formulation or device is to ensure its safety and efficacy. As such, any biomaterial designed to make a pharmaceutical device or drug carrier must be subjected to intensive processing and characterization as well as comprehensive safety testing. A biocompatible material must show acceptable interaction with the host in specific application and implant site. Biocompatibility reflects the interaction that may be affected by numerous factors related to the material. Learning that the synthesis of photopolymerized composite polymers utilizes photoinitiators and encompass generation of reactive chemical species such as free radicals as part of the photocuring process, make the issue of biocompatibility surface as an important aspect

that must be addressed and dealt with when light curing technology is utilized to prepare photo-cross-linked polymers intended for delivery in the body or used in contact with living cells and tissues (Burg and Shalaby 2013). Consequently, much of research related to utilization of photopolymerization in various biomedical applications focused on testing the possible effect of radiation source type, intensity, and duration of exposure on cells and living tissues. Also, much of research work has been reported concerning the testing of possible toxicities and compatibility of various photoinitiators and the generated free radicals (Baroli 2006).

One of the reported most comprehensive studies which extensively investigated the biocompatibility of different photoinitiating systems for cell encapsulation and tissue engineering applications was carried out by Bryant et al. (2000). Both UV and VL photoinitiators were tested. The tested UV photoinitiators included 2,2-dimethoxy-2-phenylacetophenone (Irgacure 651), 1-hydroxy cyclohexyl phenyl ketone (Irgacure 184), 2-methyl-1-[4-(methylthio) phenyl]-2-(4-morpholinyl)-1-propanone (Irgacure 907), and 2-hydroxy-1-[4-(hydroxyethoxy) phenyl]-2-methyl-1-propanone (Darocur 2959). On the other hand, the VL photoinitiators included camphorquinone (CQ) with ethyl 4-*N*, *N*-dimethylaminobenzoate (4EDMAB) and triethanolamine (TEA) and the photosensitizer, isopropyl thioxanthone. Fibroblast NIH/3T3 cell line was cultured and incubated with the photoinitiators at varying concentrations ranging from 0.01 to 0.1% w/w in the presence and absence of photoinitiating light source. The study showed that at low photoinitiator concentrations (i.e., less or equal to 0.1% w/w), all of the tested photoinitiator molecules were cytocompatible with the exception of CQ, Irgacure 651, and 4EDMAB which had a relative survival of around 50% lower than a control. In the presence of low intensity initiating light ($\sim$6 mW cm^{-2} of 365 nm UV light and $\sim$60 mW cm^{-2} of 470–490 nm VL) and photoinitiating radicals, Darocur 2959 at concentrations equal or less than 0.05% w/w and CQ at concentrations less or equal to 0.01% w/w were the most promising cytocompatible UV and VL initiating systems, respectively. To compare the effect of using cytocompatible versus non-cytocompatible photoinitiators, chondrocytes were encapsulated in a photo-cross-linked hydrogel using 0.05% w/w of cytocompatible Darocur 2959 and 0.01% w/w of cyto-incompatible Irgacure 651. Upon photoirradiation for 10 min with around 8 mW cm^{-2} of 365 nm light, cell assay conducted demonstrated that nearly all the exposed chondrocytes survived the process with Darocur 2959 while very few only survived the process with Irgacure 651 (Bryant et al. 2000).

Another study carried out to test the cytocompatibility of the photoinitiator Irgacure 2959 demonstrated that different cell lines showed variable responses to similar concentrations of the same photoinitiator. The study also showed that the Irgacure 2959 was well tolerated by many cell lines over a range of various mammalian species (Williams et al. 2005).

Finally, it is important to report here that the existing testing practices and guidelines used for the assessment of cytocompatibility are not suitable for photocured hydrogels, since it is difficult to avoid causing damage to the cells upon removing the cell-hydrogel placed in contact with cells. As such, separate protocols have to be utilized for testing the hydrogel–cells interaction. Transwell inserts

containing the hydrogel and polymeric solutions were developed as an outstanding technique for an indirect cell contact testing (Trudel and Massia 2002).

In light of the previous discussion, it is important to carry out either in vitro cytocompatibility or more informative in vivo biocompatibility studies to ensure that the used precursors, photoinitiators, and light source in the photopolymerization process are not causing toxicities to the cells and tissues or affecting the health of the human body.

4 Acrylates and Methacrylates-Based Photo-Curable Polymeric Matrices

Various polymeric composites and biomaterials have been explored for photopolymerization as matrices for use in drug delivery, tissue engineering, and other biomedical applications. The development of novel drug delivery systems in specific is a very active part of the biomedical industry due to obvious therapeutic and economic advantages in the method of drug administration. Considering the application, biodegradable polymeric materials were most commonly used as they evade the need of a surgery to remove the implanted biomaterials after the healing of the tissues and it offers the ability of triggering and guiding the tissue regeneration via degradation of the material. It is worth mentioning here that almost all the photopolymerizable biomaterials commonly have a photopolymerizable moiety in their backbone, which is traditionally located at one or both ends of the monomer or polymer chain. Acrylate or methacrylate moieties are reported to be the most commonly used in that regard as they can be covalently cross-link upon the excitation of radical generating photoinitiators (Sershen and West 2002; Qui and Park 2001). Selected examples of biodegradable polymers possessing acrylate or methacrylate photoreactive moieties with their biomedical applications are listed in Table 3.

As a result of its excellent biocompatibility and biodegradability, PEG has been extensively investigated for its biomedical applications. PEG derivatives that have been probed include acrylate or methacrylate derivatives, poly (propylene fumarate-co-ethylene glycol) (Shin et al. 2003), and PEG fumarate (Suggs et al. 1998). PEG di-methacrylate and PEG urethane-di-methacrylate have also been explored and showed good biocompatibility when successfully employed in both in vivo and in vitro studies by several groups as scaffold materials (Lin-Gibson et al. 2004). PEG-diacrylamide was also emerged as an interesting new derivative for in vivo photopolymerization. Although acrylamide is known to be very toxic, PEG-acrylamide was found to be nontoxic, because its hydrophilicity and high molecular weight will restrict access of the polymer to within the cells. Furthermore, it will undergo rapid free radical polymerization and easily attach with peptides via a conjugate addition reaction (Elisseeff et al. 1999).

Polyvinyl alcohol (PVA) has been reported to be protein nonadhesive, thus PVA offers the possibility of cell selectivity through incorporation of bioactive moieties.

Table 3 Selected examples of biodegradable photocured polymers and their biomedical applications

Polymers	Photo-cross-linked moiety	Biomedical application	References
Poly (ethylene glycol)	Methacrylate	Cartilage tissue engineering	Lin-Gibson et al. (2004)
Pluronic	Acrylate	Controlled DNA release	Chun et al. (2005)
Polyvinyl alcohol	Methacrylate	Scaffolds material	Schmedlen et al. (2002)
Polyester polyol	Acrylate	Tissue sealants	Nivasu et al. (2004)
Inulin-succinic anhydride	Methacrylate	pH-responsive drug delivery	Tripodo et al. (2005)
Polyanhydrides	Methacrylate	Orthopedic application	Burkoth and Anseth (2000)
Poly (acrylic acid)	Methacrylate	Mucoadhesive drug delivery system	Burkoth and Anseth (2000), Serra et al. (2006)
PEG-diacrylamide	Di-acrylamide	Reendothelialization promoting materials	Elbert and Hubbell (2001)
Poly (ε-caprolactone-co-D, L-Lactide)	Acrylate	Implantable drug delivery	Younes et al. (2004)
Hyaluronic acid	Methacrylate	Cell encapsulation	Bae et al. (2006)
Dextran and polyaspartamide	Glycidyl methacrylate	pH-responsive drug delivery	Pitarresi et al. (2003)
Polyphosphoester	Acrylate	Injectable scaffolds	Li et al. (2006)
Fumarate-based unsaturated poly (ester amide) and PEG	Diacrylate	Local anticancer drug delivery	Guo (2007)
Poly (Diol-co-Tricarballylate)	Acrylate	Implantable drug delivery	Shaker et al. (2012), El-Laboudy et al. (2011)

The number of photoreactive groups on the PVA chain can be significantly varied which facilitates the manipulation of hydrogel mechanical properties. In addition, the pendant hydroxyl groups on PVA offer many more accessible sites for the attachment of bioactive molecules (Schmedlen et al. 2002). Furthermore, PVA hydrogels have been scrutinized as a promising candidate of protein-releasing matrices (Peppas and Scott 1992). The use of photoactive PVA derivatives that form cross-linked hydrogels in the presence of cells and tissues functionalized with the cell-adhesive peptide RGDS (Arg-Gly-Asp-Ser) was also investigated. It was found that photo-cross-linked PVA supported the attachment and spreading of fibroblasts in a dose-dependent manner (West and Hubbell 1998; Ward and Peppas 2001).

Block copolymers of poly (ethylene oxide) and poly (propylene oxide) which are also known as Pluronic polymers and exhibit thermal gelling properties have also

been investigated. Photo-cross-linked Pluronic hydrogels have been used as delivery systems for several proteins and genes including IL-2, urease (Schmedlen et al. 2002; Fults 1990), rat intestinal natriuretic factor (Peppas and Scott 1992; Korsmeyer et al. 1983). Poly(2-hydroxyet) (poly(HEMA)) were also used as a drug carriers due to their ability to release entrapped drugs in aqueous medium as well as its good biocompatibility (Lu and Anseth 1999). Hyperbranched polyglycerol methacrylate, derived from glycidyl methacrylate also, shows great potential for drug delivery and tissue engineering (Amsden et al. 2004).

Naturally occurring polymers such as dextran, inulin (Tripodo et al. 2005), collagen (Trudel and Massia 2002; Pitarresi et al. 2003), hyaluronic acid (Trudel and Massia 2002), and polyphosphoesters (Li et al. 2006) whose biodegradability in the body is well known have been broadly explored for photopolymerization use. From among the natural materials available for photopolymerization, polysaccharides are the best choice for preparing bioerodible hydrogels used for drug delivery system. Polysaccharides are readily available and are easily undergo degradation by hydrolysis or enzymatically in certain cases. They possess hydroxyl functional groups in the backbone which can be used for the chemical modifications leading to cross-linking of hydrogels. These hydroxyl groups can also be used to covalently attach drugs or other therapeutic moieties to the hydrogel backbone (Tripodo et al. 2005; Pitarresi et al. 2003). Dextran is another natural polysaccharide that has found extensive use in the pharmaceutical field (Reynolds 1993; Kim et al. 2001). Photo-cross-linked dextran derivative containing methacrylate moieties represent a straightforward and reproducible procedure to obtain networks capable to swell in aqueous medium to form hydrogels.

Gellan Gum-based hydrogels have been proposed for tissue engineering application. These hydrogels were synthesized by reacting Gellan Gum with methacrylic anhydride in different ratios to yield photo-cross-linkable methacrylated Gellan Gum hydrogels (MeGG) with two different degrees of methacrylation (Xiao et al. In Press). This has enabled the development of MeGG hydrogels with highly tunable physical and mechanical properties with high biocompatibility. These hydrogels have been reported for a wide range of tissue engineering applications.

Jansen et al. reported on the fumaric acid monoethyl ester-functionalized poly (trimethylene carbonate) photo-cross-linkable oligomers which were synthesized and copolymerized with *N*-vinyl pyrrolidone (NVP) and vinyl acetate (VAc) to form biodegradable polymeric networks (Jansen et al. 2010). They found that the copolymerization reactions were much faster than homo-polymerization of the fumarate end-groups of the macromers. The hydrophilicity of the networks was varied by mixing NVP and VAc at different ratios. The extract of the prepared network was compatible with NIH 3T3 fibroblasts. It was found that the release of vitamin B12, which was used as a model drug, could be adjusted by varying polymeric network hydrophilicity and macromer molecular weight. A more hydrophilic and less densely cross-linked network resulted in faster release of vitamin B12. Many other polyesters-based photo-cross-linked polymers have been reported in the literature which utilized photocuring technology to prepare highly biocompatible and tunable matrices which constituted very promising carriers for

drug delivery and tissue engineering application (Shaker et al. 2010, 2012; Gu et al. 2005; Shaker and Younes 2010, 2015). The details of their preparations and applications shall be discussed extensively in the next section of this chapter.

5 Forms, Pharmaceutical, and Biomedical Applications of Photo-cross-linked Polymers

Photopolymerization has been extensively used in the last two decades in a wide range of pharmaceutical and biomedical applications and still constitutes a fundamental approach to further advances in the biomedical research in medicine such as scaffold and tissue fabrication (Cooke et al. 2003), blood vessel adhesives (Hubbell 1996), adhesion prevention barriers (Elbert and Hubbell 2001), joint replacement (Poshusta 2001), teeth restoration (Anseth et al. 1995; Khosroshahi et al. 2008), and in cell encapsulation for tissue replacement strategies (Cruise et al. 1999).

Traditionally, drug molecules are mixed with the photoreactive monomer or prepolymer in the presence of the PI prior to its exposure to the LCS at the required wavelength. Once the mix is poured into a specific mold or shaped into the required three-dimensional structure, the mass is exposed to the LCS of optimum intensity to form the drug-loaded photo-cross-linked polymer. Figure 2 shows a schematic

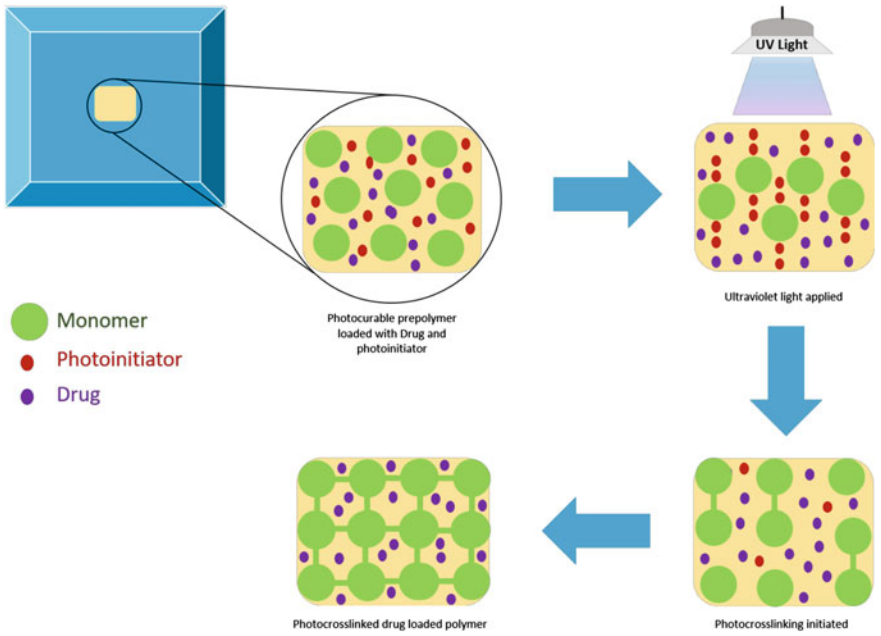

Fig. 2 Schematic representation of the stages involved in the UV photocuring process to prepare a drug-loaded photo-cross-linked scaffold

representation of the stages involved in the fabrication of a drug-loaded scaffolds or matrices. In the following sections, we shall discuss in more detail some of the main utilization and applications of photopolymerization in the biomedical and pharmaceutical fields. The discussion shall be categorized based on the physical form of the photo-cross-linked polymers and the intended application.

5.1 Photo-cross-linked Hydrogels

Photo-cross-linked hydrogels are three-dimensional polymeric networks composed of hydrophilic polymers held together by association bonds such as covalent bonds and weaker cohesive forces such as hydrogen, ionic bonds, and intermolecular hydrophobic associations (Singh et al. 2018). Their high-water content, biocompatibility, and the fact that their mechanical properties can be manipulated in such a way that they match those of many soft tissues made them gain wide popularity as controlled release carriers for drugs and proteins. Moreover, they possess high permeability to oxygen, nutrients, and other water-soluble metabolites, which make them a good niche for cells and transplantation applications (Nguyen and West 2002; Schmedlen et al. 2002; Severian 2011). In addition, the biodegradation of the photocured hydrogel matrices not only allows a tunable release of entrapped molecules, but also evades the removal of the device from body (Pitarresi et al. 2003; Reynolds 1993; Kim et al. 2001).

There are two main approaches for loading drugs into photo-cross-linked hydrogels. One approach requires the monomer to be mixed with drug, photoinitiator, and cross-linker and is photopolymerized to load the drug within the matrix as previously demonstrated in Fig. 2. In another approach, a photopolymerized hydrogel is placed to swell to equilibrium in a suitable drug solution. The drug diffuses from the photopolymerized hydrogel when it is placed in an environment causing it to swell and increases the mesh size (Reynolds 1993; Buwalda et al. 2017). It is also important to ensure that the hydrogel possesses the optimal needed cross-linking density since the drug will not be able to diffuse out of the system. At the same time, the drug should withstand the polymerization conditions and should not react with the monomers in the system. A kinetic experiment to study the effect of solute presence on the polymerization process developed by Peppas et al. demonstrated that the solutes presence result in a more heterogeneous material, a delay in the gel point and in greater microgel regions (Peppas and Scott 1992). Additionally, other studies also revealed that the presence of a low molecular weight solute increases the rate of polymerization (Elisseeff et al. 2000; Jeong et al. 1997).

Upon exposure to UV or the less destructive VL and in the presence of compatible photoinitiator, some photopolymerized hydrogels can be prepared at physiological pH and body temperature. The fast photopolymerization procedure allows cells to be seeded homogeneously within the hydrogel mass with minimal exposure to light. Furthermore, by altering monomer and photoinitiator

concentration, exposure time, and distance to light source, the cross-linking of the hydrogel to reach the gelation point can be easily controlled and therefore enabling the control of drug release from the hydrogel (Schmedlen et al. 2002).

Photo-cross-linked hydrogels are attractive to apply for localized drug delivery as they can be cross-linked in situ and hence can conform and adhere to the targeted tissue (Nguyen and West 2002). The applications of photopolymerizable hydrogels are unlimited due to the large number of drugs, hormones, and therapeutic proteins available. These applications include but not limited to sustained DNA delivery (Kim and Park 2002; Madsen and Mooney 2000), controlled release of insulin and growth factors (Younes and Amsden 2002), mucoadhesive delivery systems, and live vaccine ballistic delivery (Serra et al. 2006; Christie et al. 2006). For instance, photo-cross-linked Pluronic hydrogel has been used for sustained delivery of therapeutic genes for wound healing and tissue regeneration (Madsen and Mooney 2000). Kim and Park successfully synthesized degradable and temperature-responsive hyaluronic acid/Pluronic composite hydrogels for controlled release of human growth hormone (Kim and Park 2002). Various release profiles were attained by varying UV irradiation time and modified hyaluronic acid amounts. This demonstrated that the made hydrogels can be utilized as a potential candidate material for in vivo sustained gene delivery after fine-tuning various formulation parameters (Kim and Park 2002).

Photopolymerized hydrogel has been utilized for the controlled delivery of highly potent, but relatively toxic, anticancer drugs without inducing side effects. Kai et al., synthesized paclitaxel loaded biodegradable hydrogel by the photopolymerization of two precursors: a fumarate-based unsaturated poly (ester amide) and a PEG diacrylate. Sustained paclitaxel release over a two-month period was observed without initial burst release (Guo 2007). Other drugs such as theophylline (Pitarresi et al. 2003), gentamicin (Missirlis et al. 2006), and live vaccine (Christie et al. 2006), have also been loaded into photo-cross-linked hydrogels and shown to possess well-defined release patterns. Additionally, prepared doxorubicin encapsulated, polymeric hydrogel nanoparticles, by photopolymerization of PEG and poloxamer 407 was investigated. The study showed that the drug was released in a sustained fashion over a period of one week with minor burst observed (Missirlis et al. 2006).

Photo-cross-linked hydrogels have been also reported to be used in site specific delivery of drugs. Serra et al. for instance reported on the UV photo-cross-linked Poly (acrylic acid)-based hydrogels which were modified by grafting their backbone chains with chains such as PEG thus promoting the adhesive process (Serra et al. 2006). Finally, the aforementioned applications of photo-cross-linked hydrogels usually involve the loading of drugs in a single layer hydrogel in which drugs are uniformly dispersed. Since it is indeed challenging to fabricate one single hydrogel layer that possess all the needed physicochemical properties required for a specific application, the capability to construct multiple layered hydrogels of varied composition in a single membrane or device was explored. For example, Lu et al. investigated the use of photopolymerization of multi-laminated Poly (hydroxyethyl methacrylate) to design layered matrix-based devices with

nonuniform concentration profiles aiming at controlling the drug release. They reported that the polymerization conditions were sufficiently mild to be carried out in the presence of biological materials (Lu and Anseth 1999).

5.2 *Photo-cross-linked Biodegradable Elastomers*

Polymers possessing rubber-like elasticity, known also as elastomers, have been extensively studied for their use in various pharmaceutical and biomedical applications. Elastomers possess many advantages over other synthesized tough polymers. Their mechanical properties can be tailored to simulate soft body tissues; they have the ability to withstand the mechanical stress upon implantation in mobile parts of the human body and they can also be designed to possess a three-dimensional structure with uniform degradation pattern which make them well suited for various biomedical applications (Bruggeman et al. 2008; Storey et al. 1997; Yang et al. 2006). Additionally, the use of photo-cross-linking in preparing photocured biodegradable elastomers offers a number of advantages over the thermal or solution cross-linking techniques in preparing these elastomers (Younes 2016). The process, with thermosensitive drugs, can be carried out in situ, and the degree of cross-linking and mechanical properties of the photocured elastomer can be tailored by changing the density of photosensitive termini in the prepolymer (Shaker et al. 2010). Due to these potential advantages, many researchers intensively investigated the utilization of photo-cross-linked elastomers and their biomedical application in protein drug delivery and tissue engineering.

In one of the recent studies, Guo et al. reported on the synthesis and characterization of cross-linked elastomers based on methyl-acrylic-star-poly (ε-caprolactone-co-d, l-lactide) cyclic ester and methyl-bi-acrylic-poly(ε-caprolactone-b-poly(ethylene glycol)-b-ε-caprolactone) as potential implantable controlled drug delivery system for protein drugs. The elastomers prepared using varying molecular weight and their in vitro degradation and release of bovine serum albumin (BSA) and recombinant human interleukin-2 (IL-2) studies were conducted. The release rate of BSA and IL-2 increased with a higher degree of swelling, higher sol content, and lower cross-linking density of the elastomers. The cytocompatibility assays showed good biocompatibility (Guo et al. 2017). The same team as well explored the fabrication of insulin-loaded cylinders using a UV cross-linking process based on the same elastomers and studied the stability and in vitro release of insulin as well as its in vivo hypoglycemic effect on mice (Guo et al. 2018). The study revealed that the loaded insulin retained its bioactivity and the rate of insulin release was controlled by manipulating the polymer composition. Furthermore, in vivo studies showed that most of the insulin-loaded elastomers fabricated decreased blood glucose levels and maintained it at a low level. It was also observed that the hypoglycemic effect of the drug-loaded elastomers was directly proportional to the rate of in vitro insulin release (Guo et al. 2018).

"Younes et al. reported earlier on the use of UV photopolymerization to fabricate acrylated star poly (ε-caprolactone-co-d, l-lactide) implantable biodegradable elastomers loaded with the therapeutic protein, Interferon-gamma (IFN-γ) (Younes et al. 2004; Gu et al. 2005). The same prepared biodegradable elastomer loaded with IFN-γ, VEGF, and IL-2 has also been researched and reported lately for their suitability for sustained drug delivery (Gu et al. 2006). Retaining the protein bioactivity and prolonging the release duration was achieved by incorporating IFN-γ as lyophilized particles within the matrix prior to photopolymerization and relied on the osmotic activity of the co-formulated excipients like trehalose to drive the protein release out of the elastomer matrix. The obtained release rate was found to be constant (23 ng/day), and the release pattern was nearly zero-order with minimal burst effect. It was also found that around 83% of released protein, in the first week of release studies, remained bioactive."

In an attempt to address the quick loss of bioactivity of loaded proteins following the first week of release due to the accumulation of acidic monomers followed by a drop in the pH of the microenvironment causing the denaturation of the protein, Chapanian et al. substituted the use of ε-caprolactone in the elastomer with trimethylene carbonate (TMC) (Chapanian and Amsden 2010). They investigated the ability of UV photo-cross-linked TMC-based elastomers to release VEGF165 and hepatocyte growth factor (HGF) separately or in combination with a sequential release mode using the osmotic-driven release mechanism. VEGF165 and HGF were lyophilized separately and together with trehalose, rat serum albumin, and sodium chloride. It was found that no significant degradation of the elastomer occurred over the initial 8 weeks, during which the majority of the loaded growth factors were released. The TMC-based elastomer was able to provide a sustained release of bioactive VEGF165 and HGF for more than 10 days (Chapanian and Amsden 2010). Although the bioactivity of the loaded proteins improved compared to previous reports, the use of both organic solvents in loading the protein and utilization of UV light constituted a challenging issue that was later addressed by other researchers.

Younes et al. have recently reported on the synthesis and biocompatibility of a novel family of amorphous photoset poly(diol-co-tricarballylate)-based elastomers for use in tissue engineering and controlled delivery of small molecules and therapeutic proteins (Shaker et al. 2010, 2012; Shaker and Younes 2010; Younes 2016). These new elastomers were prepared by VL photocuring and a solvent-free drug loading approach (Shaker and Younes 2010; Younes and Shaker 2011). The elastomers possessed mechanical properties that can be easily controlled and proved to be amorphous with glass transition temperatures below physiological body temperature, making them excellent candidates as biodegradable implants in vivo. The hydrophilic and hydrophobic nature of these elastomers was controlled by changing the chain length of the aliphatic diol in their backbone structure. The study also demonstrated that the use of VL cross-linking indeed addressed many of the drawbacks associated with UV photocuring by making the polymerization conditions mild for use with biological materials, that is, for encapsulation of viable cells, loading of heat sensitive drugs or in biosensing applications. Additionally, VL

utilization may limit the need for invasive surgical procedures by allowing trans-tissue polymerizations, whereby the material is injected subcutaneously to polymerize the material in situ.

In another recent study, Younes. et al. also showed that the osmotic-driven release of drugs from those elastomers was constant, linear, and controllable. The cell-based bioactivity assays on the released IL-2 showed that more than 94% of its original activity was retained over a controlled release period of 28 days. The further in vivo studies on BALB/c mouse tumor model clearly suggested that controlled localized delivery of bioactive IL-2 from these new elastomers, at the site of tumor inoculation is sufficient to prevent tumor growth in vivo (Younes and Shaker 2011).

5.3 Other Biomedical Applications

5.3.1 Tissue Engineering

The art and science of tissue engineering has witnessed new trends with the major advances in photopolymerization technologies. Many researchers were able to fabricate three-dimensional scaffolds using stereolithography and photolithography methods as well as polymer chemistries. Stereolithography is a three-dimensional photopolymerization technique that uses an UV laser beam to photo-cure the photopolymerizable polymer. Laser beam is directed into a layer of liquid polymer, causing cross-linking to the exposed area and after covering with a new layer of polymer the process is repeated (Cooke et al. 2003). Cooke et al. reported on the application of stereolithography for the production of biodegradable three-dimensional structure tissue (Cooke et al. 2003). Photolithography method on the other hand is potentially used for the production of both single and multilayer biomaterials. Yu et al. successfully demonstrated the utilization of photolithography process to build and control the fabrication of polymer scaffolds. They reported a photolithographic method of pattering dried 2-hydroxyethyl methacrylate, which is later rehydrated before cell seeding (Yu et al. 2000). Also, Hubbell developed a simple yet rapid method of creating various shaped patterned surfaces using photopolymerizable chitosan. They reported the prepared chitosan patterned surfaces (cardiac fibroblasts, cardiomyocytes, and osteoblasts) to be stable for up to 18 days (Hubbell 1996).

An alternative method for hepatocyte transplantation involves the implantation of tissue engineered hepatocyte spheroids (i.e., hepatocytes on biodegradable polymer) which have a liver-like morphology and preserved specific metabolic function which could serve as an in vivo substitute for lost liver function. Tsang et al. have fabricated a spheroid using a multilayer photo-patterning approach. They have used a photopolymerizable PEG hydrogel which is able to support survival of hepatocyte and liver function. They incorporated adhesive peptides able to ligate integrin on these adhesion-dependent cells (Tsang et al. 2006).

Anseth et al. investigated a new class of methacrylate anhydride monomers such as methacrylated sebacic acid, methacrylated 1,3-bis(p-carboxyphenoxy) propane, and meth-acylated 1,6-bis(p-carboxyphenoxy) hexane for orthopedic applications (Anseth et al. 1995). They successfully used such monomers in tibia bone defect and preliminary histological evaluation showed good adhesion of the polymer to the cortical bone and medullar cavity. Furthermore, to secure metallic orthopedic implants, bone cements based on methyl methacrylate have been used to form rigid polymers (Kohn and Ducheyne 1992).

Photoreactive electrospinning (PRES) is a very recent technology currently utilized to fabricate photo-cross-linked electrospun nanofibers for tissue engineering applications. The principle of PRES is based on combining the conventional electrospinning method with a photo-cross-linking method applied in situ to the jet flowing from the needle to the collector (Xu 2011). Figure 3 illustrates a schematic representation of the utilization of PRES for the preparation of photo-cross-linked electrospun nanofibers.

In a very recent study, Ismail et al. (2018) reported on the fabrication and in vitro cytocompatibility of new electrospun fibrous scaffolds (EFS) based on photo-cross-linkable acrylated poly (1,10-decanediol-co-tricarballylate) (PDET) copolymer prepared utilizing UV photoreactive electrospinning process. Those ESF were intended to be used for cardiac tissue engineering applications (Fig. 4). The fabricated ESF were compared to those prepared using the sodium chloride particulate leaching process for preparing porous scaffolds. The newly prepared

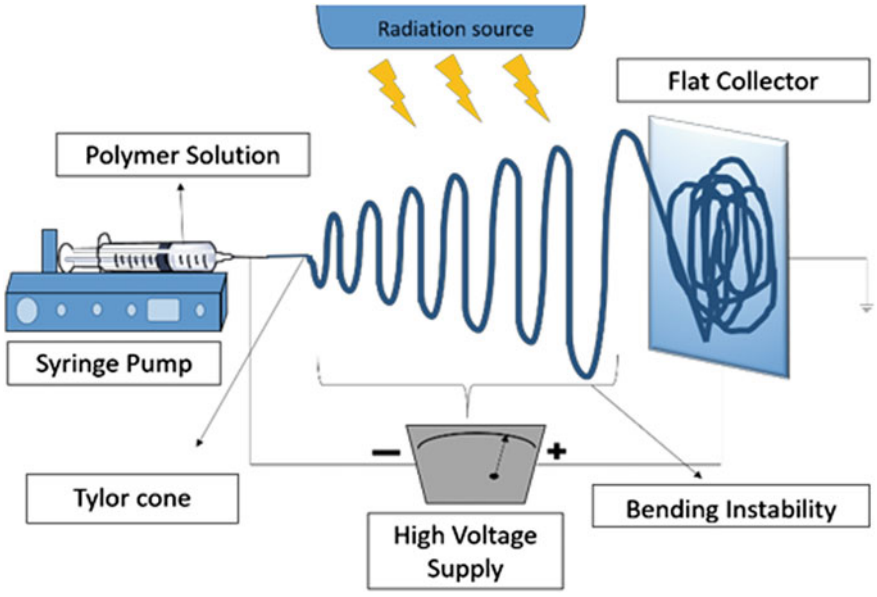

Fig. 3 Schematic illustration of the photoreactive electrospinning process to prepare photo-cross-linked nanofibers for tissue engineering applications

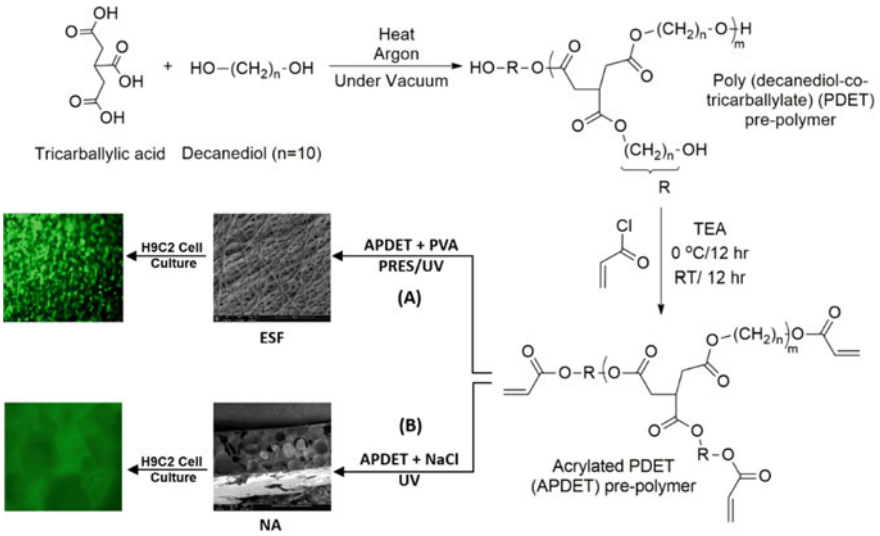

Fig. 4 Schematic illustration of the PDET synthesis and further cross-linking to prepare **a** electrospun fibers using UV photoreactive electrospinning or **b** UV photo-cross-linked scaffolds using NaCl particulate leaching technique (Ismail et al. 2018). Copyright 2018. Reproduced with permission from MDPI

photo-cross-linked elastomeric fibrous scaffolds proved to possess above 70% porosity. More importantly, the mechanical testing confirmed the elastomeric nature of the fibers required to withstand cardiac contraction and relaxation. Cell viability assays confirmed the cytocompatibility of the ESF with cultured cardiomyoblasts which also facilitated a significant increase in cell attachment and growth on the electrospun fibers compared to reference. Interestingly, the H9C2 cells also demonstrated a certain degree of alignment along the fibers, potentially due to the fiber collection method used in this study and offering the required anisotropic effect consistent with cardiac tissue engineering applications.

5.3.2 Cell Encapsulation

In cell encapsulation, transplanted cells are shielded from immune rejection by biocompatible artificial semi-permeable membrane. Such encapsulation can be achieved using photo-cross-linked polymers. The photopolymerized polymer should potentially allow allo- or xeno-transplantation without the use of immuno-suppressants. Several photo-polymeric encapsulation systems have been developed or advanced to clinical trials in humans (Elisseeff et al. 1999; Bae et al. 2006; Cruise et al. 1999).

Diabetes is one of the most significant areas of current research for encapsulation of cells, specifically the pancreatic islets of Langerhans cells that produces insulin.

Cruise et al. investigated a method of xenograft protection toward a bioartificial endocrine pancreas (Cruise et al. 1998). They illustrated the importance of interfacial photopolymerization to form PEG membranes for encapsulating islets of Langerhans. Results from this study demonstrated the in vitro and in vivo function of the photo-encapsulated porcine islets and the capability of this PEG membrane to prevent immune rejection in a discordant xenograft model. Moreover, using static glucose stimulation and perfusion assays, the encapsulated islets were shown to be responsive to glucose level (Cruise et al. 1999). Additionally, Elisseeff et al. have suggested that the feasibility of photopolymerizing system provides an efficient method to encapsulate living cells (Elisseeff et al. 1999). They described the encapsulation of bovine and ovine chondrocytes in a PEO-di-methacrylate and PEG semi-interpenetrating network using a photopolymerization technique (Elisseeff et al. 2000). Finally, a new concept for cell encapsulation was introduced by Bae et al. who developed photopolymerizable beads with methacrylated hyaluronic acid and *N*-vinylpyrrolidone. Using microinjection technique, they directly injected viable cells into the beads. Cells proliferated well within these beads which could potentially be used as injectable cell delivery vehicles for regenerating tissue defects (Bae et al. 2006).

5.3.3 Therapeutic Protein Delivery

Many of the therapeutic proteins require sustained and localized delivery. Currently, most proteins are delivered via multiple injection regimens. Also, poor stability upon storage and low patient compliance has disadvantaged their advancement to clinical approval (Gu et al. 2005, 2006; Burdick et al. 2002). Hence, there is a great need to develop better delivery systems and strategies of administering protein drugs. In an attempt to develop an implantable elastomer which can retain proteins stability and reserve their activity, Younes et al. designed a photo-cross-linked biodegradable elastomer based on poly (ε-caprolactone-co-d, l-lactide), in an attempt to deliver (IFN-γ utilizing osmotic-driven release mechanism. The delivery and release of IFN-γ from this photo-cross-linked biodegradable elastomer was achieved successfully. IFN-γ was released at a constant rate of 23 ng/day over three weeks. A cell-based bioassay demonstrated that over 83% of released IFN-γ was bioactive. Furthermore, it was demonstrated that BSA co-lyophilized with IFN-γ was released at the same rate. These findings may be clinically useful for sustained, local protein drug delivery applications (Younes and Amsden 2002).

Growth factor protein was loaded in poly (lactide-co-glycolide) (PLGA) microspheres using double emulsion technique. The microspheres were photo-encapsulated with bovine articular chondrocytes in PEG-based hydrogel. Controlled release of the active proteins was observed confirming that PEG-based hydrogel provides a method to deliver protein molecules in porous hydrogel systems (Quick and Anseth 2004).

5.3.4 Genes Delivery

Gene delivery is the process of introducing foreign DNA into host cells. It is one of the vital steps needed for gene therapy treatment and the genetic modification. Photopolymerization techniques were reported to improve the efficiency of gene delivery (Quick and Anseth 2003, 2004; Chun et al. 2005; Wieland et al. 2007). Foreign gene expression can be prolonged by sustained DNA delivery which is an important advantage for a long-term non-viral gene therapy (Quick and Anseth 2003, 2004). Anseth et al. addressed this issue by designing photopolymer matrices that enabled simultaneous encapsulation of plasmid DNA (Quick and Anseth 2003). They first protected the DNA from the impact of UV photoinitiating conditions. The study results showed that encapsulated plasmid DNA was released in its active form with an approximate 60% recovery in activity which allowed the creation of engineered tissues with enhanced control of cell behavior through controlling the release of plasmid DNA (Quick and Anseth 2003).

Controlled DNA release was also achieved by loading plasmid DNA in a photopolymerizable di-acrylated pluronic in the presence and absence of vinyl group-modified hyaluronic acid (HA). Various release profiles were attained by varying UV irradiation time and modifying the amounts hyaluronic acid. The released DNA was stable during the release period and maintained functional gene expression activities (Chun et al. 2005).

Wieland et al. investigated the photo-cross-linking of acrylated PEG-hyaluronic acid as a controlled release carrier for gene therapy vectors. The release from these hydrogels depended significantly on the physicochemical properties of both the hydrogel and the vector. The polymer content and relative composition of HA and PEG influenced the transportation of the vector through the hydrogel by modulating the swelling ratio, water content, and degradation rate. The release studies revealed that the majority of the release occurred during the initial two days and the cumulative release increased upon decreasing PEG or increasing HA concentrations. It was also demonstrated the dependence of non-viral vector release on the physicochemical properties of the hydrogel and the vector (Wieland et al. 2007).

5.3.5 Drug Delivery of Small Molecules

Controlled drug delivery can occur when a photopolymerizable polymer is combined with a drug in such a way that the active agent is released from the material in a predetermined and controlled manner. The release of the active agent may be controlled over a long period or may be triggered by the environment or other external stimuli. In any case, the purpose behind the photopolymerization use is to control the drug delivery extent and rate to achieve more effective clinical efficacy while eliminating the potential for both under- and overdosing.

Photopolymerization has been used in synthesis and design of minimally invasive implantable drug delivery systems, by utilizing in situ photopolymerization techniques. Nivasu et al. reported on the in situ photopolymerization of polyester

polyol which were prepared with succinic acid and PEG of varying molecular weights and in vitro release of loaded sulfamethoxazole from these matrices was studied (Nivasu et al. 2004). In vitro release studies with sulfamethoxazole suggested that these in situ photo-cross-linked polymers can be used as well for controlled delivery of antibiotics over a short period of time.

Photopolymerizable drug derivatives can also be used to achieve modified release of drugs, to improve the drug's efficiency in intended therapies. Lawson et al. synthesized a photopolymerizable PEG-acrylate derivative of vancomycin, which is covalently attached to a titanium implant alloy to form a bactericidal surface that is capable of preventing the infections in the setting of orthopedic hardware (Lawson and Anseth 2007). This technique achieved significantly higher dose loading than with photopolymerizable polymer coupling approaches and holds hope for the treatment of orthopedic infections.

6 Conclusion

Photocured polymers are widely used as polymeric composites for various pharmaceutical and biomedical applications. The advantages they offer have supported their recent wide applications in numerous biomedical applications. Herein we have reported on photopolymers developments extending to drug delivery, tissue engineering, and other pharmaceutical and biomedical applications. When photopolymerization and photocured systems are applied in these biomedical fields, the most important points are the compatibility and photopolymerization efficiency of the photo-cross-linked materials. Fabrication of more compatible and more efficiently curable materials will be also important for any future application.

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Shape Memory Polymer Composites in Biomedical Field

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Abstract This chapter is anticipated to provide a brief insight into shape memory polymers (SMPs). The insight comprises of the designing aspects pertaining to SMP which include a description of mechanical properties, biocompatibility, hemocompatibility, genotoxicity, histocompatibility, biodegradability, and sterilizability. The biocompatibility comprising of cytotoxicity, mitochondrial activity, membrane damage, and cytokine production is described. The main discussion is intended toward the biomedical applications of shape memory polymer composites. In addition to that, electro-active shape memory polymer composites are mentioned along with SMPs containing fillers like Ni, electromagnetic fillers, and carbon nanotubes (CNTs). The impact on the addition of these fillers on the overall characteristics of the shape memory polymer composite is discussed. The potential of different polymer materials with their applicability in the biomedical field and their current research progress is also reviewed.

Keywords Shape memory polymers · Biocompatibility · Biodegradability · Biomedical applications

1 Introduction

The effect as a consequence of which the originality of a plastically deformed material is restored on the application of an external stimulus such as heat is termed as the shape memory effect (Khan et al. 2013). This effect incorporates the change in the crystalline phase called as thermoelastic martensitic transformation. Shape

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K. K. Sadasivuni et al. (eds.), *Polymer Nanocomposites in Biomedical Engineering*, Lecture Notes in Bioengineering,
https://doi.org/10.1007/978-3-030-04741-2_10

memory materials, especially polymers, exhibit a unique property of showing transformational responses, when subjected to heating, exposed to light, on the application of pressure, placed under electric and magnetic field, etc. (Wang et al. 2016). There exists a temperature limit for such materials known as transformation temperature, below which shape memory materials behave as hard or martensitic materials categorized by self-accommodating twins. Above this temperature, these materials get softened to restore their original shape in addition to the conversion of the material into high strength austenitic material. The reverse transformation of material from austenitic to martensitic and vice versa occurs at different temperatures. The shape transformation and restoration are endorsed by the contraction and re-expansion of aligned and oriented chains due to temperature. Shape memory materials are potentially smart materials having a wide range of applications like in textile and apparel industry, space programs, packaging, aerospace, engineering field (bionics, electronic, civil), dairy products, and biomedical field (Liu et al. 2014). In the biomedical field, the shape memory materials are used as sutures, catheters, in repairing cardiac valves for drug delivery and cardiovascular treatment, orthodontic and surgical applications (Wang et al. 2017). The shape memory materials for biomedical applications require features like biodegradability and biocompatibility to avoid any prospective harmful impacts on human body like continuous pain, improper functioning. In addition, these materials possess excellent mechanical properties, better tunability to actuation temperature, and easy synthesis procedure.

Shape memory polymers (SMPs) came into existence in 1960 while designing heat-shrinkable tubes composed of cross-linked polyethylene (PE). On the basis of their structure, the SMPs are classified as shape memory blocks, shape memory foams, shape memory films, and shape memory fibers. The main synthesis procedure regarding SMPs for biomedical applications involves naturally occurring polymers like polysaccharides, natural peptides, derivatives of natural composites present in the body (lactic acid, bile juice, glycerol, etc.), and monomers (caprolactone) (Wang et al. 2017). The SMPs for biomedical applications require actuation by direct thermal treatment around human body temperature (37 °C). This temperature acts as threshold temperature below which the material might retain its original permanent shape prior to implantation due to improper actuation. Above this temperature the shape memory effect cannot be achieved. There are reports regarding the use of developed indirect heating methods using stimuli means like light, electric field, magnetic field, microwave, and ultrasound (Pan et al. 2016). The application of indirect heating prepares the shape memory material for right time actuation by raising the temperature to the threshold value. The ability of a material to show shape memory effect mainly depends on shape fixity ratio and shape recovery ratio. The shape fixity ratio signifies the capability of the material to restore its temporary shape deformation, while the shape recovery ratio signifies the capability of the material to completely recuperate its original or permanent shape. The shape transformation on actuation of such materials also leads to the significant transformation in material properties like phase separation, material permeability, mechanical, optical and electrical properties (Focarete and Gualandi 2016). These

property transformations are accompanied by miniature changes in temperature, pH, solvent, ions, enzymes, sonic field, electrical field, light and magnetic field (Meng and Li 2013).

In SMPs, there exists an abundance of cross-linking along with higher macromolecular weight (Hearon et al. 2011). In addition to that, there exists a stable polymer network and a reverse transitional switching desired for shape memory effect. The stability in polymer network entails to the original shape determination created by the arrangement of molecules, phase crystallization, cross-linkage of chemical nature, or interpenetrating polymer network. In SMPs, lock in polymer network symbolizes reversible transition switching, accountable for fixation of temporary shape. The switching transitions could be a crystallization–melting transition, vitrification glass transition, liquid crystal anisotropic or isotropic transition, reversible molecule cross-linking transition, and supramolecular association or disassociation (Shojaei and Li 2013). Pertaining to these switching transitions, the emblematic reversible cross-linkage reactions comprise of photo-dimerization, redox reactions, Diels–Alder reaction, hydrogen bonding, metal–ligand coordination, and self-assembly (Wei et al. 2014).

Considering the shape memory alloys, the shape memory effect is achieved due to the application of stress in the desired temperature range (Duerig et al. 2013). There are certain temperature stages regarding shape memory alloys, viz. austenite start temperature (As), austenite finish temperature (Af), the martensite start temperature (Ms), and martensite finish temperature (Mf). The temperature range to achieve shape memory effect or deformation temperature on the application of stress is set between austenite finish temperature and maximum martensite temperature (Perkins 2012). Comparing the amount of energy required to produce deformations in alloys, the martensitic phase requires less energy than an austenitic phase for stress-induced deformations using conventional mechanisms. The martensitic materials can accommodate up to 10% of strain when deformed by stress induction under conventional methods exhibiting pseudo-elasticity. Since the austenitic phase of shape memory is thermodynamically stable at the deformation temperature range under no stress or no load circumstances, the alloy material shifts itself back to original shape. This condition is termed as pseudo-elasticity or transformational super-elasticity as the alloy displays astonishing elastic behavior. This condition is only experienced over a constricted temperature range as at maximum martensite temperature the martensite becomes independent of stress-induced deformations. The designing of shape memory components is related to the stress–strain curves of martensite and austenite along with the temperature difference.

The metallic alloys are used for various implants due to their biocompatibility particularly during the implantation phase (Li et al. 2011). In addition to metallic alloys, the materials like electro-active polymers and ionic polymeric metal composites are also displaying same characteristic features as that of shape memory metallic alloys in the biomedical field. These materials show the same kind of shape memory effect along with damping capacity which is defined as the energy absorbed by the material in order to convert mechanical energy to heat. The shape

memory materials are deployed for biomedical applications either inside or outside the human body including dental applications, orthopedics, clamping means, as surgical tools, during endoscopy, stents, for disks cure, as pumping actuators for hearts, and delivery of drugs. In the biomedical field, the parameters required for a shape memory material to satisfy particular application area include the impact of stress, straining, working frequency, temperature variations as well as connected exhaustion (Wu et al. 2014). Therefore, the materials before application undergo modeling procedure and proper designing for desired application-related optimization. While designing, the desired shape of the shape memory material can be triggered by application of changing external electric or magnetic field. For superelastic material, the working requirement includes definite stress and temperature range. During the operation of a shape memory material, the temperature undergoes certain changes due to external temperature or by means of electric current through the material.

The shape memory materials exhibit excellent structural features, lower manufacturing cost, easy processing, elevated elastic deformations, and lower recovery temperature (Thompson 2011). The recent trends regarding shape memory materials utilizing different actuation means have been enormously rising with the demand according to their applications. This chapter aims to provide the biomedical aspects of such materials.

2 Shape Memory Polymers

Contrary to shape memory alloys, the SMPs are adaptive soft materials exhibiting shape memory effect. The SMPs act as smart materials possessing a tendency to regain their original permanent or partially deformed shape on application of external stimuli in the form of heating, electric or magnetic field or by light stimulation (Zhang et al. 2014). The polymeric materials displaying shape memory effect are not restricted to polymers in pure form, but the polymeric blends, polymer composites, as well as polymer network-based materials, also exhibit the shape memory effect. The SMPs are soft materials having a tendency of large strain recovery along with cost affordability than the alloys. The SMPs as such are appropriate for sensors, actuators, remote controls, smart textiles, robotics, and biomedical applications. Commercially, the SMPs have been used as electric wire insulation in the form of heat-shrinkable PE tubes. The simplicity in the polymer structure, however, limits their developments as shape-changing materials and practical applicability (Zhang et al. 2015). In addition to that, the SMPs in comparison with shape memory alloys show some drawbacks like lower mechanical strength and low shape recovery stress. These limiting factors can be trounced by the proper fabrication process.

Generally, the stimulus provided to SMPs is in the form of temperature. The temperature governing the shape transitions lies in the proximity of glass or melting transition temperature range to deform the shape of the material (Gunes and Jana

2008). The recovery of permanent shape after deformation and temporary shape fixation is achieved by cooling of the material. Due to temperature-based transitions, the mechanical strength of SMPs lies in the range of 5–100 MPa while that of shape memory alloys is in the range of 700–2000 MPa (Yu et al. 2010). In addition to that, the SMPs have recovery stress in the range of few 1/tens to few tens of MPa, while in shape memory alloys, the recovery stress can attain values higher than 800 MPa. The range of mechanical strength, as well as recovery stress, can be reinforced in SMPs by incorporation of high modulus inorganic or organic fillers. Pertaining to biomedical applications, one of the important criteria to be followed regarding SMPs is the consideration of proper designing. Based on the design, the properties of the material vary to a greater extent, especially in the biomedical field. The designing requirements for SMPs provide validity of materials concerned with biomedical applications which are listed in the next section.

3 Designing Aspects of Shape Memory Polymers

The compatibility of SMPs in the biomedical application is due to the combination of their functionality and tunability properties. This combination presents the SMPs as an attractive option with consideration of designing entailing to their proper exploitation in the biomedical field. Shape memory behavior is pragmatic in several polymer systems with different morphologies and molecular structures. As per reports, the shape memory effect is not only a consequence of molecular structure, but the material morphology and the processing methods also play a vital role (Meng and Hu 2009). The shape memory behavior of polymers is explained on the basis of the cyclic tensile analysis, strain recovery examination, bending trials, and shrinkage determination tests. The shape memory behavior follows the sequential shape deformation procedure. Initially, by suitable processing, the temporary shape of the polymer is fixed followed by the recovery of permanent shape from temporary shape by means of external stimulus like heating. The polymers reported for shape memory effect include cross-linked PE, trans-polyisoprene (TPI), poly(styrene-co-butadiene), poly-norbornene, PE/nylon-6-graft copolymer, and cross-linked PE-poly(vinyl acetate) copolymer (Hu et al. 2005).

The cross-linked PE was reported to exhibit shape memory effect when provided external stimulus in the form of heat revealing large deformation recovery and as such was utilized in applications like electric wiring (Ware et al. 2010). The structure of PE consists of intertwined chains distinguished into amorphous and crystalline regions. The cross-linked structure is induced by the application of ionizing radiation and leads to the formation of a three-dimensional (3D) network in amorphous regions. On the other hand, the crystalline regions retained temporary deformed shape on cooling the material below the melting point of crystalline regions. However, heating the material above melting point eliminates the shape recovery property of the material (Hearon et al. 2013). Hence, the shape recovery in cross-linked PE owes to cross-linked structure and the entropy of elasticity. The

designing aspects of SMPs include considerations of mechanical properties, biocompatibility, biodegradability, and sterilizability which are discussed in the next section.

3.1 Mechanical Properties

The polymers with a wide range of mechanical and physical properties demonstrate better adaptability in biomedical perspective especially for requirements of human tissue. The SMPs possess physical properties identical to that of soft biological tissues, thereby enabling the growth of smart polymeric materials in biomedical applications beyond the explored features of hard biological tissues. SMPs are physically and mechanically very active polymers and represent a division of polymers with response stimulation (He et al. 2008). The matching of physical properties of SMPs and biological tissues is essential in designing the smart material prototypes intended to substitute natural tissue functionality. Generally, the biological tissues are under a variety of physiological circumstances like compressive stress condition, tension and shear stress during weight loading, heart pumping, and circulation of blood, respectively (Lu et al. 2017). As such, the SMPs implanted instead of the biological tissue must possess the capability of performing the same function as that of the tissue and deal with the forces that the tissue is subjected to under normal functioning. For instance, the smart material used for scaffolds for bone tissue implant must possess stiffness and strength in addition to functionality of the natural bone tissue. In SMPs, the shape transformation is unidirectional involving a temporary programmable shape and a final permanent shape as shown in Fig. 1. However, the activation can take place by heat, mechanical stimulation, and by the combination of both in a stepwise manner.

In the first phase as shown in Fig. 1a, the SMP is in original shape and undergoes thermal treatment and the material is heated above the activation temperature (mainly glass transition temperature or melting point temperature). After thermal treatment, the SMP gets deformed to a temporary shape followed by cooling below activation temperature and the steps followed in this phase are termed as programming. During cooling, the temporary shape of SMP is maintained. The SMP then undergoes the second phase of activation as depicted in Fig. 1b in which it is again heated in the range of activation temperature. During the second phase, the SMP returns to its original shape and this phase is termed as recovery. The thermal activation is attained by either direct heating method or indirect heating method. The former method is the main method of thermal activation without aiding from any filler (Yakacki et al. 2011), whereas the latter method uses a variety of fillers and particles accompanied by resistance- or induction-based heating or heating by lasers. Contrary to thermal activation, there are reports regarding solvent activation based on immersion of the SMP in water. The immersion of polymers in water leads to relaxation of polymer chains thereby decreasing the glass transition temperature (T_g). The interaction of polymer directly

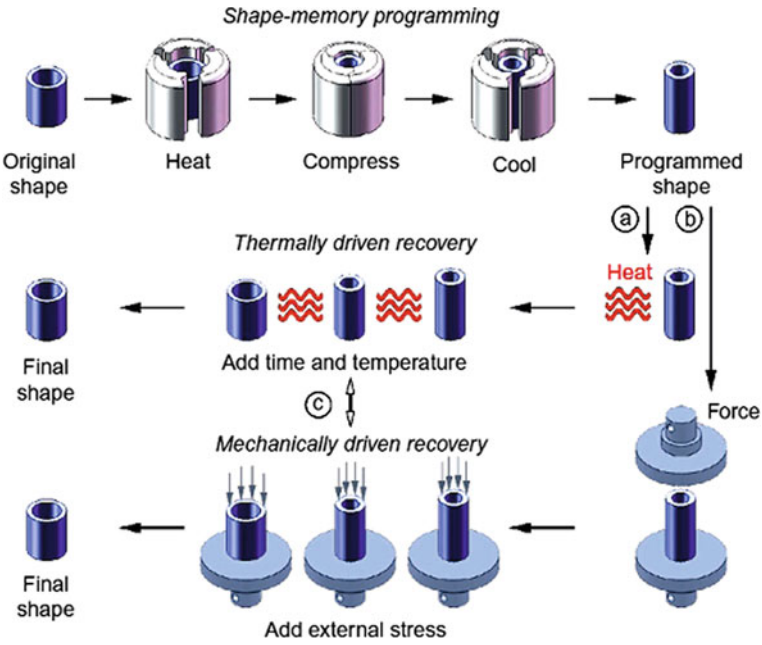

Fig. 1 **a** Schematic representation of SMP driven by thermal activation, **b** mechanical activation, and **c** a combination of mechanical force and temperature-based activation (Yakacki et al. 2011). Copyright 2011. Reproduced with permission from Elsevier

with water is known as bound-type interaction, while as the indirect interaction leading to swelling of the polymer is known as free-type interaction. In free-type interaction, the swelling of polymer leads to disruption of intermolecular bonding or mechanical softening called as plasticization (Safranski et al. 2013). The final phase transformation occurs as a consequence of mechanical force in the form of external stress stimulus as shown in Fig. 1c. After stress stimulation, the original shape of SMP is recovered.

In SMP, the change in entropic elasticity of polymer has an impact on overall shape memory effect in polymer (Yakacki et al. 2011). The programming of SMPs into a momentary shape and recovery from this momentary shape to original shape is observed at the macroscopic level. The polymer chains of SMPs in original state at the macromolecular level are at low energy state initially. The parameters like cross-linkage, chemical, and physical interactions in SMPs cause the temporary shape fixation. During programming of SMPs, the polymer chains undergo energy state transformation. The energy transformation is from low energy state to a state of higher energy accompanied by cooling below activation temperature leading to polymer fastening. Due to the instability of polymer at higher energy state, the polymer tends to come back to allow energy state in its original form. This transformation in SMPs from energy states is neither escorted by vitrification nor by crystallization (Meng and Hu 2009). The shape recovery of the polymer is however

achieved by application of thermal energy, by which the polymer chains regain their low energy state and the whole process of shape recovery is similar to that of an entropic spring. Instead of thermal energy application in shape recovery, there are reports suggesting application of mechanical force as the stimulus for polymer shape recovery entailing to energy state transformation (Yakacki et al. 2011). The activation via mechanical stimulus leading to shape transformation accompanying changes in energy states is very swift. Hence, shape recovery can be accomplished in SMP either by thermal or mechanical assistance or combination of both is also an alternative.

In addition to mechanical property consideration while designing the SMP, the other properties worthy of consideration include the polymer rigidity and flexibility. By consideration of flexibility and rigidity, the consequences on the biological tissues can be minimized (Zhang et al. 2014). The SMP in biomedical applications must inhibit optimization of characteristics for better functionality like the catheter used as a biomedical device. The catheter requires stability in the characteristic optimization as well as flexibility. Generally, there are two types of biomedical catheters, viz. soft catheter and stiff catheter. The soft catheter should be flexible for movement compatibility within the body, while the stiff catheter is designated for easy functionality outside the body. The wide range of mechanical properties along with high tunability and versatility places SMPs in prime focus as far as biomedical applications are concerned.

3.2 Biocompatibility

Biocompatibility aspect of SMP designing is the most vital aspect related to the configuration of material for biomedical applications. This property enables the ability of the polymer material to perform within a living organism by means of the suitable host response. Thus, the prime concern is the non-cytotoxicity of smart material (Sokolowski 2010). The viability of smart material is attained by means of in vitro cytotoxicity analysis thereby enabling cell feasibility and cell membrane reliability to evaluate biocompatibility. Biocompatibility tests validate the creation of non-toxic SMP systems (He et al. 2008). SMPs designed for biomedical credibility, analyzed by cell viability, undergo reduction of tetrazolium compound into an insoluble and colored formazan product. The cell viability tests include MTT and MTS types of analysis (Govindarajan and Shandas 2014). Contrary to cell viability test, cell membrane assessment is achieved by incorporation of lactate dehydrogenase (LDH) and trypan blue tests by means of well-choreographed etiquettes. The cell membrane integrity evaluation is attained via LDH examination which works on the principle of cytotoxicity of compounds and shattering of cell membranes. The trypan blue cell membrane integrity test uses blue dye to stain dead cells thereby evaluating cell viability by the application of hemocytometer (cell counting apparatus). In contrast, LDH test operates on the basis of rupturing of cell membranes while releasing LDH enzyme. The rupturing of cell membrane

leads to the pyruvate reduction to lactate and reduced nicotinamide adenine dinucleotide (NADH) oxidation to NAD + state (Chadwick et al. 2012). As a consequence of redox reaction, the presence of LDH is detected by means of a spectrophotometer. Both the tests are obliged with extra precaution requirements while choosing components during sculpturing of the SMPs.

Biocompatibility analysis involves techniques to study material stability, cytotoxicity, pyrogenicity, cellular functional response, physiological functional response, and protein adsorption. These studies help in the evaluation of SMPs by inspecting the material at the cellular and subcellular levels to avail the genetic behavior (Turan et al. 2016). By means of genetic behavior, the existence of the plasma membranes disruption or mitochondrial damage or by nucleus impairment leading to the death of cell can be evaluated. In addition to that, the response of the body to the exposure of SMP causes triggering of the inflammatory response, which leads to the same evaluations of the death of cells and damage of tissue. According to international standards, the procedures for biocompatibility investigation is in vitro thereby availing the investigation of noxiousness of SMPs by means of direct contact with the cells accompanied by extracts of SMPs on cells called as cytotoxicity or cytocompatibility. To determine the general toxicity of SMPs inside or outside the human body, no single method can cover all the required aspects, especially in vitro testing. Therefore, in vitro toxicity testing, there are various established assays by virtue of which the measurements like cytotoxicity, hemocompatibility, genotoxicity, and histocompatibility are carried out.

3.2.1 Cytotoxicity

There are numerous ways of attaining cell cytotoxicity of inspected extracts or elements. Specifically, in cytotoxicity, there are measurements related to mitochondrial activity and cell membrane integrity evaluation using LDH. In addition to that, there is an establishment of cytokine production to indicate the cellular pro-inflammatory reaction carried out with immortalized cells like V79, L929, and 3T3 (Boncler et al. 2014). The test comprises of assessment of extracts attained by submerging the CHEM sample in Dulbecco's Modified Eagle's Medium in accordance with standard practice of American Society for Testing and Materials (ASTM) F619. The solution is kept in incubation for 2–7 days followed by the addition of water and the extract to L929 cell. The overall cell culture is prolonged up to 48 h, and finally, the cell feasibility is estimated by means of MTT 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide colorimetric biochemical assay (Sigma Tox-1 kit, Saint Louis, US) measuring the living cell activity using mitochondrial activity (Tanzi et al. 2015). The results based on absorbance at 570 nm articulated as the relative ratio of the cultured control cells and cultured plastic tissue are listed in Table 1. From the table, it is clear that after 2 days, the results are showing the difference of $p > 0.05$ between the controlled and

Table 1 MTT absorbance values for L929 cells cultured in the presence of 2 and 7 days MEM extracts of untreated (control) and plasma-sterilized (PL) CHEM foams

Material		Two days	Seven days
CHEM 3520	Control	62.75 ± 3.44	86.93 ± 6.25
	PL	66.11 ± 3.39	93.52 ± 2.87
CHEM 5520	Control	55.67 ± 8.21	99.07 ± 4.80
	PL	56.77 ± 5.74	93.02 ± 6.04

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plasma-sterilized CHEM specimens displaying almost similar absorbance values at both the time points of incubation. To achieve better results in vitro cytotoxicity test, the sample testing must be carried out in plasma-sterilized samples only. The cytotoxicity includes tests like mitochondrial activity, membrane damage, and cytokines production.

Mitochondrial Activity

The mitochondrial activity can be perceived by the application of MTT and resazurin (7-hydroxy-10-oxido phenoxazin-10-ium-3-one) (Al-Nasiry et al. 2007). The MTT evaluation is the most common screening method used for measurement of cell viability. The evaluation is done on the basis of the reduction of tetrazolium salt by mitochondrial succinic dehydrogenizes in feasible cells. This reduction results in the formation of purple-colored formazan crystals. These purple crystals are insoluble in aqueous solutions specific to the cell surroundings. The evaluation begins with the insertion of the cells in suspension in a 96-well microtiter plate and development of these cells in a humidified atmosphere containing 5% CO_2 in air at the temperature of 37 °C (Kuźma et al. 2012). This is followed by exposure of cells to SMP extract pursued by cautious removal of supernatant. This is followed by the addition of MTT solution to the plate placed at 37 °C. The feasible cells cause reduction of MTT to blue-colored formazan crystals. The reduction process takes almost 2 h after which the crystals of formazan are dispersed in dimethyl sulfoxide (DMSO) or isopropanol/HCl mixer. The absorbance of the feasible cells exposed to SMP material on the multi-functional plate reader at 570 nm is measured in contrast to the unexposed feasible cells.

MTT is extensively used due to its inexpensiveness; still, it suffers from a few demerits like the criteria of solubility of formazan crystals in DMSO or HCl/isopropanol. As such, this evaluation leads to the killing of cells thereby allowing single measurements at a single point in time. The other demerit being the variability in the results caused by the alterations in metabolic cellular activity (Kavanagh et al. 2011). The alterations are as a consequence of reduction taking place in only metabolically active cells without altering the number of cells. Mitochondrial activity determination can be viable by means of Alamar Blue ® test and Presto Blue ® test.

Membrane Damage

The analysis pertaining to membrane damage is accessed using LDH test. LDH is an enzyme which is stable inside cytoplasm of all cells, and its quick release into the cell culture supernatant predicts the damage of plasma membrane of the cells (Park et al. 2016). The detection by means of LDH and method of quantification are optically chromophore-based methods. Hence, these are the broadly used quantitative tests to determine toxicity in SMPs owing to simplicity, reliability, quick, cost-effectiveness, and giving up reproducible outcomes. The membrane damage test follows a two-step procedure in which the centrifugation of supernatant occurs at 500 g for 10 min (Turan et al. 2016). In the first step, NAD^+ is reduced to NADH and H^+ followed by lactate oxidation to pyruvate accompanied by catalysis of LDH. In the second step, there is the utilization of NADH and H^+ by an enzyme called as diaphorase which catalyzes the tetrazolium salt reduction to a colored formazan salt. The LDH activity measurements are taken using a standard LDH kit like Sigma TOX7-1KT.

The procedure requires the mixing of proper fractions of supernatant with warm reagent in a 96-well plate, and the microplate spectrophotometer system is used to record absorbance (Park et al. 2016). The LDH measurements yield the quantity of LDH released during cell analysis and cell membrane damage. The amount of LDH is directly related to the production of formazan at a specific time, or the quantity of color formation during the test is directly related to the quantity of leaked and analyzed cells, while the amount of LDH for every cell has been already established.

Cytokines Production

This test in cytotoxicity involves detection of cytokines and immunologically active molecules using an enzyme-based immunosorbent tests or enzyme-linked immunosorbent assays (ELISA) (Turan et al. 2016). Since the immune cells of the immune system are peripatetic, as such the immune system suffers from communication dilemma. The immune system cells detect any inflammatory stimuli thereby presenting an antigen to lymphocytes. As a consequence of lymphocytes along with other cell effects, the antigen is cleared and repaired the damaged tissue. These lymphocytes move inside the body via circulation through tissues and organs resulting in the formation of ordered structures in the lymphoid tissues. The ordered structure formation causes a quick response to an antigenic offense in the body. In order to address the issue, the immune system requires communication networks that can act in the vicinity or at a distance, exclusively or inclusively, and momentarily or in a persistent manner. The networks allowing such response in immune system possess an amazing kind of cell membrane-bound and soluble messenger. One of such best-categorized group of networking messengers is cytokines.

ELISA is a plate-based test to identify and measure cytokines like TNF-a, interleukins (IL-6, 8, 10, etc.) in the co-culture supernatants in the cytotoxicity of SMP (Turan et al. 2016). In ELISA, one of the essential criteria is immobilization of antigen to a solid surface followed by the complexion of antigen with an antibody related to an enzyme. The measurements are attained by calculation of conjugated enzyme activity by means of incubating the substrate to yield quantified product (Shah and Maghsoudlou 2016). The main ingredient in the detection procedure is a vastly definite antigen–antibody reaction. Usually, the cultured supernatant collection is done after cytokines to be analyzed are entirely generated. The antigen and antibody measurements are done using a spectrophotometer thereby enabling the measurements regarding absorbance of the solution in ELISA reader plate. ELISA is also executed in a 96-well microtiter with disadvantages like high cost, the bulkiness of ELISA readers, the requirement of costly reagents, and longer time period for incubation.

3.3 Hemocompatibility

The hemocompatibility of SMPs intends toward the development of standards for the interaction of blood and material during surgical sutures, stents, or dentistry (Motlagh et al. 2006). Since blood can respond to shape memory materials in different ways, therefore it is essential to assess blood compatibility of shape memory materials so that the unwanted triggering by shape memory materials can be avoided. Hemocompatibility can be assessed by means of coagulation of blood, the function of platelets, hematology, and activation of complement system. In blood coagulation test, hemocompatibility of SMPs is evaluated by means of clotting factor cascade activation (Turan et al. 2016). The evaluation is attained by the use of prothrombin activation time thereby evaluating the extrinsic and regular passageway of the activated coagulation cascade. However, the evaluations of intrinsic and regular coagulation passageways are attained by measurement of partially activated thromboplastin time. The time evaluation leads to the determination of thrombin activity or fibrin polymerization. The other way for hemocompatibility evaluation is by measurement of platelet response comprising of counting the number of platelets, their structural evaluation, and analysis of components released. However, the most commonly used assay is the platelet adhesion (Motlagh et al. 2006). The degree of platelet adhesion leads to the evaluation of the material's potential to be thrombogenic. In platelet adhesion, preparation of platelet-rich plasma occurs from fresh blood samples by centrifugation (1500 rpm) for 15 min. Almost 50 µl of this freshly prepared platelet-rich plasma is allowed to interact with SMP positioned in a 24-well plate through incubation at 37 °C. After incubation, the SMP along with platelet-rich plasma is washed using NaCl aqueous solution (0.9 wt%) 2–3 times followed by fixation of the samples by means of glutaraldehyde solution (2.5 wt%) overnight at 4 °C. This is followed by second washing using NaCl aqueous solution (0.9 wt%) with synchronized immersion in

30, 50, 75, 90, 95, and 100% (v/v) ethanol/water solutions for 10 min each (Turan et al. 2016). The sample morphologies are observed after drying and gold sputtering of the samples using scanning electron microscope. The platelet count on each sample is taken by platelets calculation in six different areas.

The other way of hemocompatibility assessment is done by enumeration of cellular and plasma components of the blood known as hematology by means of hemolysis. Hemolysis refers to the election of erythrocytes containing hemoglobin which are damaged either partially or completely. It is an easy and trustworthy test regarding measurements of blood biocompatibility of materials. The normal value for hemolysis is less than 5%. For hemolysis test, a new whole blood sample of human is taken from a fit donor (Zhou et al. 2011). The blood samples are then rinsed in for 30 min at 37 °C using 1.5 ml of aqueous NaCl solution (0.9 wt%). Simultaneously, the negative and positive controls are provided by unprocessed aqueous NaCl solution (0.9 wt%) and distilled water, respectively. Approximately, 0.8 ml of blood is diluted in 1 ml of aqueous NaCl solution (0.9 wt%) and 30 ml of this diluted solution is supplemented to the samples followed by incubation for 30 min. The solution is simultaneously centrifuged at 3600 rpm for 5 min, and finally, the supernatant absorbance is calculated at 545 nm. The hemocompatibility can also be determined by complement activation in which an element of an intrinsic system consists of enzyme, plasma proteins, and receptors, which are activated for cell analysis called as complement system. After the initiation of complement activation, the ejection of peptide anaphylatoxins (C3a, C4a, and C5a) occurs resulting in binding of these humoral messengers (peptide anaphylatoxins) to suitable receptors on macrophages, mast cells, neutrophils, monocytes, and smooth muscle cells yielding cell assessment (Bamberg et al. 2010).

3.4 Genotoxicity

Genotoxicity enables the study related to the basic perception of materials consequences that may result in damage of genetic code of the host and donor organism. The resemblance in genetic compositions of living organisms provides an authoritative means to envisage the similar effects between different species (de Lima and Fraceto 2014). The genotoxicity assessment can be attained by allium cepa chromosome aberration test, comet analysis, micronucleus test, and cytogenetic analysis. In *Allium cepa* chromosome aberration test, the ratio between the number of cells displaying changes at different cyclic phases and number of cells in the division yields the measurements pertaining to a damaged portion of the cells (Gonzalo et al. 2015). The relative indices are determined in terms of mitotic index, change index, or alteration index for each treatment and negative control values. The test based on the ratio of the number of cells involved in the division to a total number of cells is termed as a mitotic index. This test is useful in monomer

evaluation of the polymer in addition to degraded products of the polymer and its composites.

On the other hand, comet assay is used in the determination of the capacity of the material causing DNA lesions. It actually gives the damage capacity of the material at a pretest stage, when no repair processes are possible. This test does not involve cell division and hence is fast, easy, and cost-effective. This test is possible in vitro as well as in vivo methods requiring two controls (positive and negative). The cells undergoing this test are crippled in agarose gel thereby exposing its genetic material after undergoing lyse process (Tice et al. 2000). The analysis of materials requires electrophoresis, and the material involved could have resemblance with the tail of a comet. The results of this test are either positive meaning small fragments of DNA are migrating faster than the larger ones or negative meaning vice versa.

The micronucleus test is an in vivo method for screening of chemicals causing chromosomal breakdown effects (Benites et al. 2006). This testing substance is generally done in small mammals, and its effects are taken from the exfoliation of bone marrows. Like comet test, micronucleus test is also fast and easy but lacks accuracy. Contrary to micronucleus test, cytogenic analyses are exposure-based analyses in which samples are exposed to a particular chemical at different concentrations for different time periods. Any toxicity present is measured in accordance with a reference mutagen leading to incline or decline in micronucleus frequencies.

3.5 Histocompatibility

It is difficult for an in vitro system to exactly replicate the biodynamics of the human body. This difficulty arises due to lack of regulatory factors like hormones, enzymes, nervous system, and immune system. In addition to that, the in vitro system lacks biotransformation and passage for excreta elimination. Hence, it becomes essential to test any material designed for biomedical applications in vivo system using animal models before testing on a human, since no animal genus presents a generic or ideal model of genetics relevant to an anatomy of human beings. Therefore, for any biochemical, physiological, anatomical, psychological, and pathological consideration, a proper animal model should be selected (Motlagh et al. 2006). The guidelines and standards for biocompatibility testing on animal are illustrated by the regulating organizations like Food and Drug Administration (FDA), US and European pharmacopeia, ASTM, the International Organization for Standardization (ISO), and National Institute of General Medical Sciences (Turan et al. 2016).

Histological evaluation of tissues reveals the groups of cells comprising of fibroblasts, macrophages, osteoclasts, besides various bioactive products like enzymes, cytokines, and growth factors in loose and well-fixed implants. In histological evaluations, the inflammatory response of SMPs after implantation in

animal models is studied (Benites et al. 2006). The interaction between SMP and the tissue in histocompatibility is investigated by means of histological and histomorphometric evaluations. The evaluation of histological studies is taken from subcutaneous implants and organs of the model animal during predetermined time periods. The retrieved organs or implants undergo fixation in periodate-lysine-paraformaldehyde solution at 4 °C for 1 and 2 days, respectively (Lendlein et al. 2010). After fixation, the investigations regarding tumor formation in the organ are carried out. The sections of paraffin (5 mm) are stained with Ki67 (dye), hematoxylin, and eosin from the subcutaneous explants. The staining acts as a marking procedure for cell proliferation. This is followed by retrieval sections of paraffin stained using hematoxylin and eosin on histological slides. The slides are examined by a pathologist measuring the lymphocytes count, macrophages, mast cells, eosinophils, and neutrophils of each sample at each time interval. The slide examination is possible by both dark and light microscopy. Whereas in histomorphometric evaluation, the specimens containing tissue covering undergo fixation in 10% formalin followed by dehydration in a graded series of ethanol and finally are implanted in paraffin. The implanted specimen is sliced in the transversal direction into 6 mm segments. These segments are again sliced at three random points normal to the long axis of tissue capsule. After second slicing, staining of sections of paraffin with hematoxylin and eosin is carried out. The stained specimens are photographed covering all sections using a Zeiss Imager Z1 jointly with the AxioCam MRc5 camera, via AxioVision 4.6.3 software (Carl Zeiss MicroImaging GmbH, Germany) (Turan et al. 2016). From the photographs, histological evaluation is attained. The images provide an insight into the impacts produced on the tissue.

3.6 Biodegradability

The biodegradability in SMPs used in biomedical applications is primarily concerned with the degradation processes by means of oxidation or hydrolytic reactions. Biodegradability is one of the important aspects regarding shape memory designing yielding durability measurements of the materials. The SMPs used in biomedical applications as permanent implants must be non-biodegradable. Their non-biodegradability property will provide resistance to any degradation by the body and will certify their extensive durability and performance (Lendlein et al. 2010). Contrary to that, the SMPs used for temporary functioning should inherit biodegradability. The biodegradability provides a brief functioning time of the material and after their functional period the SMP material is removed using the surgical procedure. The SMP undergoes biodegradation prior to its use, in order to avail rate of biodegradation measurements. The paradigm of biodegradability is mostly practicable in the field of tissue engineering, where the manageable rates of degradation during scaffold construction permit the coordination between natural tissue growth and scaffold degradation. In SMPs, by regulating the rate of

biodegradation, control over overall material is obtained especially in drug delivery systems.

The amalgamation of shape memory property and biodegradability results in the formation of multi-functional materials useful in minimally invasive surgeries. The presence of polymer permits insertion of bigger implants of compressed shapes into the human body via small cut (Turan et al. 2016). The implant after receiving stimulation inside the body changes its shape in accordance with its application. Biodegradability in SMPs can be accessed in presence of weak, hydrolyzable bonds cleaving under physiological conditions. SMPs can be classified as bulk-eroding and surface-eroding SMPs on the basis of biodegradability (Lendlein et al. 2010). The bulk-eroding SMPs display nonlinear characteristics, while surface-eroding SMPs display linear degradation. In bulk-eroding SMPs, degradation is characterized by hydrolysis of chemical bonds at the material center and the diffusion of water in the polymer material happens more rapidly than degradation resulting in nonlinearity of degradation profile. On the other hand in surface-eroding SMPs, there is a loss of material at the surfaces only due to mass relief at the material–water interface. The mass relief is larger than the diffusion of water resulting in linear and well-expected mass loss profiles. As such, the bulk-eroding materials like PLA permit the hydrolytic diffusion and permeability desired for tissue engineering applications. Contrary to that, surface erosion materials like polyanhydrides and polyorthoesters are desired for delivering constant drug release kinetics while sustaining its structural and mechanical properties amid degradation. The type of degradation can be determined on the basis of reactivity of polymer when diffused in water (Al-Nasiry et al. 2007). The degradation does not depend on water diffusion only but also depends on labile bond degradation rate, material diffusion, monomer solubility, homogeneity, processing technique, device geometry, and size. The degradation of SMPs can be adjusted by varying the chemical composition of the polymer or by blending and surface modifications.

3.7 Sterilizability

It is mandatory for all medical equipment to be sterilized prior to their use. In medical applications, the commonly used sterilizing reagents include ethylene oxide and low-temperature plasma. In case of SMPs, sterilization must be obligatory without any quality compromise. Pertaining to the shape memory effect activation, the other parameters like thermal and chemical stability cannot be neglected. The methods and guidelines for SMP sterilization are established by FDA. According to the standards, the SMPs should be exposed to ethylene oxide, irradiations, and steam (Lyu and Untereker 2009).

The sterilization methods inherit some advantages and disadvantages to their credit. The sterilization by conventional steam method uses high-temperature range and hence cannot be used for thermal SMPs. The high temperature presents a potential threat to the morphological structure of the SMP (Ulery et al. 2011). To

address this issue, cold sterilization method was developed. But the temperatures in that too were relatively higher in the range of 30–60 °C along with other issues. On the other hand, low-temperature methods of sterilization are inappropriate for biodegradable polymers due to their high deteriorating character induced by irradiation via chain scission. In addition to that, the cold sterilization technique using low plasma produces its consequences on the surface of the polymer by means of plasma etching and cytotoxic effects. The best sterilization considered is ethylene oxide sterilization. But water-activated SMPs cannot be sterilized by that method because of humidity factor.

The impact of plasma sterilization at low temperature and ethylene oxide on SMP network composed of poly (ε-caprolactone) dimethacrylate and *n*-butyl acrylate revealed noteworthy statistical variation pertaining to cell analysis especially in vitro cell screening tests (Tice et al. 2000). However, in chorioallantoic membrane tests (CAM), sterilization produced no impact on the angiogenesis (the growth of blood vessels). In CAM test (in vivo), a fertilized chicken egg is partially peeled pursued by placement of polymer on the outer skin of the egg in the shell free area, followed by incubation. The in vitro and in vivo results are calculated by the amount of ethylene oxide or silicon particles remain in the polymer material and surface modification due to low-temperature plasma sterilization. From the test, it can be established that the presence of polymer produces no effect on the neighboring tissue; however, the sterilization method has its prime significance.

4 Shape Memory Polymers in the Biomedical Field

The SMPs inherit an extraordinary ability of response to external stimuli. The stimulus–response can be in the form of heat in thermo-responsive materials, stress or pressure in mechano-responsive materials, current or voltage in electro-responsive materials, magnetic response in magneto-responsive materials, response to pH of solvent or water or moisture in chemo-responsive materials, stimulus–response in the form of light in photo-responsive materials and in the form of sound in ultrasound-responsive materials (Lendlein et al. 2001). The thermo-responsive SMPs include homopolymers and copolymers. The response to a thermal stimulus is a consequence of the intrinsic thermal transitions producing shape memory effect. The intrinsic transitions are glass transition temperature (T_g) and melting transition (T_m) (Zhang et al. 2014). The melting transition takes place over a smaller range of temperature, while glass transition takes place over a higher temperature range. The melting transitions are considered more for shape transitions involving the application of strain beyond the thermal transition. After strain introduction, cooling beneath the thermal transition takes place to secure the SMPs' deformed shape. The maintenance of temporary deformed shape is because of the development of the crystalline domains (in a T_m transition) or abrupt decent in free volume (in a T_g transition) thereby restricting motion of molecular chains. Subsequently, the temporarily deformed SMPs exposed to thermal stimulus above

transition temperature lead to an increase in mobility of polymer chain and elicit elasticity-driven shape regain process based on entropy.

The shape memory homopolymers include amorphous thermoplastic poly (para-phenylene) (PPP), thermoplastic polyurethane based on polycaprolactone and polydimethylsiloxane, thermoplastic polyurethane/poly(ethylene-alt-maleic anhydride) blends, and graphene nanoplatelet composite (Collins et al. 2016). The studies on PPP reveal the effect of temperature and time on its shape recovery characteristics. Consequently, the shape memory copolymers include polyurethane and poly (urea-urethane) copolymers, PE melt modified by ethyl acrylate/acrylic acid copolymers, poly(norbornyl-POSS) copolymers, ethylene–vinyl acetate copolymers etc., (Kausar 2016). Copolymer-based shape memory systems form an interesting class of SMPs due to their applicability in the biomedical field. These materials are versatile and have the ability to blend and counterpart the required properties of distinct parts of the molecules by copolymerization. In addition to that, the copolymer systems in linear form utilize phase segregation between hard and switching segments which provides control over the shape memory effect of the material. For instance, in polyurethane and poly (urea-urethane) copolymer system, urethane and urea functional groups possess strong intermolecular interactions and hence act as hard segment. On the other hand, polymer moieties act as switching segment.

In chemo-responsive SMPs, the shape memory effect is achieved by softening, swelling, or dissolving the polymer in desired solvents. The softening-induced shape memory effect occurs in those polymers responding to some solvents like water, *N*,*N*-dimethylformamide (DMF), toluene, methanol etc., (Kausar 2016). The shape recovery is attained by diffusion of solvent molecules into the polymer network like polyurethane. The absorbed solvent acts as a plasticizer and depresses the interaction forces among macromolecules thereby increasing the flexibility of macromolecule. This causes depression of cohesive energy and lowering of transition temperature. In swelling-induced shape memory effect, the polymers like polystyrene used for traditional packaging display shape recovery after immersion in DMF through chemical conjunct interaction. The conjunct interactions leading to swelling of the polymer network are interpreted as shape recovery. Due to the induced shape memory effect, the polymers like polyurethane block copolymer prepared from polyhedral oligomeric silsesquioxanes achieve over 70% shape recovery upon complete dilution in water.

The SMPs reported for biomedical applications include triple-shape memory polyurethane (TSMPU) consisting of poly(ε-caprolactone) (PCLU), methylene diphenyl diisocyanate (MDI), and *N*, *N*-bis-(2-hydroxyethyl) cinnamamide (BHECA). This resultant SMP was found to be biocompatible when examined by Alamar blast test on osteoblast cells (Lv et al. 2008). The schematic four step synthesis route of this biocompatible SMP is shown in Fig. 2. The first step comprises of synthesis of poly(ε-caprolactone)-diols (PCL-diols) (HO-PCL-OH) by typical ring-opening polymerization as shown in Fig. 2a (Xu and Song 2010). The precursors for the synthesis of PCL-diols (HO-PCL-OH) are ε-CL (10 g, 87.7 mmol), EG (0.155 g, 2.51 mmol), and $SnCl_2$ (0.05 g) in a 50-mL bottom flask

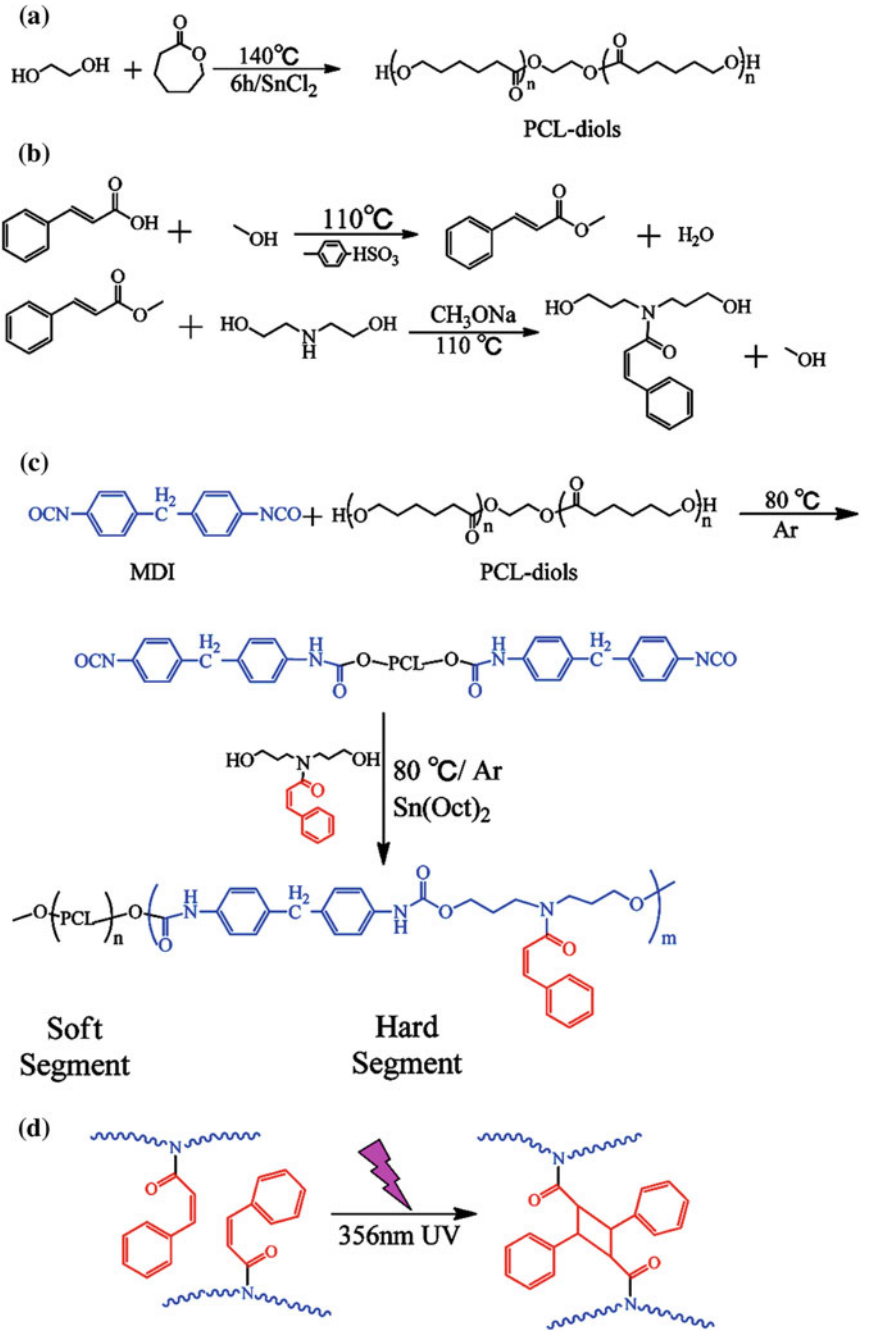

Fig. 2 Schematic representation of the synthesis route of **a** PCL-Diols, **b** BHECA, **c** photosensitive PCLU with Pendant Cinnamon Groups, and **d** TSMPU prepared by UV light cross-link with a 365-nm wavelength (Wang et al. 2013). Copyright 2013. Reproduced with permission from American Chemical Society

with a stopcock. The device in which reaction is carried out was kept under vacuum for the duration of 3 h followed by polymerization at 140 °C for 6 h. After polymerization, the polymer is purified by successively dissolving the polymer in dichloromethane followed by precipitation using ethanol and drying of final precipitate using the vacuum at room temperature.

The second step comprises of synthesizing BHECA by means of ammonolysis reaction using methyl cinnamate recrystallized in ethanol and diethanolamine (DEA) via the ammonolysis reaction as shown in Fig. 2b (Wang et al. 2013). The precursors for the synthesis of BHECA are methyl cinnamate (4.86 g, 0.03 mol), sodium methylate (0.029 g), and DEA (6.31 g, 0.06 mol). These precursors were poured into a 100-mL flask and heated to 120 °C under constant stirring and reduced pressure forming yellow-green viscous solution after 2 h. Form this viscous solution, BHECA is separated by means of precipitation with 150 mL of a liquid mixture of ice water and HCL. The yield after precipitation is a white solid which undergoes purification through column chromatography using 1:1 dichloromethane/petroleum ether. Finally, the purified white solid is obtained which is dried under vacuum for 24 h. From this dried solid, about 85.3% of BHECA is obtained (Lv et al. 2008).

The third step comprises of preparation of PCLU by means of solution copolymerization at the temperature of 85 °C in DMF (Lv et al. 2008). The photo-induced PCLU was synthesized by two ways as shown in Fig. 2c. The PCL-diols (2 g) was added to 100-mL three-necked round flak under constant magnetic stirring at 80 °C for 3 h under vacuum to avoid moisture intervention. This was followed by the addition of MDI (0.0676 g) into the same flask connected to back glow device and gas (Ar) protection device. The reaction was carried out for 2 h at 80 °C under constant stirring in Ar atmosphere. Finally, the BHECA dispersed in DMF was added in a dropwise manner to $Sn(Oct)_2$ as a catalyst. A light yellow-colored viscous liquid was acquired, which was precipitated in hexane to yield white solid. The precipitated white solid was then dried using the vacuum at room temperature for 48 h. Finally, the fourth step as shown in Fig. 2d comprises of preparing TSMPU from PCLU dissolved in 20-mL DMF irradiated at 365 nm wavelength using 100 W UV light for 10 min. The photo-cross-linked PCLU solution was dispensed in PTFE plate (2 × 2 cm) at 65 °C for 24 h followed by drying under vacuum for 48 h. Finally, 1.1 mm thick TSMPU films were obtained with TSMPU as a soft segment and diphenylmethane diisocyanate (MDI), *N*, *N*-bis (2-hydroxyethyl) cinnamamide (BHECA) as the hard segments, respectively (Lv et al. 2008).

The other SMPs used in the biomedical field include star-shaped polyurethane synthesized with multiple-arm PCL coupled with MDI and chain extended using 1, 4-butylene glycol (BDO). The six-arm PCL copolymer is additionally cross-linked by means after application of electrospinning. If the structure is fibrous instead of bulky structure, faster shape recovery response was reported (Tanzi et al. 2015). The other reported shape polymers include biodegradable shape memory copolymer composed of D, L-lactide copolymerized with trimethylene carbonate, PCL-diacrylate SMP foams coated with polydopamine (PD), polyurethane cellular

solids for less invasive surgeries, thiol-ene/acrylate systems, polylactic acid (PLA)-based shape memory materials and polyurethane-based shape memory polymers. The SMPs are mostly endorsed for less invasive surgeries, where a device is compressed to a compact shape in order to pass through a smaller incision and later the transformation of the device to its full shape inside the body.

5 Electro-active Shape Memory Polymer Composites

The SMPs which can be triggered by application of stimulus such as electricity form electro-active SMPs. The SMPs are filled with suitable fillers to achieve better triggering and shape recovery through electricity. The fillers incorporated with SMP include metallic fillers, conductive fibers, CNTs, and carbon particles (Tanzi et al. 2015). The incorporation of fillers leads to the change in the values of electrical conductivity to a greater extent. The impact of fillers over SMPs is mentioned in the next section.

5.1 Shape Memory Polymers Containing Metallic (Ni) Fillers

The incorporation of magnetic particles with polymers resulted in the formation of chains on the application of a magnetic field in the cured process. The incorporation reduces the electrical resistance to a significant extent. When Ni is added as filler to polymer network, the single chain formation is observed at the 1 volume fraction percentage of Ni. If Ni concentration is increased, multi-chains are formed with no clear recognition of Ni. After five stretching shape recovery cycles, the overall material still contains Ni chains. The presence of Ni chains in polymer matrix indicates their possibility for cyclic actuation and reduction of overall electrical resistivity (Yu et al. 2011). The resistivity reduction is accompanied by the presence of conductive chains acting as conductive channels to connect isolated aggregations of other fillers (like carbon black). The increase in electrical conductivity enhances their applicability in shape memory composites for biomedical applications.

5.2 Shape Memory Polymer Containing Electromagnetic Filler

The incorporation of surface-modified super-paramagnetic nanoparticles with SMP matrix results in the formation of composites with compound shape transitions. The transitions are achievable on the application of electromagnetic field (Tanzi et al.

2015). The thermosetting composite composed of oligo(e-caprolactone) dimethacrylate/butyl acrylate with 2–12 wt% of magnetic nanofillers acts as nanoantennas during magnetic field heating. The shape transition is attained without any temperature elevation in such materials. The electromagnetically induced shape memory effect is detected in the specimen {oligo(e-caprolactone) dimethacrylate/butyl acrylate with 2–12 wt% of magnetic nanofillers} by heating the sample at 70 °C followed by cooling. The heating causes shape deformation into a helical structure which is cooled by the formation of oligo(e-caprolactone) crystallites leading to the recovery of temporary deformed helical shape. The helical shape is retained in the absence of external forces after the programming process. The concluding shape of the SMP with magnetic nanofillers resembles a rod structure with some flexions as a result of friction.

5.3 Shape Memory Polymer Containing CNTs as Filler

The conducting SMPs containing CNTs as fillers recover their shape on the application of electrical current as per reports (Yu et al. 2011). The conducting SMP–carbon nanotube assembly is formed from chemically surface-modified multi-walled carbon nanotubes (MWCNTs). The modified MWCNTs are dissolved in a solvent containing nitric acid to improve interfacial bonding between the polymer and the filler. The increase in MWCNT composition leads to increase in electrical conductivity. The electrical conductivity of modified MWCNT is greater than that of unmodified one at same concentrations. The modification using an acid causes an increase in the defects in the lattice structure of carbon–carbon bonds created at the nanotube surface. The mechanical and electrical properties are both dependent on the surface modification of the nanotubes to yield the desired shape memory effect. In the electro-active SMPs, the shape memory effect is proportional to the concentration of fillers and also to the degree of surface modification. SMP–MWCNT composites consisting of surface-modified MWCNT display enhanced mechanical properties, energy conversion efficiency, and stress at 100% elongation based on MWCNT concentration. Besides these, the hybrid fillers like micro-carbon powder and short carbon fiber are also incorporated with SMPs to enhance their electrical conductivity.

6 Biomedical Applications of SMPs

The SMPs are used as active medical devices like the removal of blood clots by the laser-activated device, biodegradable intragastric implants for obesity problems, surveillance of shape of a human ear canal, stents for stroke prevention. (Westbrook

et al. 2011). For blood clot removal, the device is introduced into the blood vessel through minimum invasive surgery as shown in Fig. 3. The blood clot removal follows a three-step protocol. In the first step as shown in Fig. 3a, the corkscrew SMP device in its secondary straight shape is inserted at the position of the clot by means of a catheter to pierce the clot. In the second step as shown in Fig. 3b, the inserted device is heated using a diode laser converting it into its primary corkscrew shape, and in the last step as shown in Fig. 3c, the clot is captured by the device and removed from its position. The laser activation of the device leads to deformation of SMP coils into a permanent shape. The deformed shape causes the mechanical removal of the blood clot (thrombus).

On the other hand, obesity problem can be circumvented by restriction of appetite by means of biodegradable intragastric implants. The SMP prior to implant is in the form of a capsule and inflates after being implanted inside the stomach as shown in Fig. 4. The implantation takes place through an endoscopic tool having

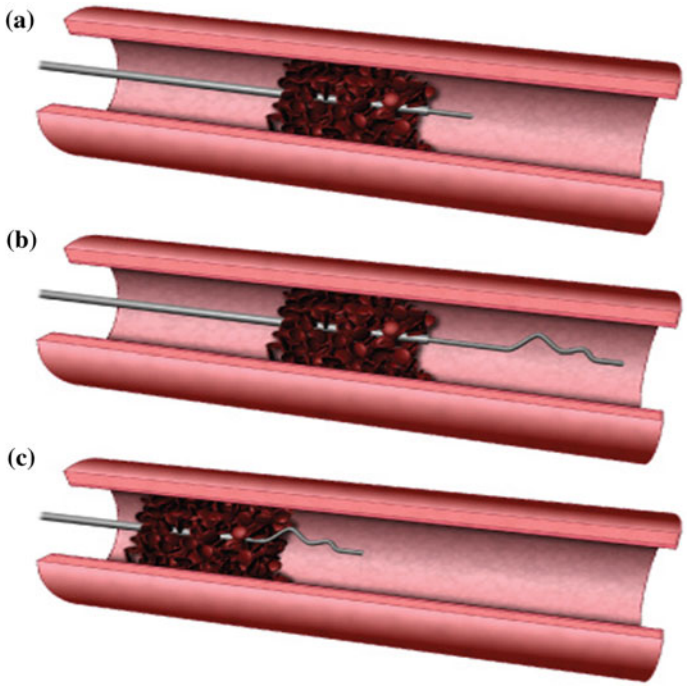

Fig. 3 Three-step protocol for blood clot removal: **a** insertion of SMP device in its secondary shape, **b** heating of the device and conversion to its primary shape, and **c** capturing and removing of the clot (https://www.flickr.com/photos/llnl/ 2845). Reprinted under creative common license

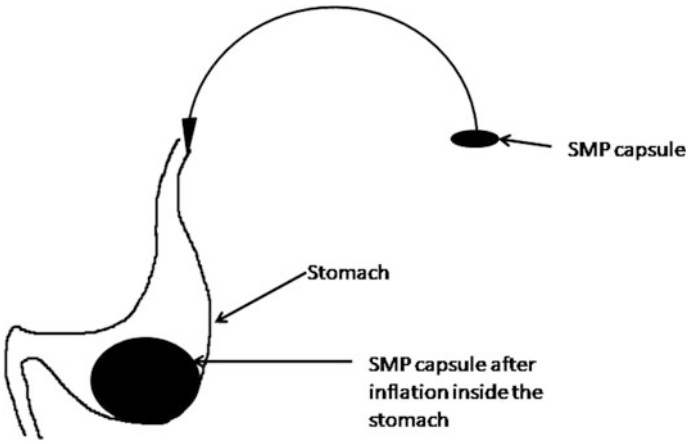

Fig. 4 Schematic sketch of SMP gastric implantation

the ability to stimulate SMP inflation and deflation. Once implanted, the person feels less hungry due to the space occupancy of the inflated SMP. The implant inflates after an estimated time duration thereby providing a feeling of satiety to the obese patients on the intake of little quantity of food. After its functioning duration, the same endoscopic tool is used to deflate SMP and is removed from the site inside the stomach.

In shape surveillance of human ear, SMP in the form of foam is used as measuring device to fit the hearing aid device properly (Westbrook et al. 2011). The foam contains commercially available polyurethane foam with a T_g switching transition and with recovery after 83% compression. Contrary to that, in the prevention of strokes composite coils consist of tantal and a polyether urethane (T_g = 33 °C). In the combination, tantal is used for diagnostic detection thereby acting as radio-opaque filler without altering any shape recovery effect of polyether urethane. The recoiling of the composite coils acts as a cushion to absorb the effects of the shock.

The SMP as ingenious dialysis needle adapter has been reported. In dialysis adapter, a compact SMP tube is inserted through the dialysis needle, which inflates thermally on contact with blood to produce an equilibrium shape that splits the cross section (Kumar et al. 2010). The SMP can sheathe through the needle during dialysis. The setup was established to trim down intimal hypertension and stenotic lesions through reduction of vascular wall stress (Safranski et al. 2013). The vascular wall stress reduction, in turn, is due to descent in flow separation and oscillations.

Magnetically triggered SMPs used in tumor therapy circumventing the use of direct heating have been reported (Zhang et al. 2014). The SMP filled with

magnetite is installed into the tumor location via minimally invasive surgery. This treatment involves heating at a localized position without causing any heat alterations to the surrounding healthy tissues. During astrocytosis (brain implantation), commercial epoxy is used as a self-deploying neuronal electrode to minimize the surrounding tissue damage. The neuronal electrode provides immediate deficiency exploration post-implantation and boosts the electrode compliance. It was observed that slow implantation rates reduce the post-implantation tissue damage.

The treatment of endovascular embolization of fusiform aneurysms and stents is another medical application of SMP. The prototype uses a combination of SMP stent and SMP foam to uphold opening of the lumen in the artery and activation of embolization of an aneurysm, respectively (Ortega et al. 2007). The stimulus used for triggering is provided in the form of photo-thermal actuation using a laser. The shape recovery is due to a photo-thermal effect, where heat production occurs due to absorption of light. The SMP used in stent utilizes glass transition-based thermoplastic shape memory polyurethane and Diaplex MM5520 doped with a platinum-based dye. The stent-based treatment involves expansion of SMP in which the equilibrium state is chosen and compact SMP is fixed on optical fiber forming light diffusion and SMP system. From the effectiveness of expansion, the credibility of SMP for the treatment can be determined.

Apart from the above-mentioned applications, the biodegradable SMPs are also interesting candidates for biomedical applications like drug delivery carrier, fasteners, self-tightening sutures, and orthodontic appliances (Wang et al. 2017). However, the biodegradable SMP requires switching temperature in close proximity to body temperature. In drug delivery, a biodegradable material consisting of citric acid-based elastomers at clinically relevant temperatures for drug-eluting devices with slow release has been reported. The SMP composed of cross-linked poly(ethylene glycol) (PEG)-PCL copolymer networks with T_m in the range of body temperature having both biocompatibility and biodegradability has been reported for drug delivery (Serrano et al. 2011). In addition to that, biodegradable PCL/Tsp POSS loaded with theophylline, shape memory nanocomposite films have also been reported. In drug delivery, an additional material is added to the SMP network to increase the drug release at the desired position. Similar sort of results follows when SMPs are used in fasteners or in sutures and dentistry. In these fields, the SMPs are used either as implants or for recovery of the functionality of a tissue or an organ. The different polymers used in biomedical applications are listed in Table 2.

There has been keen interest in the development of science and technology of polymers for biomedical usage. These polymers must adhere to the very rigid standard and must be non-toxic, non-carcinogenic, biocompatible, and in no way injurious to the biological environment.

The overall applications of SMPs in the medical field can be listed as:

Table 2 Polymers used in different biomedical applications

Polymer type	Applications
Poly(methyl methacrylate)	Bone cement, middle ear orthopedic surgery, dentures, prosthesis, and intraocular lenses
Poly(2-hydroxyethyl methacrylate)	Cartilages, burn treatments, as matrix in drug delivery system, and contact lenses
Poly(2-(dimethylamino) ethyl methacrylate)	In devices meant for drug delivery and radical scavenging agent
Poly(methyl methacrylate)-co-(methacrylic acid)	As gel for encapsulation of biological materials, tablet coatings, biofilm on medical implants
Polyester	Tissue fixation device, repair of hernia, heart patches, vascular graft prostheses, sutures
Polytetrafluoroethylene	Heart patches, vascular graft prostheses, detachment of retina
Polyurethane	Pumping artificial material for heart, prostheses of heart valve, balloon, vascular graft prostheses, blood compatibility coating
Polymethyl methacrylates	Denture material, bone prostheses, bone cement, artificial teeth, bone replacement (cranial), intraocular lenses, dialysis membrane
Polyvinyl chloride	Extracorporeal devices, hemodialysis or hemoperfusion, blood tubing, cardiac catheters, blood bag and IV infusion set, endotracheal tubes, surgical tapes, sheet, oxygenator, artificial heart, blood pump, artificial limb
Ultrahigh MW PE	Acetabulum in total hip prostheses, artificial knee prostheses
Polypropylene	Oxygenator membrane, prostheses of finger joint, absorbable sutures
Silicone rubber	Hydrocephalus shunts, catheters, membrane for oxygenator, artificial skin for burn dressing, plastic surgery implant, artificial heart, heart-assisted pump, drug release system, atrioventricular shunts, ear prostheses, facial prostheses, artificial heart valve, tendon, finger joint repair, tracheal prostheses, bladder prostheses, bladder patch, prostheses, retinal detachment, heart pacemaker leads
Polycarbonates	Membrane for oxygenator, hemodialyzer, plasmapheresis membrane

- Intracorporeal (implanted) materials
- Temporal devices
- Surgical dressing
- Sutures
- Adhesives
- Polymeric intermedullary nails
- Polymer fiber composite bone plates
- Semipermanent devices
- Tendons
- Reinforcing meshes

- Heart valves
- Joint reconstruction and bone cement
- Tubular devices
- Soft tissue replacement
- Interocular and contact lenses
- Drug delivery implants
- Complex devices
- Artificial kidney/blood dialysis
- Artificial lungs/blood oxygenator
- Artificial pancreas/insulin delivery system
- Artificial heart
- Paracorporeal or extracorporeal materials
- Catheters
- Blood bags
- Pharmaceutical containers
- Tubing
- Syringes
- Surgical instruments, etc.

In particular, to understand the applicability of SMPs in the biomedical field, the example of PE seems to be appropriate. High-density PE is used in pharmaceutical bottles, nonwoven fabrics, and caps. Low-density PE is found in flexible container applications, nonwoven disposable and laminated (or coextruded with paper) foil, and polymers for packaging. In the medical field, PE is used in the knee joint and total hip replacements (orthopaedics) as shown in Fig. 5a, b. PE is sandwiched between the femur with metallic coating and tibia for knee joint surgery. Similarly, in hip replacement, PE is made in the shape of a cap and is placed between the femoral head and acetabular shell.

7 Conclusions

The SMPs are the quite interesting class of smart materials with a bright future, especially in the biomedical field. Their biocompatibility and biodegradability add icing to the cake and can serve as the replacement of conventional SMPs. In this chapter, we have briefly summarized shape memory alloys, SMPs, the designing aspects comprising of mechanical properties, biocompatibility, and sterilizability. The SMPs designated for biomedical applications were also discussed briefly. It is clear that the demand for SMP will only rise in the coming times due to their versatility. Their applicability will increase in different aspects of biomedical engineering. There is also great scope regarding SMP engineering to suit a particular application.

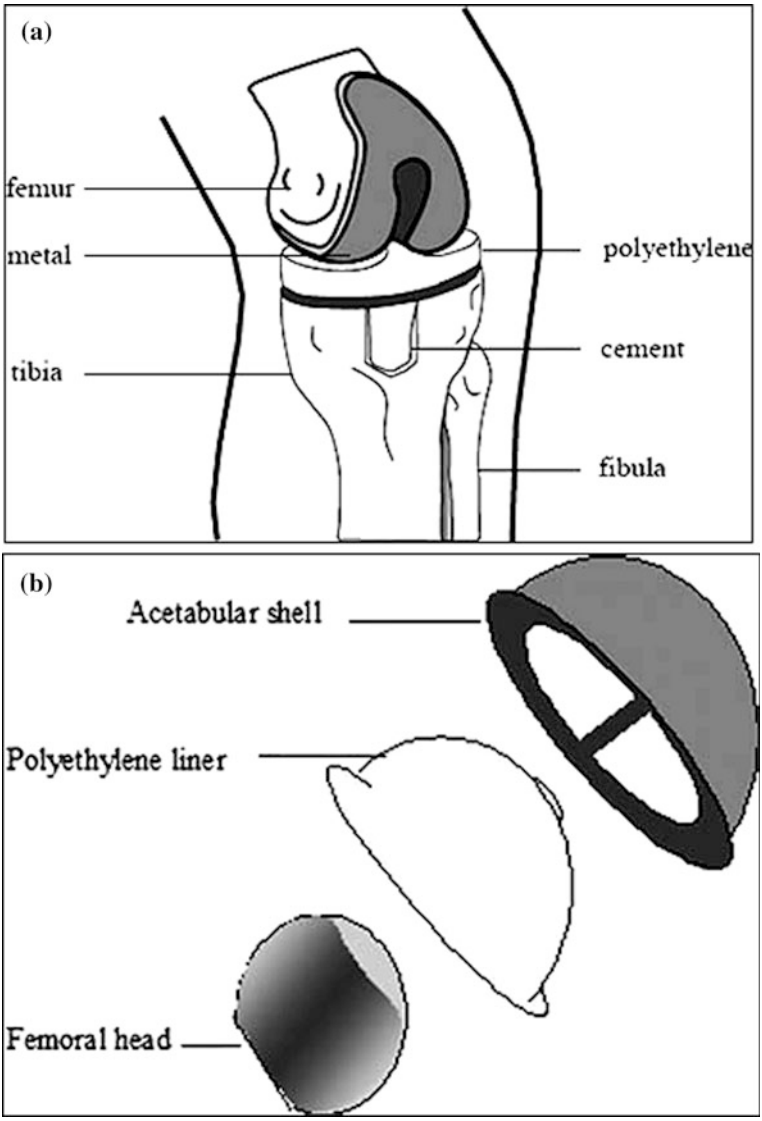

Fig. 5 Polyethylene used in **a** knee joint and **b** hip replacement

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Silver Nanoparticles and Its Polymer Nanocomposites—Synthesis, Optimization, Biomedical Usage, and Its Various Applications

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Abstract Nanomaterials have emerged as an extremely valuable asset in the world of material science. It's unique, and substantial properties lurk scientist all over the world into incorporating them in various material synthesis. Composites are yet another powerful tool for the development of specific material according to our needs. Fusion of the above-mentioned two mighty tools results in birth of a whole

The original version of this chapter was revised: Belated corrections have been incorporated. The correction to this chapter is available at https://doi.org/10.1007/978-3-030-04741-2_13

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K. K. Sadasivuni et al. (eds.), *Polymer Nanocomposites in Biomedical Engineering*, Lecture Notes in Bioengineering,
https://doi.org/10.1007/978-3-030-04741-2_11

new domain called nanocomposites. This unit provides details about different aspects of nanomaterials, composites, and their categories. This chapter talks thoroughly about the basics behind the various synthesis process involved along with optimization of various parameters related to fabrication of such nanocomposites. Among the pool of nanocomposites, silver nanoparticles and the composites based on these particles have harnessed much attention because of the striking properties of Ag nanoparticles like high electrical and thermal conductivity, chemical stability, catalytic activities, antimicrobial properties, nonlinear optical behavior, and surface-enhanced Raman scattering. Synthesis and development of AgNPs in the literature have been mentioned, and techniques have been reviewed. Detailed discussions based on each individual property have also been carried out along with exploring the applications in numerous varied fields.

Keywords Nanomaterials · Composites · Nanocomposites · Ag nanoparticles · Biomedical · Applications

1 Introduction

A "composite material" is defined as a mixture made up of materials having strikingly different physical and chemical properties on the macroscopic levels (Fadiran et al. 2018). The resultant material usually possesses properties different from those of any of their constituents. By using composites, it is possible to have properties like high strength and stiffness at high temperature, corrosion resistance, ability to withstand extreme temperature conditions, and desirable thermal expansion coefficient. Composite materials comprise of two phases: the matrix which is generally the continuous phase and the other phase(s) embedded in this matrix is known as the "reinforcement." A variety of unique combinations of these matrices (e.g., polymers, carbon, metals, and ceramics) and reinforcements (e.g., particles, fibers, and layered materials) have been employed for the synthesis of various composite and nanocomposite materials.

Quite recently, nanocomposites have garnered a lot of attention since they are nearly 1000 times tougher than their bulk counterparts. Sincere steps have been taken, and lots of work is still undertaken towards creation of controlled nanostructures using novel and innovative techniques. The field of synthesis and characterization of nanocomposites of both organic and inorganic materials is a rapidly growing area of research. The characteristic properties of nanocomposites materials synthesized depend mainly on the features of the fundamental material from where it is originating. In terms of physical properties, nanocomposites and conventional composite materials differ a lot in terms of surface area, where

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nanocomposites have strikingly high surface to volume ratio. The matrix materials are having various properties such as it binds the dispersed phase together. It protects the dispersed phase from chemical action and keeps it in proper position and orientation (Ajayan et al. 2003). It is commonly observed that with polymer nanocomposites, the properties associated with chemistry, extent of thermoset cure, mobility of polymer chains, conformation of polymer chains, extent of ordering in polymer chains can all differ from the interface between the reinforcement and the bulk of the matrix.

1.1 Types of Nanocomposites

1.1.1 Ceramic Matrix Nanocomposites

This category of composites has ceramic as the main portion of the volume. Ceramic is a chemical compound which is part of the group of oxides, nitrides, borides, etc. More often, the second component of the ceramic matrix nanocomposites consists of a metal as their second component. Theoretically, both the components, i.e., the metallic and the ceramic component, are finely dispersed in each other in order to get uniformly distributed and embedded into each other to elicit the particular nanoscopic properties. These results in the formation of nanocomposites, which shows improvement in their optical, electrical, and magnetic properties (Kruis et al. 1998), and apart from optical, thermal, conductive, electrical properties, it shows tremendous corrosion resistance and other protective properties (Popelka et al. 2018).

1.1.2 Metal Matrix Nanocomposites

Metal matrix nanocomposites are made up of reinforced metal as matrix to form composites. These kinds of composites can be divided into two categories, i.e., continuous and non-continuous reinforced materials. One of the most important categories of nanocomposites is where carbon nanotube and metal are embedded as matrix to form composites (CNT-MMC), which is new emerging trend of materials that is being worked upon taking full advantage of the characteristic features of CNTS which includes high tensile strength and electrical conductivity. CNT-MMC has properties aptly required for the development and synthesis of synthetic techniques that will lead to the production of nanocomposites which will be advanced in many aspects. Although carbon nanotubes metal matrix composites possess various optimal properties, recent research emphasizes mostly upon the synthesis techniques consisting of boron and carbon nitride reinforced metal matrix composites (Bakshi et al. 2010).

1.1.3 Polymer Nanocomposites

Polymer nanosciences are the study and application of nanoscience in field related to polymer-nanoparticle matrices. These kinds of composites are made up of a polymer/copolymer with nanoparticles/nanofillers dispersed in the polymer matrix. These reinforcements could be of a variety of shapes (like platelets, fibers, spheroids) one among which at least should have dimension in the range of 1–50 nm. These systems have strict requirements in each of its steps. The mixing/compounding should be controlled and optimized, dispersion should be stabilized, and orientation of the dispersed phase should be controlled for all MPS.

The transition of any particle from micro to nano is due to drastic changes in its physical as well as chemical structure, which further appears in the form of unique properties. The enhanced surface area-to-volume ratio, which further accelerates as the particles get smaller, leads toward the increasing dominant behavior of atoms in comparison with the surface area of particle. This greatly affects the properties of such particles when they react with other particles. Now, since nanoparticles have a higher surface area, there is more likely greater one-to-one interaction with the other kinds of particles present inside. This in turn increases the mechanical strength, thermal resistivity, and many such factors of the mixture. Addition of nanoparticulates to a polymer matrix enhances its performance by inclusion of the nanoscale filler (Evangelos 2007). These are also called nanofilled polymer composites. Uniform dispersion of the filler is essential as it substantially improves the properties of the composites. Nanoparticles like graphene, carbon nanotubes, molybdenum disulfide, and tungsten disulfide are more generally used as reinforcing agents for the fabrication of mechanically strong biodegradable polymeric nanocomposites for applications in bone tissue engineering. These nanocomposites have huge potential in terms to be used as a novel, mechanically strong, lightweight composite as substitute for bone implants. These emphasizes the relation that inclusion of mechanical reinforcement is largely dependent on the nanostructure morphology, defects, amount of dispersion of nanomaterials in the polymer matrix as well as cross-linking density of the polymer. Hence, extremely low amount of filler is needed to achieve the desired requirements. In general, these kinds of polymeric nanocomposites are opening up a whole new generation of macromolecular materials having low densities along with multifunctional properties (Paul and Robeson 2008; Fayyad et al. 2018).

1.1.4 Polymer/Silver Nanocomposites

Nanoproducts and nanoparticles produced with the help of nanotechnology depict significant physicochemical properties differing from the bulk materials (Ponnamma et al. 2018). Among them, silver nanoparticles (AgNPs or nanosilver) have strikingly huge popularity owing to their unique physical, chemical, and biological properties in comparison with gold and platinum, their counterparts (Sharma et al. 2009a, b). Silver nanoparticles are precisely interesting regarding usage in the industries concerning

polymer composites since these particles have remarkable properties like excellent electrical and thermal conductivity, surface-enhanced Raman scattering, chemical stability, catalytic activity, and nonlinear optical behavior (Krutyakov et al. 2008). Although they are frequently described as being "silver," some of them really comprise a huge amount of silver oxide. A variety of shapes are possible for such nanoparticles which can be devised based on the application required. The most commonly used shapes are spherical. Other shapes like diamond, octagonal, and thin sheets are also quite popular. The silver nanoparticles are currently under investigation for their usage in human health treatments. In laboratory, studies are being carried for assessing potential efficacy, toxicity, and costs.

Some of the other highlights of polymer/silver nanocomposites in between the wide range of available hybrid materials are their unique properties (Temgire and Joshi 2003; Zheng et al. 2001). In particular, the antimicrobial action of silver has led to its increased usage in numerous applications like incorporation in apparel, footwear, paints, wound dressings, appliances, cosmetics, and plastics (Brett 2006). It has been reported previously that the dispersed silver ions are responsible for biological actions, especially against microorganisms (Raffi et al. 2008; Choi et al. 2008). Generally, inorganic nanomaterials can be effortlessly bonded to the polymer matrix for the synthesis of a metal complex (Radheshkumar and Münstedt 2005; Espuche et al. 2005). The ability of the polymer matrix in preparation of composites is to form a metal chelate as well as its application as an ion capping agent (Khanna et al. 2005). Varied forms of magnetite and silver nanocomposites in dispersed form are used as corrosion inhibitors (El-Mahdy et al. 2013, 2014; Atta et al. 2011; Blinova et al. 2009). Polymer acts as an excellent host for embedding nanoparticles as well as terminates the growth of the particles by controlling the nucleation process, and the Ag nanoparticles enhance their overall performance (Li et al. 2012).

2 Methods of Synthesis

2.1 Synthesis of Silver Nanoparticles

Silver nanoparticles can be synthesized by physical, chemical, and biological approaches. Evaporation–condensation and laser ablation are the most important physical approaches. In evaporation–condensation method, the particles are generated using an evaporation–condensation technique (Scheibel and Porstendörfer 1983). Sample amount of bulk silver is kepton the ceramic crucibles which are further kept inside the ceramic boat to be finally kept in a tube furnace. The silver is evaporated from the center of the furnace at a very high temperature. The metal vapor formed is carried outside the furnace. The dilution is carried out using inert N_2 gas streams which makes sure that only the silver particles are present in the furnace. Due to such sudden temperature shock, the silver vapor tends to condense which leads to formation of primary nanoparticles. These particles coagulate to form agglomerates of the nanoparticles. It has been previously reported that with

such setup of particle generation formation of chain-like silver agglomerates, bonds consisting of spherical primary particles can be formed (Weber and Friedlander 1997; Ku and Maynard 2006). The evaporation/condensation technique is quite simple; however, it lacks in many aspects. This technique consumes a large amount of energy and is quite slow. Also, it requires the development of nanoparticles in large concentrations. However, in cases where long-term synthesis is required, this method is the most reliable one (Jung et al. 2006). At high concentration with high heater surface temperature, spherical NPs without agglomeration were observed.

Laser ablation synthesis in solution (LASiS) is the other commonly used methods for obtaining colloidal solution of nanoparticles in a variety of solvents (Amendola and Meneghetti 2009; Amendola et al. 2006). LASiS is the process in which laser ablation of a bulk metal plate dipped in a liquid solution is used to generate the condensation of a plasma plume formed which in turn is utilized for the synthesis of nanoparticles. Previously, LASiS has proved itself as a reliable alternative in comparison with conventionally used reduction methods including chemicals for the development of noble metal nanoparticles (NMNp). LASiS is clearly greener approach which will be harmless for the environment. Laser ablation of metallic bulk materials in solution has been used for the synthesis of silver NPs in lot of studies (Mafune et al. 2000, 2001; Kabashin and Meunier 2003; Sylvestre et al. 2004; Dolgaev et al. 2002). The efficiency of ablation as well as the characteristics of the produced nanosilver particles by laser ablation depends largely upon the type of laser used along with the surfactant requirements (Kim et al. 2005; Link et al. 2000; Tarasenko et al. 2006; Kawasaki and Nishimura 2006). One of the major advantages of using laser ablation in place of other technique is that no chemical agents are required for this process (Tsuji et al. 2002). Silver nanospheroids (20–50 nm) have been synthesized by the application of femtosecond laser pulses at 800 nm (Tsuji et al. 2003). The synthesized particles were studied and compared with those of colloidal particles prepared by nanosecond laser pulses. As a consequence, it was observed that the formation efficiency for femtosecond pulses was significantly less in comparison with that for nanosecond pulses. The particulate size of colloids matter obtained by femtosecond pulses was quite less dispersed than that of colloids prepared by nanosecond pulses. Furthermore, it was also observed that the ablation efficiency was quite less in water than that in air.

The most commonly used method for the production of silver NPs is via chemical reduction of materials. Conventionally, reducing agents like sodium citrate, ascorbate, sodium borohydride ($NaBH_4$), elemental hydrogen, polyol process, Tollens reagent, *N*,*N*-dimethylformamide (DMF), and poly(ethylene glycol)-block copolymers are used for reduction of silver ions (Ag^+) in various solutions. These agents reduce Ag^+ which lead to the formation of metallic silver (Ag^0). Afterward, these are agglomerated into oligomeric clusters. This in turns initiates the formation of metallic colloidal silver particles (Wiley et al. 2005; ChumanovEvanoff and Evanoff 2004; Merga et al. 2007). Protective agents are used which also protect the NPs from getting adsorbed, binded, or agglomerated (Oliveira et al. 2005).

There is an urgent need regarding development of high-yield, low-cost, non-toxic, and environmental-friendly procedures for synthesis of metallic

nanoparticles. Therefore, the approaches concerning biological and greenways for the synthesis of nanoparticles become important in this regard. A vast number of biological resources which are available in nature including plants and plant products, algae, fungi, yeast, bacteria, and viruses can be employed for synthesis of nanoparticles. It is noteworthy that both unicellular and multicellular organisms have been known to produce intracellular or extracellular inorganic materials. Chemically, synthesis of AgNPs requires a silver salt (usually $AgNO_3$), a reducing agent (i.e., ethylene glycol) and a stabilizer or aping agent (i.e., PVP) which will control the growth of the NPs as well as regulate them from aggregating. The living organisms are quite capable of replacing the reducing agent and the stabilizer in the biological synthesis of AgNPs. These reducing and regulating compounds can be picked from bacteria, fungi, yeasts, algae, or plants (Sintubin et al. 2012). It has been reported that the AgNPs in the particle size of 4 ± 1.5 nm was formed using the metal-reducing bacterium, *Shewanella oneidensis*, with a silver nitrate solution (Suresh 2010). This method of synthesis is based on utilizing natural bacteria. This would be economical, simple, and reproducible and would consume less energy in comparison with harmful chemical synthesis routes.

2.2 Microwave Synthesis and Related Properties of Silver Nanoparticles Synthesis

The conventional methods to synthesize AgNPs include physical, chemical, and biological methods. The typical processing methods for nanosized silver particles includes: (1) the classical Turkevich preparation of metal colloids, (2) reversed micelle process, (3) photoreduction, (4) ultrasonic radiation, and (5) ^{60}Co g-irradiation.

Through the above-mentioned processes, we can synthesize AgNPs consisting of varying shapes and sizes, but these processes are limited to Ag colloids having low concentration (in millimoles) and in presence of suitable stabilizers and surfactants, which are difficult to remove from the surface of the nanoparticles after synthesis, which further hinder the catalysis process and disrupt physical nature of the NPs. Also, the conventional methods of the preparation of AgNPs have lower yield, higher cost, and lower size control over the produced NPs. Thus, a recently developed method of NP synthesis via microwave (*MW*) heating is adopted to counter these disadvantages. The advantage of MW heating is that it provides uniform heating of the solvents and reactant mixtures, which leads to uniform nucleation and growth of the agglomerates, which in turn leads to the formation of homogenous smaller nanoparticles (Ajayan et al. 2003). MW heating is a new emerging technology for rapid synthesis of various inorganic NPs. In MW heating-assisted silver NP synthesis, we can have better control on size distribution of the synthesized NPs compared to conventional thermal convection heating having the same reactant compositions and having larger silver yield. The first and

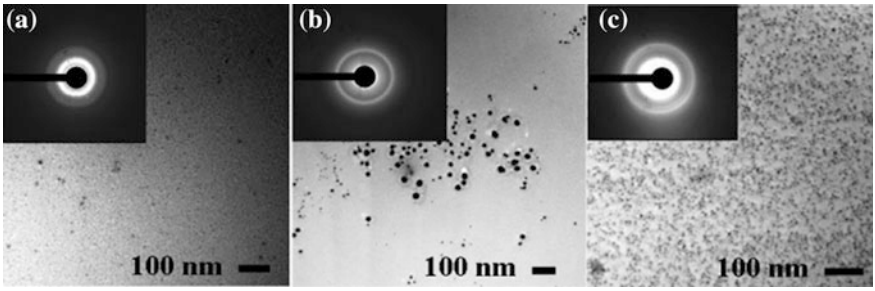

Fig. 1 TEM images of Ag and Pd nanostructures synthesized using MW irradiation in the presence of PVP as capping agent **a** Ag with **a**-D-glucose. **b** Ag with sucrose. **c** Ag with maltose (Huang and Yang 2004). Copyright 2004. Reproduced with permission from Elsevier

foremost process of large-scale AgNP synthesis by MW heating was demonstrated by Yin et al. in 2003 in which the NPs were prepared from aqueous solution of silver nitrate and trisodium citrate in the presence of formaldehyde as reducing agent (Chen et al. 2008).

The MW synthesis of AgNPs is basically a "bottom-up" process that involves capping agents such as surfactants and polymers to stop the growth of the agglomerates at nanoscale regime. These capping materials are often harmful and detrimental to the environment in view of green chemistry (Huang and Yang 2004; Mukherjee et al. 2001). Thus, a variety of methods of synthesis have come up in last few years for green synthesis of the nanoparticles using environment-friendly polysaccharides that are biodegradable and environmentally benign. Some of the methods are spontaneous reduction using MW heating-assisted methods using aqueous solution of **a**-D-glucose, sucrose, and maltose as reported by Verma et al. (Mukherjee et al. 2001), the TEM images of which AgNPs are shown in Fig. 1, synthesis of gold and silver nanoparticles using polysaccharide both as reducing and a stabilizing agent as reported by Huang and Yong (Mukherjee et al. 2001), use of fungus Verticillium to prepare silver and gold nanoparticles as reported by Mukherjee et al. (Pal et al. 2009; Sreeram et al. 2008).

With time, different variations have come up in the process of MW-assisted synthesis of AgNPs, such as MW-assisted green synthesis using organic capping agents as mentioned above, and some variations are listed in Table 1.

2.3 Synthesis of Polymer/Silver Nanocomposites

2.3.1 In Situ Polymerization

Silver nanoparticles are also synthesized using a quite simple yet effective method following in situ methodology. It is a one-step method of fabrication of nanoparticles which uses the corresponding precursors for the synthesis. The nanoparticles

Table 1 Variations of AgNP synthesis by MW irradiation

Process variation	Results obtained	References
AgNP prepared from MW irradiation from an aqueous solution of silver nitrate and trisodium citrate in the presence of formaldehyde as a reductant	Silver citrate colloids support the nucleation of AgNP by reduction with formaldehyde under MW irradiation	Chen et al. (2008)
Generation of nanospheres of Ag via MW-assisted spontaneous reduction of noble metal salts using an aqueous solution of a-D-glucose, sucrose, and maltose	Bulk and size-controlled synthesis of nanostructures of Ag having varying shapes and sizes can be generated from aqueous sugar solutions using MW irradiation	Huang and Yang (2004)
Carboxymethyl cellulose sodium (CMS) is used to work both as a reducing and a stabilizing reagent in the reaction to produce AgNP from the solution using MW heating	The AgNPs prepared by this green synthesis method are uniform and stable, which can be stored at room temperature for a period of 2 months without any significant change	Mukherjee et al. (2001)
AgNPs were prepared by MW irradiation of ($AgNO_3$) solution in ethanolic medium (which acts as reducing agent) using (PVP) as a stabilizing agent	Spherical, highly monodispersed AgNPs were synthesized under MW heating	Saifuddin et al. (2009)
Use of starch as a template and reducing agent in the controlled, directed, and MW heating-assisted synthesis of AgNPs and comparing them	Comparing altogether the MW-assisted, controlled, and directed heating methods of AgNP synthesis, MW heating was found to give better results for reduction of Ag ions to AgNPs as they had smaller particle size and particle size distribution. The pure AgNP produced by MW heating is more suitable for medical and biological applications, as non-toxic stabilizing agents were used in this work	Singh and Raykar (2008)
Novel rapid, simple, and "green" combinatorial synthesis approach for the synthesis of metallic nanostructures of noble metals such as AgNPs by using a combination of culture supernatanant of *Bacillus subtilis* and microwave (MW) heating in water in the absence of a surfactant or soft template	The kinetics of AgNP synthesis using the cell filtrates in combination with MW irradiation indicates that the rapid synthesis of nanoparticles would be suitable for developing a green nanotechnology biosynthesis process for mass-scale production	Wang et al. (2010)
MW synthesis applied to prepare stable Ag nanofluids in ethanol by reduction of $AgNO_3$ with polyvinylpyrrolidone (PVP) and used as stabilizing agent, having Ag concentrations of 1% by volume	Stable nanofluids containing AgNPs of 30 and 60 nm have been prepared by MW-assisted one-step method. MW method being fast is suitable for large-scale production of nanofluids	Li et al. (2011)

(continued)

Table 1 (continued)

Process variation	Results obtained	References
AgNPs were prepared by MW irradiation of silver nitrate solution with carboxymethyl chitosan as reducing agent and a stabilizer	The AgNPs were chemically generated in the $AgNO_3$ and CMCT alkalic aqueous solution by MW irradiation, and sizes of the NPs were varying between 2 and 20 nm range having FCC structure	Li et al. (2011)
MW-assisted synthesis of cellulose–Ag NC with AgNPs dispersed homogenously in the cellulose matrix using cellulose solution, $AgNO_3$, and ascorbic acid in N, N-dimethylacetamide (DMAc)	This MW-assisted method does not need any seed/template/surfactant and thus is a convenient and fast pathway for large-scale and low-cost production of cellulose-based NCs	Zhao et al. (2014)
A facile MW-assisted method to fabricate cellulose–Ag NC by reducing $AgNO_3$ in EG, which acts as a solvent, a reducing reagent, and a MW absorber in the system, thus canceling the requirement of additional reductant	Cellulose–Ag NCs with superior antimicrobial properties have been successfully produced through this MW-assisted method	Singh and Rawat (2016)
A simple, green, MW-assisted method of synthesizing AgNPs was developed using sodium alginate as stabilizer and reducer	Use of environment-friendly and renewable materials like sodium alginate for the synthesis of AgNPs in an aqueous medium offers a number of benefits in fields such as biomedical, textile, and pharmaceutical applications. MW irradiation accelerates the formation rate of particles	Chen et al. (2009)
AgNPs were rapidly synthesized using aqueous leaf extract of *O. majorana* and *C. sinensis* on MW irradiation	MW irradiation and its mode of heating make the synthesis of the NPs fast, uniform, and reproducible. AgNPs showed superior antibacterial activity toward *E. coli* and *B. subtilis* pathogens. It is a green process for the production of SNPs and is completely free from toxic solvents and chemicals	Melvin et al. (2014)

can be directly grown using this method. The most important advantage of this route is that it prevents particle agglomeration, maintaining a good spatial distribution in the polymer matrix at the same time whereas, the major drawback of this method is the slight probability of left unreacted educts in course of the reaction. This might be having influence on the properties of the final product.

2.3.2 Ex Situ Polymerization

The ex situ synthesis method is more suitable wherever large-scale industrial applications are required. The key challenge related to this method is preparation of

Fig. 2 Schematic illustration of silver/polypyrrole/graphene (Ag-PPy/Gr) nanocomposite synthesis (Dhibar and Das 2017). Copyright 2017. Reproduced with permission from Wiley

nanoparticles which possess higher dispersibility in the polymer and have long-term stability against aggregation. In the ex situ method, firstly the silver nanoparticles are formed and these are then dispersed into a polymer matrix. The nanoparticles that are formed possess higher dispersibility in the polymer and have long-term stability against aggregation. Dispersion of nanoparticles is generally obtained through sonication (Guo et al. 2014).

Dhibar et al. reported a simple method to synthesize silver/polypyrrole/graphene (Ag-PPy/Gr) nanocomposite as an efficient supercapacitor electrode material as shown in Fig. 2. The graphene sheets are homogeneously coated by polypyrrole polymer in presence of silver nanoparticle. The Ag-PPy/Gr nanocomposite achieved a specific capacitance of 472 F/g at a 0.5 A/g current density. The presence of both silver nanoparticles and graphene is the key factor for the enhancement of the electrochemical properties of the nanocomposite.

3 Applications of Polymer/Silver Nanocomposites

3.1 Biomedical Applications

Figure 3 illustrates the various applications of silver nanoparticles in the biomedical field including antimicrobial activity, protein detection, cancer therapy, clinical fabrics, antimicrobial catheters, and biological assays. The wide applicability of the

silver nanoparticles is due to the novel properties of the nanoparticle, which help with applications in good biocompatibility. Table 2 summarizes the biomedical applications of the silver nanoparticles.

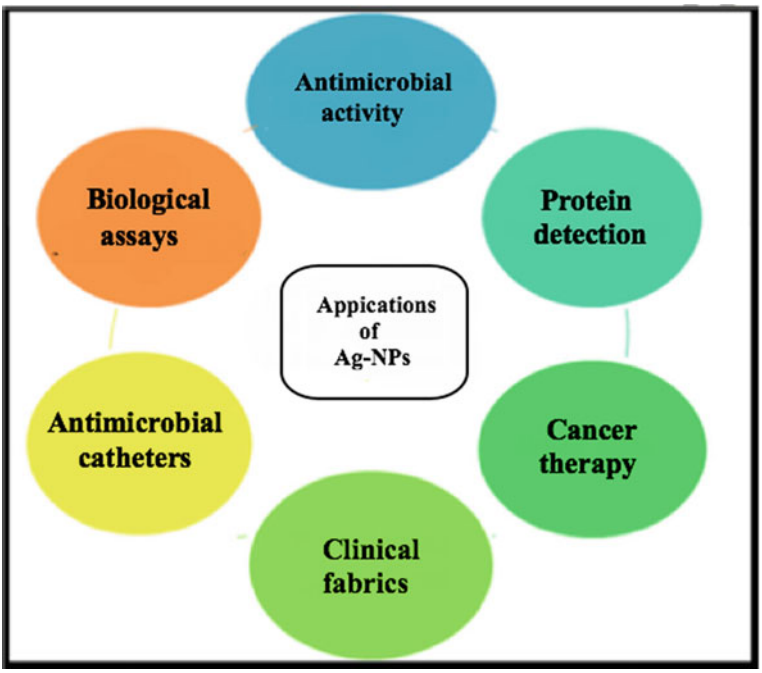

Fig. 3 Biological applications of AgNPs

Table 2 Biomedical application of AgNPs and their mode of action

Biomedical applications	Mode of action	Reference
Dressing for surgical wound	Disruption of cell membrane and electron transport	Sondi and Salopek-Sondi (2004)
Antifungal agent	Production of ROS	Mallikarjuna and Varma (2007)
Portable water filters	Release of Ag^+ ions	Pal et al. (2007a, b)
Antibacterial agent	DNA damage	Yin et al. (2004)
Coatings for medical devices	Disruption of cell membrane and electron transport	Noorbakhsh et al. (2011)
Infected wound and diabetic foot treatment	Production of ROS	Sondi and Salopek-Sondi (2004)

3.1.1 Antibacterial Agent

Silver nanoparticles (AgNPs) have now been established as an effective biocidal agent and acts on a wide range of both gram-negative and gram-positive bacteria as shown in Fig. 4a (Jones and Hoek 2010). It has also been successful in demonstrating its antibacterial property on drug-resistant bacterial strains, qualifying it to be a potential candidate for pharmaceutical use (Lara et al. 2011). Several studies have been carried out on the mode of antibacterial action of AgNPs on bacteria and summarized in Table 3.

Sondi et al. 2003 investigated the effect of AgNPs on *E. coli, Vibria cholera, P. aeruginosa,* and *Syphillis typhus* using advanced microscopic tools. AgNPs were able to restrict bacterial growth at concentrations beyond 75 μg/mL (Sondi and Salopek-Sondi 2004). The cell wall damage was inspected and has been inferred to be caused due to the high level of interaction of AgNPs with compounds containing phosphorus and sulfur. Moreover, the results suggest that an oxygen-rich environment induced the antibacterial activity of AgNPs in comparison with an anaerobic environment. These interactions can be assumed to be the reason for prevention of DNA replications, which eventually lead to bacterial death (Melaiye et al. 2005; Feng et al. 2000; Zhang et al. 2008; Nasrollahi et al. 2011).

Another study reported the antibacterial activity of AgNPs against *S. typhus, E. coli, B. subtilis,* and *Klebsiella mobilis* in where the nanoparticles had an average size of 14–40 nm (Kim et al. 2012).

Three probable antibacterial mechanisms have been proposed (Sondi and Salopek-Sondi 2004; Kim 2007; Yin et al. 2004). They can elicit an antibacterial response by hindering the production of ATP and DNA replication due to uptake of

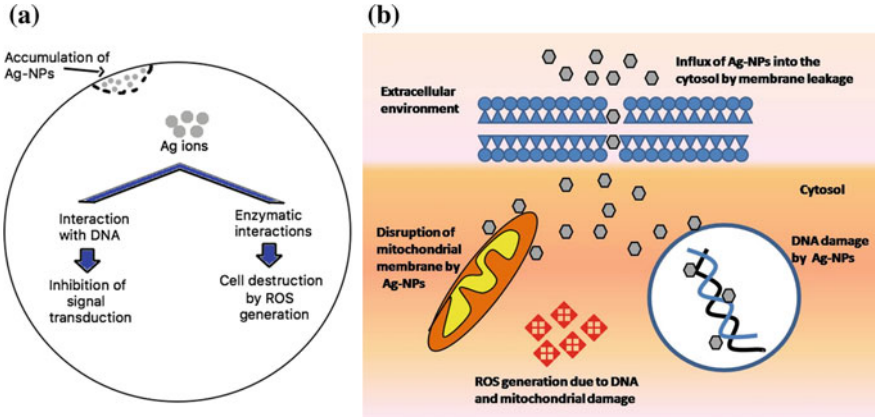

Fig. 4 **a** Modes of action of silver nanoparticles on bacteria. **b** Cellular basis of the antimicrobial activity of AgNP-coated catheters (Jones and Hoek 2010). Copyright 2010. Reproduced with permission from Springer

Table 3 Antimicrobial effects of AgNPs

Type	Microbial strain	References
AgNP powder	*E. Coli*	Sondi and Salopek-Sondi (2004)
AgNP powder	*Salmonella typhus*	Morones (2005)
AgNPs in aqueous media	*S. aureaus*	Shrivastava et al. (2007)
AgNPs in culture media	*Streptococcus* sp.,	Le (2012)
AgNPs	*V. cholerae*	Le (2012)
AgNPs	*T mentagrophyte*	Roe et al. (2008)
AgNP-coated plastic catheters	*C. albicans*	Panáček et al. (2009)
AgNPs	*Candida spp.*	Monteiro et al. (2011)
AgNPs	*T. rubrum*	Monteiro et al. (2011)
AgNPs	*Candida glabrata*	Elechiguerra et al. (2005)
AgNPs	HIV-1	Rogers et al. (2008)
AgNPs	HBV	De Gusseme et al. (2010)
AgNPs	MNV-1	Matsumura et al. (2002)
AgNPs	MPV	Sondi et al. (2003)

free silver ions or by the generating reactive oxygen species or by damaging the cell membranes (Fig. 1). However, the exact mechanism is yet to be unraveled.

Silver is known for its fantastic antimicrobial and antibacterial properties and has rapid healing properties (Imai et al. 2010; Jing et al. 2005). Every year, thousands of patients, all over the world, die succumbing to infections from the contracted post-injury of surgery. AgNPs have shown good and desirable properties in prevention of contraction of infectious bacteria such as *E. coli* (found on contaminated wounds), Enterococcus, *Staphylococcus aureus*, *Candida albicans*, Staphylococci, and *Pseudomonas aeruginosa*. Li et al. in 2011a, b measured the growth of *E. coli* (gram-negative bacteria) and *S. aureus* (gram-positive bacteria) for antibacterial activity in cellulose–silver nanocomposites. They found that for both the bacteria samples, the growth of the bacterial assay was retarded, showing the antibacterial activity of the cellulose–silver nanocomposite (Eswaraiah et al. 2011). In 2013 Zhao et al. synthesized AgNPs by green MW synthesis using sodium alginate as stabilizer and reducer to study antibacterial activity of the AgNPs on same *E. coli* and *S. aureus* bacteria. The results showed good antibacterial activity from both gram-negative *E. coli* and *S. aureus* bacteria, with higher antibacterial activity for *E. coli*. This can be attributed to the fact that gram-positive bacteria have thicker cell wall than gram-negative bacteria, thus leading to lesser penetration of AgNP and consequently lower antibacterial activity (Chen et al. 2009). They are widely used as an antibacterial silver coating for dressing the wounds.

These days owing to its antibacterial properties silver nanoparticles are extensively incorporated in apparel, footwear, paints, wound dressings, appliances, cosmetics, and plastics. Silver nanoparticles are highly stable, which supports the production of silver nanoparticle embedded in homogeneous paints. These serve as an optimal coating material. It can be used to cover various surfaces including

wood, glass, and polystyrene. Moreover, the surface coated with the nanopaints exhibits antibacterial properties (Kumar et al. 2008).

3.1.2 Antifungal Agent

Fungal infections are on the rise, and fungi are being recognized as major pathogens (Enoch et al. 2006). AgNPs have now been known to demonstrate antifungal activities. AgNPs have been reported to act against *C. albicans* by cell membrane disruption and inhibition of normal budding (Kim et al. 2009). The results of the study to investigate the antifungal activity of AgNP-coated plastic catheters affirmed the complete inhibition of *C. Albicans* (Roe et al. 2008). Minimum inhibition against *C. albicans* was revealed at 0.21 mg^{-1} using naked AgNPs. AgNPs were also effective in growth inhibition of yeasts against the tested human fibroblasts. Antifungal activities have also been reported in case of *C. glabrata* and *Trichophyton rubrum* (Noorbakhsh et al. 2011).

Nasrollahi et al. 2011 investigated the antifungal effects of AgNPs on *Candida albicans* (ATCC 5027) and *Saccharomyces cerevisiae* (ATCC 5027) and found that AgNPs has considerable antifungal activity in comparison with other antifungal drugs (Das et al. 2015). The study was carried out using the technique of minimum inhibitory concentration (MIC), and the drugs tested along with AgNPs were amphotericin B and fluconazole. They also found several changes in the membrane reactions of yeasts which was visualized using scanning electron microscopy (SEM).

Kim et al. (2012) evaluated the antifungal properties of AgNPs on various plant pathogens. AgNP sat concentrations ranging from 10 to 100 ppm along with 18 different plant fungi were used for this study. Fungal inhibition was calculated, and the results showed various levels of antifungal activities of AgNPs (Park et al. 2014). WA-CV-WB13R AgNPs were found to be potent against most fungi, and significant inhibition of fungi was observed at 100 ppm concentration of AgNPs. Therefore, AgNPs seem to possess antifungal characteristics which can aid in prevention of fungal infections.

3.1.3 Antiviral Agent

Apart from being an antibacterial and antifungal agent, AgNPs have also been recognized as antiviral agents. The first report on the antiviral study of AgNPs on HIV-1 reports that the interaction occurs through the preferential binding of AgNPs to the sulfur residues of glycoproteins on the membrane which eventually inhibits the binding of the virus to other host cells. The interaction was reported to be size-dependent in which NPs of 1–10 nm yielded attachment to the virus. The binding of AgNPs with the virus results in the prevention of CD4-dependent virion binding, fusion, and infectivity which makes AgNPs an effective virucidal agent (Lara et al. 2011). The effects of AgNPs on H1N1 influenza A virus has also been

investigated, and AgNPs were shown to induce apoptosis in MDCK cells (Xiang et al. 2011). The antiviral effects of AgNPs are based on their binding to cells that target host cells proteins.

Park et al. (2014) evaluated the efficacy of AgNPs against the inactivation of bacteriophage X174, murine norovirus (MNV), and adenovirus serotype 2 (AdV2) by using molecular methods. Ag30-MHCs were able to demonstrate the highest level of inactivation into viruses (Raimondi et al. 2005). Although the antiviral mechanism of AgNPs is yet to be elucidated, they exhibit great potential as antiviral agents (Galdiero et al. 2011).

3.1.4 Antimicrobial Catheters

Reduction in infections at hospitals was observed when AgNPs were used for coating plastic catheters (Roe et al. 2008). In vitro and in vivo determination of silver release from these devices was carried out using radioactive silver. These improved catheters demonstrated commendable in vitro antimicrobial activity and also prevented the formation of biofilms against pathogens as shown in Fig. 4b. These catheters are capable of sustained releasing silver ions at a specific target site. The released silver ions cause leakage of the cell membranes of microbial cells, thereby entering the cytosol. Once inside the cell, the Ag ions start damaging the mitochondrial membrane. This leads to the initiation of apoptosis and also the generation of reactive oxygen species (ROS). The ROS thus generated along with AgNPs cause DNA damage inside the cell. The ROS also causes the oxidation of certain proteins which eventually render them incapable to carry out their designated roles (Fig. 2). Due to the non-toxic and efficient antimicrobial action, AgNPs may be a boon in the prevention of infections arising due to long-term use of catheters.

3.1.5 Antimicrobial Therapeutic Gel

AgNPs are now being used for therapeutic purposes, especially for dealing with wounds caused from burns. A gel of antibacterial AgNPs was used, and it was found to be as effective as conventional silver compounds even at a 30 times lower concentration (Jain et al. 2009). Toxicity studies reported the mitochondrial localization of AgNPs (IC_{50} = 251 μg ml^{-1}). AgNPs resulted in apoptosis resulting in healing of wounds without leaving behind scars. The effect of AgNPs gel in Sprague-Dawley rats was studied, and the results rendered it completely safe for tropical use. Therefore, AgNP gels can be considered to be an efficient alternative to other antimicrobial agents used conventionally for tropical use.

3.2 Clinical Fabrics

Contamination of clinical clothing is common due to the highly contaminating environments prevalent in the hospitals. Pathogenic bacterial strains have the capability to survive up to 3 months on fabrics worn by patients or healthcare professionals. These strains sometimes are potent enough to survive on freshly laundered clothes as well. The transfer of these strains from nurses' uniforms, surgical wounds to patient beddings and clothing is very likely. These strains are often transferred to the visitors clothing creating a wide web of pathogenic environment. The investigation on the efficacy of AgNP-impregnated clinical scrubs was carried out, and it was found that modified scrubs had lower bacterial counts on them (Freeman et al. 2012). The results confirmed the use of AgNP-impregnated fabrics was highly effective in the reduction of bacterial contamination in hospitals.

3.3 Cancer Therapy

Compared to the conventional forms of cancer therapy, photodynamic therapy is recognized as a promising noninvasive method of treatment. It involves the targeting of a tumor followed by its destruction caused due to irradiation with UV light of specific wavelengths (Ghosh and Das 2015). When AgNP are irradiated by UV light, electron and hole pairs are created leading to the generation of oxidative radicals (Serpone et al. 2006) which eventually destroys the tumor cells. However, the focus on the aspect of toxicity needs to be evaluated largely in the future. AgNPs have also been known for its capacity in biosensing. The plasmonic properties of nanosilver make it an ideal candidate regarding this aspect. These biosensors can be used for biosensing abnormal proteins and can find their application in diagnosis of a wide array of diseases including cancer (Zhou et al. 2011).

3.4 Biological Assays

The escalating research using an OMICS approach leads to the generation of colossal amounts of data which requires high-throughput screening technologies (Klasen 2000). The array technologies are being used for such analysis, and they are also almost reaching their saturation points due to the huge number of array elements. A 3D approach, based on optical "bar coding" of polymer particles in solution can be used for reliable detection and analysis (Han et al. 2001). Single quantum dots of compound semiconductors like AgNPs were successfully used for replacing organic dyes in various biotagging applications (Parak et al. 2003).

3.5 Protein Detection

Proteins play an essential role for maintenance of human well-being. Immunohistochemistry involves the use of nanoparticles for the identification of interaction between proteins. However, this technique is not very successful in detection of simultaneous interactions. Surface-enhanced Raman scattering spectroscopy is used for the identification of single molecules that has been dyed. There can be drastic improvement in the multiplexing of protein probes by the combination of these methods in a single nanoparticle probe. Gold nanoparticles coated with solution of Ag(I) and hydroquinone have been successfully used for the detection of the substrate in question. Apart from the recognition of small molecules, proteins can also be recognized by modifying the probe to contain surface antibodies. Since now, no cross-reactivity has been reported of this method (Cao et al. 2003).

3.6 Other Miscellaneous Applications

Energy storage devices (batteries and supercapacitors) possess capacity to store electrical energy to be used at a later time. Incorporation of Ag nanoparticles into these polymers can upshot their electrochemical storage capacity. Hydrogen storage applications using silver nanoparticle increase high efficiency of fuel cells which is used in transportation, portable uses, and stationary installations. Another application related to inclusion of silver nanoparticles in polymer nanofibers is that they speed up the hydrolysis of the bulk material. Pertaining to their unique properties, such as surface area, nanoparticles have found to be highly active catalytically. Silver nanoparticles exhibit strong catalytic properties for hydrolysis and electrolysis of organic materials, particulary when they are used to manufacture and conversion into silver nanoparticle/polymer composites (Bu et al. 2013; Salehi-Khojin et al. 2013).

Thermal conductivity of polymers is a vital property when it comes to applications of polymer related materials. Traditionally, polymers themselves have intrinsic thermal conductivity of the lower order than those for metals or ceramic materials. These are good thermal insulators at room temperature. Further elevation of this thermal insulating quality can be achieved via incorporating silver nanoparticles into these polymers. Applications with requirement of high degree of thermal conductivity are generally required in a lot of fields. Hence, they become useful in electronic packaging, encapsulations, and satellite devices.

Silver nanoparticles can be combined with metal-enhanced fluorescence (MEF) and surface-enhanced Raman scattering (SERS) to effectively harvest sunlight. These may also be used as antireflection coatings, light-based sensors for cancer diagnosis (Mrlik et al. 2018). Ag nanoparticles are used effectively in density storage media to increase its capacity, nanomagnetic particles to create improved

detail and contrast in MRI images. The presence of the nanoparticles up to an optimum amount facilitates the dipole direction to align well under external electric fields, which in turn leads to increase in the polarization of the entire film. On the other hand, the nanoparticles agglomerate to enhance the charge transport, which results in increased leakage current and decreased piezoelectric properties. Ag nanoparticles may be useful in medical centers to reduce contamination in polluted derange and liquid wastes materials as well as some other devices. It can also be used to protect medical and laboratory equipment to provide protection against interfering signals, including FM, TV, emergency services, dispatch, and pagers. It can also be utilized to protect the equipment at the FM or TV broadcast facilities. Silver nanoparticle-based selective colorimetric sensor has been successfully applied for the determination of Cd(II) ions in groundwater and industrial effluent wastewater samples. This method could also be used as colorimetric assay for sensing applications of ammonia in water. The silver nanoparticles incorporated in polymer matrix give the better dielectric constant which gives better ability to store electric potential energy under the influence of alternative electric field. Silver nanoparticles are used in conductive inks, and their incorporation into such composites enhances the thermal and electrical conductivity. Ag nanoparticles embedded into polyaniline resulted in an increased electrical conductivity and improved dielectric properties by two orders of magnitude in comparison with pure polyaniline matrix and are generally used in microelectronic devices. Nanosilver can prove to be very useful and handy in the textile industry by embedding them into the fiber (spun) or embedded in filtration membranes of water purification systems.

4 Polymer-/AgNP-Based EMI Shielding

Quite recently, electronics and communication have witnessed a technology boom. This have been realized with the development of advanced products like cellular phones, high-speed communication systems, military wireless devices, advanced radars, etc. Sometimes electromagnetic waves are emitted out from the electronic circuits. These EM waves combine and create hindrance in the normal functioning of other electronic circuits. Adjacent electronic devices experience several malfunction by processing several noise signals. This interference is known as Electromagnetic Interference (EMI). It has been reported that exposure to electromagnetic waves for a substantial amount of time may poses health hazards to the human life (Kalia 2015). Therefore, a considerable amount of efforts in terms of research has been put toward development low-cost and lightweight EMI shielding materials which can minimize the impact of EMI (Chen et al. 2014; Meng et al. 2018; Azim et al. 2006). EMI shielding is the property of a material which can attenuate EM waves or a part of it either by reflection and/or by adsorption (Azim et al. 2006). Reflection occurs because of the impedance mismatch between incident wave and shielding material (Li et al. 2013). For lowering the impact of the

absorption loss, the shield should have nomadic charge carriers and/or electric or magnetic dipoles which will interact with the EM field in the radiation (Yu et al. 2012; Choi et al. 2017). EM waves attenuate due to ohmic and heat losses of material when it enters in a current induced medium. This is known as absorption loss, and to deal with this problem, such kind of materials should have high amount of conductivity as well as permeability (Lee et al. 2016). EMI shielding works upon the principle of the good electrical conductivity of materials (Kim et al. 2016). However, major disadvantages associated with them are that they suffer from poor chemical resistance, corrosion, high density, and difficulty in processing. On this backdrop, the advent of conductive polymers and polymer composites has taken place. Flexibility, processibility, corrosion resistant, light weight are some of the key attributes of conducting polymer composites which makes them an ideal alternative for metal-based EMI shielding materials. However, modification of these polymer-based composites is highly desirable since they consume a large filler loading yet lack in providing adequate conductivity to the material (Lee et al. 2016). Polyaniline and polypyrrole (PPy) are the widely used conducting polymers for EMI shielding applications providing shielding efficiency in the range of 26–30 dB. Nanocomposites with thicker film offer better shielding efficacy, where absorption remains the principle shielding mechanism. Processability of these films can be enhanced by suitably blending with synthetic resin; however, shielding efficiency gets constrained in this process (Lee et al. 2016). Fillers with higher aspect ratio (higher length and/or lower diameter) provide more paths to create contact with each other which in term helps in providing higher electrical conductivity to the system. Higher aspect ratio of the filler provides more surface area; hence, percolation threshold gets lowered and shielding efficiency gets increased. The large surface area is also beneficial as it helps in multiple reflections near the surface. EM radiation at higher frequency penetrates only near the skin of material, and it is known as the skin depth. In this perspective, metallic nanowires with superior electrical conductivity are used in polymers nanocomposites. Initially, copper nanowires were used as reinforcement. However, oxidization under atmospheric condition limits the usage of copper in the nanocomposites, and thus, silver nanowires were introduced to the system (Ahmed et al. 2015). EMI shielding materials sometimes require flexibility and transparency of film for specified applications such as transparent coatings. Silver nanowires can be incorporated on the flexible substrate to obtain flexible transparent films. Hu et al. paved synthesized silver nanowires in assistance with polyethylene oxide (PEO) on flexible substrate of polyethylene terephthalate (PET). Further, a layer of transparent poly(ethersulfone) (PES) was given to prevent the corrosion of silver nanowires, and a sandwich system with enhanced shielding efficiency was fabricated (Gashti et al. 2015). Weak adhesion forces between Ag nanowires and substrate often restrict the viability for commercialization of the product in the field of transparent conducting films. Poly(diallyldimethyl-ammonium chloride) (PDDA) has been used as a substrate to mitigate the adherence problem. Li et al. in their research prepared a sandwich material consisting poly(diallyldimethyl-ammonium chloride) (PDDA) and AgNW as bottom layer and graphene oxide (GO) and PDDA as a overcoating

layer (OCL). The top layer has been fabricated in layer-by-layer (LbL) assembly route (Kwon et al. 2001). In another approach to increase the compatibility of Ag nanowires with different resin 3-Aminopropyltriethoxysilane (APTES) silane has been used as surface modifier (Kreuer 2001). Over the years, several methods have been incorporated with an aim to provide effective shielding effectiveness along with several other auxiliary yet essential properties as stretchability, flexibility, and transmittance. The overview of the literature on Ag nanoparticle-incorporated polymer nanocomposites for EMI shielding applications has been summarized in Table 4.

Table 4 Summary of the literature on Ag nanoparticle-incorporated polymer nanocomposites for EMI shielding

Key attributes in process	Obtained results and inferred conclusions	References
In situ polymerization of pyrrole. Variable loading of AgNPs (0.5–10 wt%)	Maximum shielding effectiveness (SE) was observed in the range of −30 to −35 dB for 5 and 10% Ag-loaded films	Lee et al. (2016)
Variation in deposition sequence of. Ag NWs and MWCNTS on cellulosic papers	Ag NW as top layer hybrid papers displayed better electrical conductivity compared to the hybrid cellulose papers with MWCNT top-coating layer	Mamlouk and Scott (2012)
Ag NWs were coated on cellulose papers by dip coating method Coatings were stabilized by poly (vinylpyrrolidone) (PVP)	Light weight, flexible material for EMI shielding applications	Zhang and Chen (2011)
Microporous SBS (styrene-b-butadiene-b-styrene) polymer was prepared from sugar templates Microporous SBS were dipped in silver precursor solution Infiltrated precursors were reduced to obtain the composites	Porous structures enables higher loading of AgNPs After 300 stretching cycles EMI SE values were still around 30 dB in 8–12 GHz frequency ranges	Agel et al. (2001)
AC electrodeposition of Ag into porous aluminum oxide templates Solution processing technique AgNWs in polystyrene matrix	Higher percolation threshold was observed with Ag NWs compared to multi-wall carbon nanotubes EMI SEs with Ag NWs/PS composites were found 31.85 dB at 2.5 vol. % filler loading	Ahmed et al. (2015)
Coating on wool surface with polypyrrole (PPy) by one-step UV-induced polymerization $AgNO_3$ was used as catalyst for oxidation of pyrrole monomers	Lightweight textile-based EM shielding material for civil applications	Wang et al. (2014)

(continued)

Table 4 (continued)

Key attributes in process	Obtained results and inferred conclusions	References
Large-scale industrial reduction of AgNPs from lucose and silver nitrate at low temperature	10 wt% AgNPs in PVA matrix results in EMI SE of maximum 51 dB in the 1 GHz frequency Increasing filler loading reduces skin depth	Matsui et al. (1986)
Incorporation of Ag nanoflakes and AgNP decorated multi-wall carbon nanotube on NBR matrices Finally, bar coating on polyimide films	Reflction was dominant shielding mechanism. Maximum SE was observed 75 dB at1 GHz	Matsui et al. (1986)
Use of poly (diallyldimethyl-ammonium chloride) for enhancement of adhesion strength between Ag NWs and the substrate	Aggregation of Ag NWs gets reduced	Kwon et al. (2001)
PVDF-$BaTiO_3$-Ag composites were prepared by ultrasonic mixing, followed by solvent evaporation and finally hot pressing	EMI SE of PVDF can be enhanced with incorporation of nanolevel or micron level $BaTiO_3$ powders Small volume of Ag inclusion-enhanced SE significantly	Arranz-Andrés et al. (2013)
Enhancement of corrosion resistance of Ag NWS through poly (ethersulfones) (PESs)	EMI SE can be enhanced by increasing the thickness of Ag NWs	Gashti et al. (2015)
Use of APTES silane (aminopropyltriethoxysilane) for enhancement of compatibility of AgNPs with hydrophilic and hydrophobic resin	Loading of filler can be reduced up to 4 times by incorporating Ag NWs compared to AgNPs in epoxy resins	Kreuer (2001)

5 Polymer-/AgNP-Based Supercapacitor

There is a continuous search for new material to meet the requirements of high power density, long durability, moderate energy density, and long cycle for novel applications in energy storage.

Supercapacitors have attracted much attention due to their excellent high power density, safe operation, easy handling, and long cycle life. In order to achieve fast charging devices for the purpose of energy storage, supercapacitor devices are designed such as to traverse the gap between the batteries and capacitors. These energy storage devices are considered as the future of the next-generation electric vehicles. Supercapacitors can be used for harnessing more regenerative breaking energy and will deliver rapid acceleration due to their ability to charge and discharge quickly. Based on the variety of charge storage mechanism, supercapacitors are classified into two subclasses: (i) electrical double-layer capacitor (EDLC) where the capacitance comes from the charge separation at the electrode–electrolyte

interface and (ii) pseudo-capacitors where the pseudo-capacitance comes from the faradaic reaction occurring at the electrode–electrolyte interface (Sawangphruk et al. 2013; Lee et al. 2015; Das et al. 2017).

Nowadays, conducting polymer has attracted much attention because of its properties such as high electrical conductivity, chemical stability, and environmental firmness (Zang et al. 2008). An extensive review was reported by Snook et al. describing the background of conducting polymers as supercapacitor electrode materials (Abdelhamid et al. 2015). The cost-effective approach for fabrication of high-performance supercapacitor polymer composite materials with tunable energy and power densities is in high demand, and Table 5 summarizes the supercapacitors based on the silver/polymer composites. Thus, the synthesis of polymer/silver nanoparticle films as electrodes for supercapacitor offers the advantages of lower cost and high charge density in comparison with metal oxides. Over last few years, polymer-nanoparticle-based nanocomposites supercapacitors have gained prominence. The combination of two or more individual components enhances the electrical, mechanical, and thermal properties of the entire composite system. The combination of polymers with nanoparticle with attractive properties results in the formation of a material with unique electronic properties. The incorporation of

Table 5 Overview of supercapacitors based on various AgNP/polymer nanocomposites

Composition	Method	Capacitance result	References
Polyacrylic acid/polypyrrole/silver composite	Chemical polymerization method	Specific capacitance 226 F g^{-1}at 10 mV s^{-1} and energy density of 17.45 Wh kg^{-1} at 0.5 m A cm^{-2}	Patil et al. (2013)
AgNP film on PET substrate	Roll-to-roll process	(i) Specific capacitance of T/EDLC-(49.5 F g^{-1} at 5 mV s^{-1}) (ii) Specific capacitance of L/EDLC-(99.4 F g^{-1} at 5 mV s^{-1})	Yeo et al. (2014)
AgNP–PANI–graphene	In situ polymerization technique	The specific capacitance of 142 F/g^{-1} at applied current density of 1.5 A/g^{-1} was found for AgNP–PANI–graphene/CFP	Sawangphruk et al. (2013)
AgNP electrode on (PVA–H3PO4)	The roll-to-roll printing process	The areal capacitance of 45 mF cm^{-2} at 0.3 mA cm^{-2} was obtained for the electrode	Lee et al. (2015)
PEDOT: PSS–AgNP	Dip coating technique	The specific capacitance of about 140 F g^{-1} at 20 mVs^{-1} was obtained for PEDOT: PSS–AgNP electrode	Patil et al. (2016)
PGs–Ag (GPGs)	Compression method	The specific capacitance of 253 F/g at 1 A/g was obtained for PEDOT-coated GPGs (PGPG) electrode	Das et al. (2017)
Ag-(PPy/Gr) nanocomposite	Simple mixing	The specific capacitance of 472 F/g at a 0.5 A/g current density was obtained for Ag-PPy/Gr nanocomposite	Dhibar and Das (2017)

silver nanoparticles in polymers decreases the resistivity of the polymers with an acceptance level of specific conductance. Silver nanoparticles have unique optical, electrical, electrochemical, and catalytic properties. Thus, silver nanoparticles are employed with the selection of the organic and inorganic phases to develop specific properties in the novel materials.

So far, numerous strategies have been employed toward attainment of vividly unique and different conductive polymer nanostructures and devices based on it. Numerous methods have been employed for the synthesis of polymer silver nanoparticle nanocomposites via chemical or electrochemical treatment for various electronic applications. Afzal et al. studied the structural and electrical properties of the PANI/silver nanocomposite. Moreover, the optical and electrical transport properties of a PANI/silver nanocomposite were extensively studied by Gupta et al. (2010) PANI/silver nanocomposite as a function of silver weight percentage for vapor sensing application was studied by Choudhury (2009). The electrochemical properties of PANI/silver nanocomposite films were studied by Zhou et al. (2009). According to Patil et al. (2013), polyacrylic acid/polypyrrole/silver shows supercapacitive behavior of the electrodes by using cyclic voltammetry and charge–discharge test (Patil et al. 2013). For PPY/PAA/Ag composite electrodes, maximum specific capacitance 226 F g^{-1} at 10 mV s^{-1} and energy density of 17.45 Wh kg^{-1} at 0.5 mA cm^{-2} was reported.

Recently, there is an increasing interest in the development of flexible/bendable and lightweight supercapacitor for energy storage. Yeo et al. 2014 focus on the fabrication of flexible supercapacitors by printed silver nanoparticle films on polyethylene terephthalate substrate. The thermal and laser annealing treatment was employed to increase the conductivity of silver nanoparticle films effectively. The silver nanoparticles are linked together to form a continuous and bulk metal through melting and solidification steps. In comparison with the conventional thermal processed supercapacitor, superior electrical and thermal properties were obtained for laser-processed supercapacitors. The supercapacitors were fabricated by roll-to-roll process for developing wearable electronics. The thermally processed/electric double-layer capacitor (T/EDLC) shows 49.5 F g^{-1} specific capacitance at 5 mV s^{-1} as compared to laser-processed/electric double-layer capacitor (L/EDLC, 99.4 F g^{-1} at 5 mV s^{-1}). Two times higher overall improvement was reported for laser-processed/electric double-layer capacitor.

Sawangphruk et al. (2013) synthesized nanocomposite of silver nanoparticle–polyaniline–graphene (AgNP–PANI–graphene) by an in situ polymerization technique as shown in Fig. 5. Silver nanoparticles and graphene were obtained by their respective precursor, i.e., silver nitrate and graphene oxide. These materials act as co-oxidizing agents which enables the conversion of aniline monomers to PANI in the AgNP–PANI–graphene nanocomposite system. With increasing interest in the field of flexible supercapacitors, AgNP–PANI–graphene composites were dispersed in acetone and then coated on flexible carbon fiber paper (CFP) by simple spray-coating technique.

The electrochemical kinetic properties of the prepared electrodes were examined using cyclic voltammetry and galvanostatic charge–discharge methods. The specific

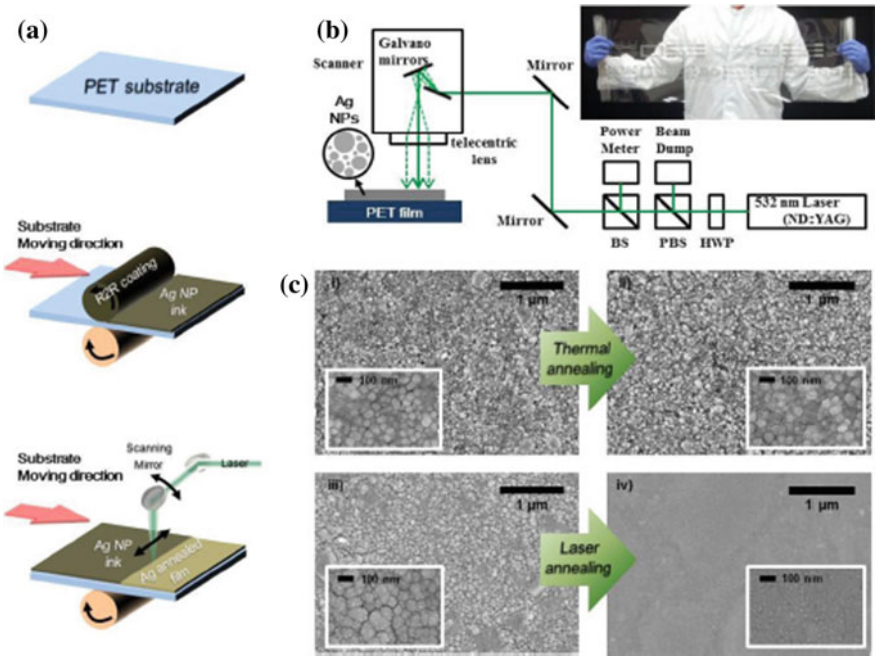

Fig. 5 Illustration of **a** Ag nanoparticle ink is deposited on the PET film. **b** Schematic diagram of optical experimental setup. **c** SEM image of fabricated AgNP films (Sawangphruk et al. 2013). Copyright 2013. Reproduced with permission from Royal Society of Chemistry

capacitance of 142 F/g^{-1} at an applied current density of 1.5 A/g^{-1} was found for AgNP–PANI–graphene/CFP. After the charge–discharge test, the AgNP–PANI–graphene/CFP electrode shows capacity retention of up to 3000 cycles with 97.5% of the original specific capacitance.

Among recent reports, Lee et al. (2015) fabricate solid supercapacitor with flexible silver nanoparticle current collector by a roll-to-roll printing process. The laser annealed silver nanoparticle electrode depicts excellent electrical conductivity. The as-prepared flexible electrodes with silver nanoparticle current collector along with active materials were sandwiched with a polymer medium layer (polyvinyl alcohol–phosphoric acid) as shown in Fig. 6. Both the electrolyte and separator are assembled together to form flexible supercapacitors that can be easily bent up to 135 °C. These kind of fabricated flexible electrodes were studied for electrochemical properties using cyclic voltammetry and charge–discharge test. The electrode retains its properties and performance even under physical disturbance such as bending. The areal capacitance of 45 mF cm^{-2} at 0.3 mA cm^{-2} was obtained, which was then marginally declined to 32 mF cm^{-2} at 3 mA cm^{-2}. In order to evaluate the cyclic stability of the supercapacitor based on laser annealing, the assembling supercapacitor was inspected with the help of galvanostatic charge–discharge measurement at 5 mA cm^2 for 1200 cycles under varied kinds of bending

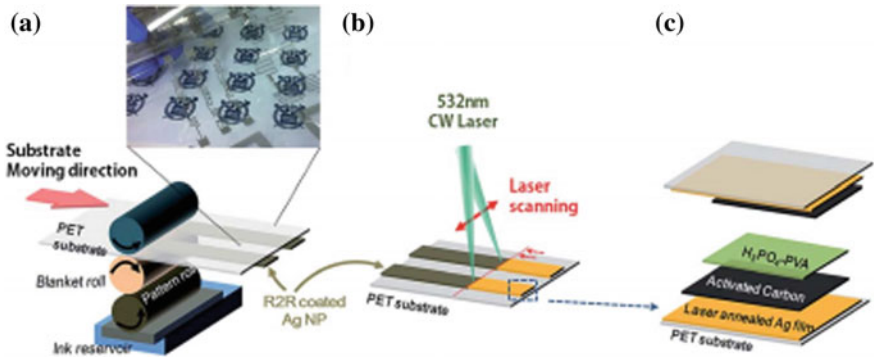

Fig. 6 Schematic depicting the fabrication of flexible Ag electrodes through **a** R2R gravure offset printing followed by **b** focused laser sintering. **c** Fabrication of an all-solid-state supercapacitor using Ag electrodes as current collectors (Lee et al. 2015). Copyright 2015. Reproduced with permission from Royal Society of Chemistry

conditions. The flexible supercapacitors exhibited electrochemical function of over 1200 operating cycles even under intense stressful bending conditions.

Recently, Patil et al. (2016) reported the synthesis of poly(3,4-ethylenedioxythiophene): poly(styrene sulfonate) (PEDOT: PSS)-silver nanoparticles (AgNP) electrode by a very simple yet cost-effective dip coating technique mainly used for supercapacitor application. Cyclic voltammetry was employed to study the supercapacitor behavior of the electrodes by three electrode systems with 0.1 M H_2SO_4 electrolyte. 140 F g^{-1} at 20 mV s^{-1} specific capacitance was obtained for PEDOT: PSS–AgNP electrode.

Very recently in 2017, Patil et al. (2016) reported PEDOT-coated GPGs composite for supercapacitor application which retains their specific capacitance even after the application of large compression. They also possess the ability to recover elastically even from a hundred compression–expansion cycles. Initially, the macroporous cross-linked polymer (PG) was impregnated with polyphenols derived from organic green tea. As the PG is insulating in nature, the conductivity was introduced by the deposition of gold on its surface. The gold was deposited by using two-step methods; firstly, the silver nanoparticles are formed using in situ reduction on the PG walls using polyphenols. Afterward, the gold films are deposited on these same walls. The gold coated PGs (GPGs) were then deposited on the surface of poly(3,4-ethylenedioxythiophene) as a pseudocapacitive material. The PEDOT-coated GPGs (PGPG) was then evaluated for electrochemical studies. The specific capacitance of 253 F/g at 1 A/g was found for PEDOT-coated GPGs (PGPG). Upon compressing the device to 25% of its original size, the capacitance was found to be 243 F/g. Thus, the large compression does not affect the performance of the device. Moreover, the macroporous nature of these PGPG makes it an ideal choice to fulfill the PGPG pores using gel electrolyte.

6 Polymer-/AgNP-Based Fuel Cells

Fuel cells are one of the promising means for generating power in the twenty-first century. Compared to the coal combustion engine, the fuel cell is highly efficient and eco-friendly. Recently, the polymer electrolyte membrane fuel cells encountered several drawbacks such as high fuel crossover and cost-effectiveness. This has diverted the focus of the researchers on making PEMs with low fuel crossover, high proton conductivity, durability, thermal stability, maximum power density, high proton conductivity, and low cost (Wang et al. 2013; Tedsree et al. 2011; Trogadas et al. 2011). This material has very promising applications in view and with regard of the progress in catalytic systems, electronic and photovoltaic devices, fuel cells, sensors, biomaterials, among various others. Recently, hybrid organic–inorganic composite membranes have arisen as an effective alternative approach toward application in the field of a fuel cell. This review mainly focuses on the study of polymer nanocomposites toward fuel cell application. In order to establish and maintain the basic standards of environment and clean energy technologies, they should be powered with fuels acquired from renewable and nonpolluting source with cost-effectiveness. Till now, many efforts are made by various researchers for the development of these technologies (Tang et al. 2011; Nguyen et al. 2012).

Currently, the available commercial fuel cells face the huge challenge of high manufacturing cost, mainly because platinum (Pt) is used as a catalyst to accelerate the reactions. Platinum is the major cost contributor in the fabrication of fuel cell which results in a high price of fuel cell stacks. In order to overcome these challenges, other catalysts need to be explored. Out of various metal complexes, silver (Ag) and nickel (Ni) are the cheaper catalysts used in alkaline media. The silver nanoparticles (AgNPs) exhibit significant physicochemical properties due to its high surface area and reactivity. Precisely, the low cost of silver nanoparticles replaces other noble metals such as (Au, Ru, Pt, and Pd) to become the best catalyst in fuel cells. The fuel cell application involves certain components like polymer in the proton exchange membrane, binder for the electrodes, and matrix for bipolar plates (Ostapova and Al'tshuler 2012). The electrodes typically comprise of nanoparticles as catalyst particles and polymers as a binder. The nanoparticles deposited with polymeric binder are designed to deliver improved performance over the conventional electrodes. The incorporation of nanoparticle in the proton exchange membrane enhances the proton conductivity and also improves the mechanical properties. The polymer serves as high surface and provides protection against the fouling of the metal surface, a scaffold for high dispersion and anchoring of the metal particle. Several kind of polymers are being used in fuel cell applications, such as a hyperbranched polymer with a hydroxyl group at the periphery, cross-linked sulfonated poly(ether ketone), sulfonated polybenzimidazole copolymer, phosphoric acid doped polybenzimidazole, sulfonated polyarylenethioethersulfone, and sulfonated polybenzimidazole. The availability of the finely dispersed particles in the polymer ensures high surface area and possible

enhancement of the unique characteristics of the composites. However, the one of the most important contributory factors adding toward the membrane decaying which in turn eventually limits the lifetime of polymer electrolyte fuel cells (PEFCs) and its degradation is this only (Chang et al. 2013; Park et al. 2014; Seo et al. 2015). The degradation in the PEFC is a multi-step mechanism. This review talks in detail about the technologies involved with Ag nanoparticle-based polymer nanocomposites fuel cell interests (Şimşek et al. 2016).

Over the last few years, several excellent comprehensive reviews have been published in the study of polymer silver nanocomposites for fuel cell application. Jiang et al. produced an extremely active electrocatalyst for oxygen reduction reactions (ORRs) in an alkaline media via coating carbon-based silver nanoparticles along with Pd (Pd@Ag/C) using a galvanic displacement method (Stoševski et al. 2016). Both the Pd and Ag coated catalyst were fabricated by employing galvanic displacement process along with the usage of carbon-supported silver nanoparticles as substrate. The ORR current degradation rate for the Pd@Ag/C was about 154 A cm^{-2} h^{-1}. The incorporation of Pd@Ag/C targeting the ethanol oxidation was found to be inactive making it a promising non-Pt catalyst for ORRs in alkaline media for the direct alcohol fuel cells (Stoševski et al. 2016; Jiang et al. 2010).

So far, the production of hydrogen from formic acid restricts at room temperature by the sufficiently active and/or selective solid catalysts. According to Tedsree et al., the Ag nanoparticle coated with a thin layer of Pd atoms can significantly enhance the production of H_2 from formic acid at ambient temperature (Mi et al. 2007). They have reported a new class of catalyst (Ag–Pd core–shell) with interfaces and can be tailored for structural and electronic effects. This catalyst affectedly promotes the production of hydrogen from the decomposition of formic acid, which favors the processing and separation at room temperature. The production of catalyst offers a number of exciting possibilities for the development and exploitation of small portable PEM fuel cell devices (Mi et al. 2007; Tedsree et al. 2011).

Trogadas et al. have focused on the efficiency of freestanding silica-supported metal (Pt, Pd, Ag, and Au) nanoparticles for (PEM) degradation in an actual working fuel cell (Frackowiak et al. 2006). The fuel cell performance and the macroscopic rate of PEM degradation were examined, depending upon the effect of incorporating the metal nanoparticles into Nafion. The composite membranes were prepared by unsupported and silica-supported Au, Ag, Pt, and Pd nanoparticles. Compared to the Nafion membrane (control), the addition of these freestanding nanoparticles lowers the fluoride emission rate (FER) by 35, 60, 80, and 90%, respectively. These results emphasize toward the fact that the incorporation of certain selected metal nanoparticles having radical scavenging abilities proves to be a promising approach toward mitigation of PEM degradation in a full-fledged operating fuel cell as shown in Fig. 7 (Frackowiak et al. 2006).

Tang et al. studied the synthesis of flexible and unique network structure of polyaniline (PANi) and polypyrrole (PPy) supported by Pt and Ag catalysts having membranes in the form of eggshells (Stankovich et al. 2006). The uniform dispersion of Pt and Ag nanomaterials along with the polymers resulted in the

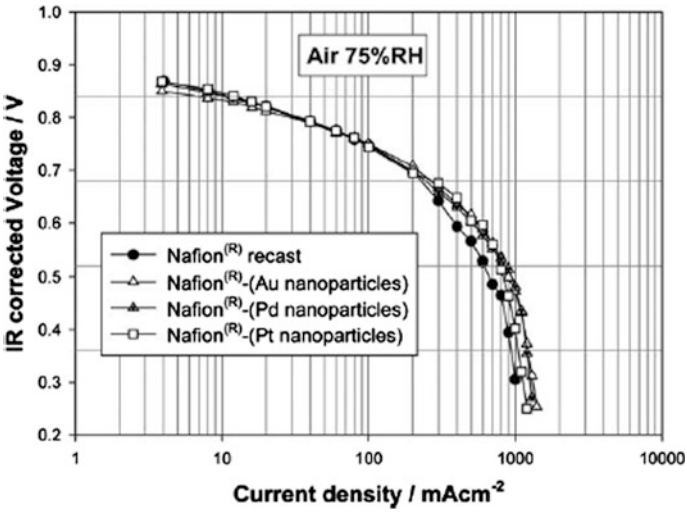

Fig. 7 Image depicting the performance of Nafion and composite Nafion (metal nanoparticles) membrane-based MEAs at 80 °C and 75% RH using air as oxidant and hydrogen as fuel (Frackowiak et al. 2006). Copyright 2011. Reproduced with permission from Elsevier

formation of catalysts depicting much higher electrocatalytic activities than those of bare Pt and Ag electrodes. The role of the conducting polymer network supports highlighted in this study could be of great importance and can eventually be applied for the designing and development of numerous efficient and effective MOR catalysts; also, these PANi and PPy supported Pt and Ag catalysts. The above-mentioned desirable properties allow these materials to be successfully used in high-temperature PEMFCs and other fields (Stankovich et al. 2006; Tang et al. 2011).

Nguyen et al. successfully synthesized Pt nanoparticles by modified polyol and using silver nitrate as an effective structure-modifying agent (Hirata et al. 2004). The as-prepared nanoparticles could be further used as an efficient catalyst for polymer electrolyte membrane fuel cells (PEMFCs) and direct methanol fuel cells (DMFCs) since they exhibited the complexity in terms of surface structure and morphology (Hirata et al. 2004; Nguyen et al. 2012).

In early publications, Ostapova et al. provide a study on the cross-linking of polymers based on macrocyclic polyphenols (Peng et al. 2008). In particular, the metacyclophaneoctols can serve as a matrix of proton-conducting membranes and electrode materials for generating chemical current sources. The metacyclophaneoctols were produced from coking coal, the main source of raw materials for the production. Furthermore, the conductometric and potentiometric studies were performed for the properties of polymetacyclophaneoctols and metal/polymer nanocomposites. According to the study, the H^+ form of polysulfonatotetraphenylmetacyclophaneoctol with 0.2 S/cm electrical conduction corresponds to the best performance characteristics for proton exchange membranes of hydrogen fuel cells.

Moreover, the polysulfonatotetraphenylmetacyclophaneoctol comprising 2% palladium and 10% silver was chosen as a material for the positive electrode, at which oxygen is reduced.

With the increase in technological demands, the polymer electrolyte membranes comprised of highly conductive metal nanowires for novel current collectors were fabricated in such a way to develop an extremely high stretchable function for flexible fuel cells. Moreover, this flexible current collector maximizes the clamping forces under bent conditions resulting in the reduction of ohmic resistance. These fuel cells show an increase in the power density with a decrease in radius of curvature of the cells. Recently, flexible power sources have been extensively studied by various researchers. Chang et al. synthesized polydimethylsiloxane-coated flexible current collect layer of silver nanowires by using a successive multi-step growth method for enhancing the length of the silver nanowires (Zang et al. 2008). Under high bending conditions of silver nanowires electrode, considerable improved electrical conductivity was achieved. The cell achieved a power density of 71 mW cm^{-2} under various bending conditions (Fig. 8).

Park et al. discuss the flexible polymer electrolyte fuel cell fabricated by polydimethylsiloxane coated with very long Ag nanowires percolation network (VAgNPN) current collector (Afzal et al. 2009). The cell shows a decrease in the tendency of electrochemical performances with an increase in torsion.

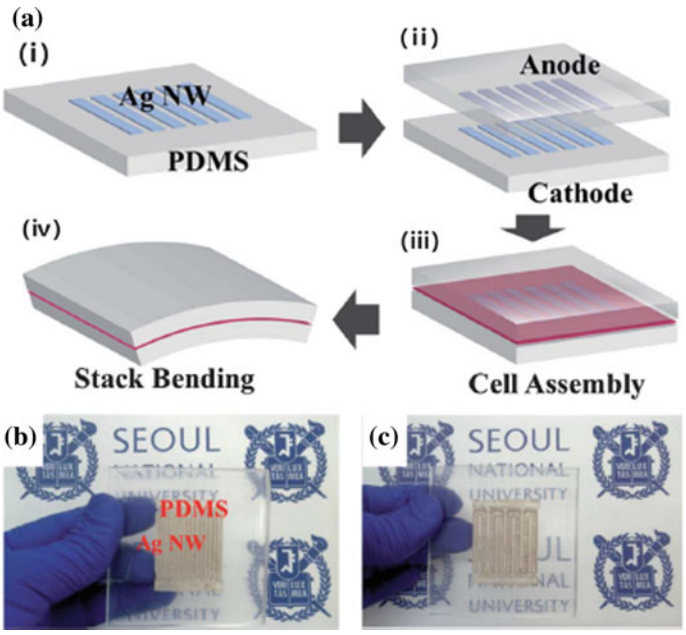

Fig. 8 Schematic of the process for fabricating p Ag NW percolation network electrode patterns on the flow channel patterned PDMS for bendable fuel cell (Zang et al. 2008). Copyright 2013. Reproduced with permission from the Royal Society of Chemistry

The investigation of electrochemical impedances shows loss of performance of flexible fuel cell with an increase of ohmic and faradaic resistances. The maximum power densities 16.8 and 10.9 mW/cm^{-2} were observed for a flexible fuel cell at no torsion and 25° of torsion. The result shows the decrease in the tendency of power density with increase of torsion.

Recently, Seo et al. devoted major time and attention in the synthesis of graphene nanosheet-supported Pd, Pd_3Ag, Pd_3Fe, and Pd_3Co nanoparticles through impregnation along with heat treatment (Gupta et al. 2010). These catalysts having similar metal particle size were used to compare the oxygen reduction reaction (ORR) activity under both acidic and alkaline conditions. The results of electrochemical testing exhibit the ORR activity of high loading Pd and Pd alloy catalysts on GNS. The exhibition of excellent ORR activity by GNS-supported Pd or Pd-based alloy nanoparticle catalyst makes it a strong potential candidate for replacing Pt for usage as cathode electrodes of fuel cells shown in Fig. 9.

Among the recent reports, Şimşek et al. synthesized multifunctional polymer electrolytes by various fabrication methods (Choudhury 2009). Polymer matrix (intercalated poly(vinyl alcohol)/octadecylamine montmorillonite), with partner polymer [poly(maleic anhydride-alt-methyl vinyl ether)], NaOH, and Ag-carrying polymer complexes was fabricated via solution blends as shown in Fig. 10. These fabricated novel nanofiber electrolytes are the potential candidates for applications in energy harvesting and fuel cell nanotechnology.

Very recently, Ivan et al. report the synthesis of carbon-supported silver nanoparticles (Ag: NPs/C) with the help of gamma irradiation-induced reduction

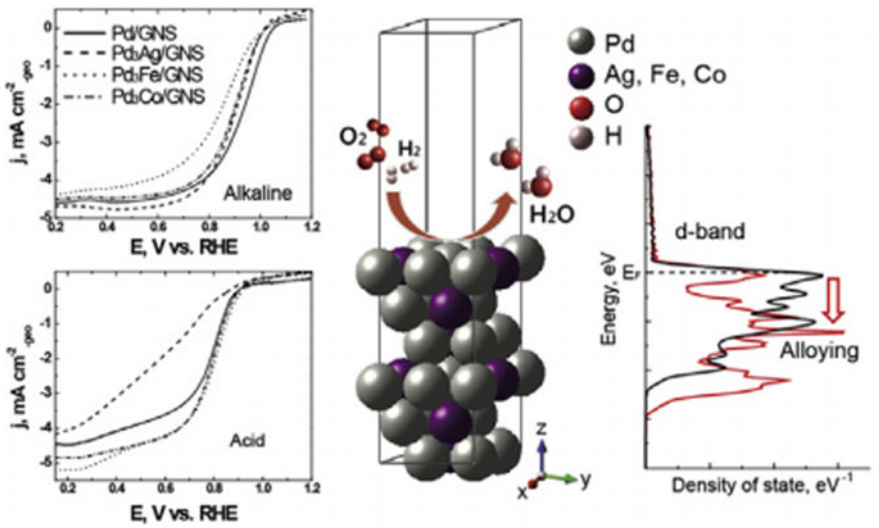

Fig. 9 Schematic of oxygen reduction reaction, ORR, performances of graphene-supported palladium (Pd) and palladium alloys (Pd_3X: X = Ag, Co, and Fe) catalysts (Gupta et al. 2010) Copyright 2015. Reproduced with permission from Elsevier

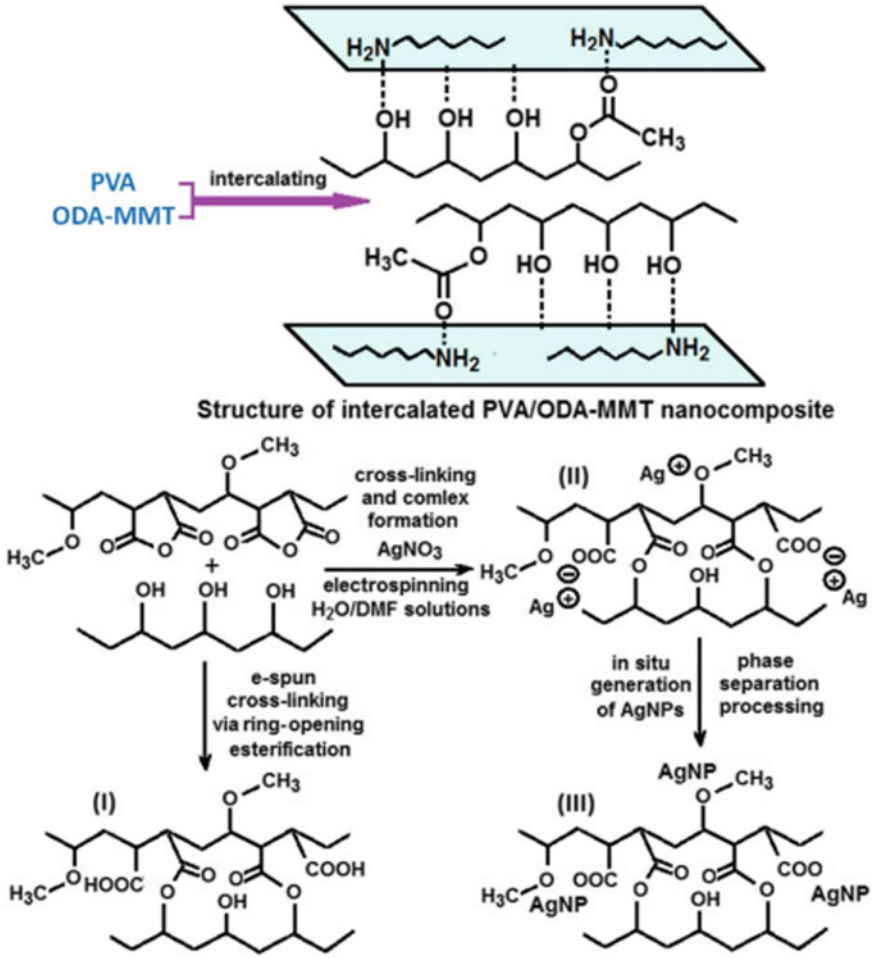

Fig. 10 Schematic depicting the synthetic pathways and chemistry of the multifunctional nanofiber structures (Choudhury 2009). Copyright 2016. Reproduced with permission from Wiley

method; the morphology is shown in Fig. 11 (Zhou et al. 2009). The as-prepared Ag: NPs/C was studied by rotating ring disk method. These can be potentially used as an electrocatalysts in alkaline fuel cells.

Marcos et al. focus on the permeation of silver nanoparticles in poly [sulfonated-co-AA] and poly[styrene sulfonated-co-AA] membranes with the help of electrochemical techniques (Patil et al. 2013). This report indicates the fact that sulfonated copolymer in the medium is more permeable toward the diffusion of silver nanoparticles in comparison with non-sulfonated film. Moreover, in the electrodes, the presence of polymeric film does not affect the redox process Ag^{+}/Ag^{0}. These membranes are a promising material for application in the development of fuel cells.

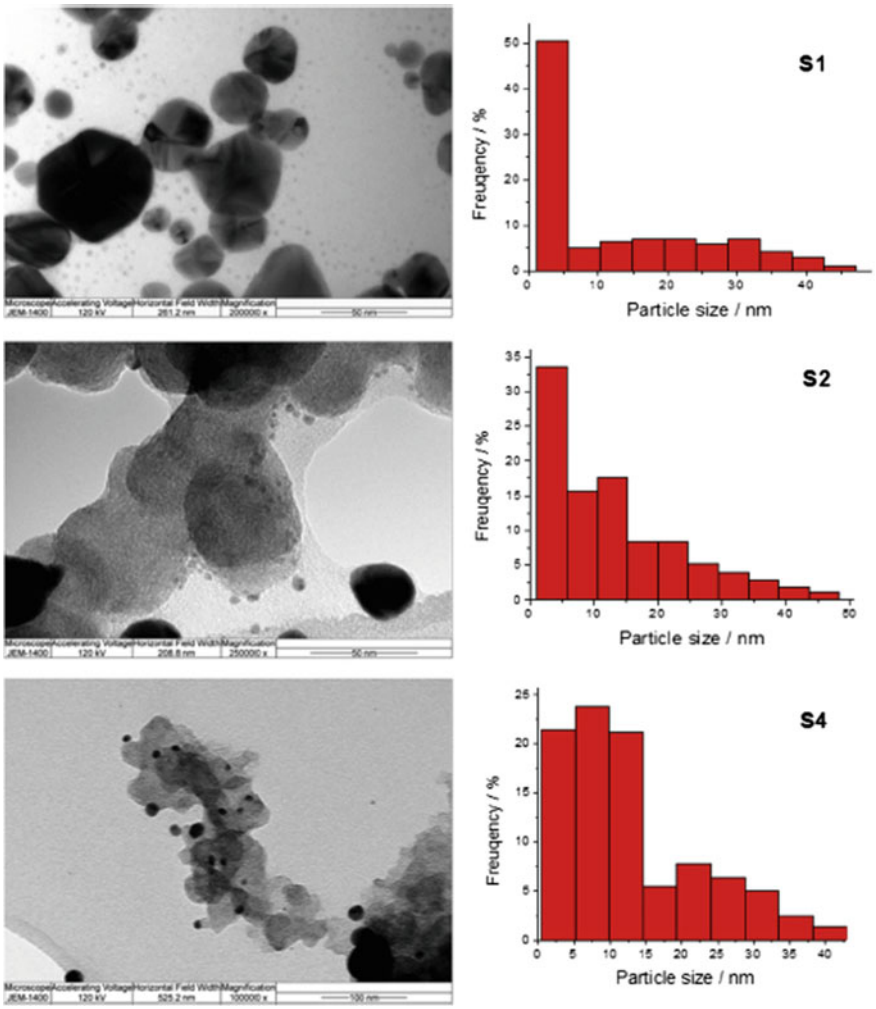

Fig. 11 TEM images of Ag:NPs/C/polymer electrocatalysts with corresponding Ag particle size distributions (Zhou et al. 2009). Copyright 2009. Reproduced with permission from Elsevier

7 Polymer-/AgNP-Based Sensors

Conducting polymer nanocomposites are widely reported as potential sensors with good sensitivity, response/recovery time, stability, durability, and selectivity. Nanoparticles significantly enhance these parameters which are very much essential for the commercialization; however, the selectivity and durability still remain as challenges. Many sensors work quite exceptionally under controlled laboratory atmospheres, whereas target detection in a complex environment stands difficult. PANI is an important polymer in fabricating sensors of various kinds. For instance,

PANI/AgNP sensors detect methanol vapor at room temperature with excellent repeatability and reversibility. The composite showed an increase in voltage when exposed to methanol vapors, and the value decreased when it was placed in nitrogen. PANI influences the composite microstructure by creating a porous fibrous structure with small grain size which enables superior methanol vapor detection compared to pure AgNP. PANI/tin oxide nanocomposites are also reported for its sensing performance toward aqueous ammonia. Several interactions such as hydrogen bonding, chemical bonding, and van der Waals forces exist between the vapor molecules adsorbed and PANI. Due to this effect, the conductivity of PANI increases when exposed to acidic atmosphere and decreases when exposed to basic atmosphere. When the sensor is kept in aqueous NH_3, the resistance value changes abruptly depending on the concentration. The response time and recovery time for the sensor to NH_3 exposure were, respectively, 1–7 and 14 min. At high NH_3 concentration (30%), the sensing material showed faster response.

NH_3 sensing at room temperature was studied for the P3HT:1.00 mol% Au/AgNP nanocomposite films by Kruefu et al. The samples were synthesized by single-step FSP process and further optimized. The optimal composite showed better NH_3 sensing over ethanol, CO, H_2S, NO_2, and H_2O compared to neat P3HT, 1.00 mol% Au/AgNP, and other composites. The higher sensing performance is because of the catalytic effect of Au/AgNP nanoparticles and the porous blended nanoparticle structure. Detection of aqueous HCl vapors at different concentrations (10, 20, and 30%) was done using PANI/AgNP composite. The resistance value decreased when exposed to the vapors and at 30%, and fastest response was achieved. Deprotonation happening in PANI reduces it from the emeraldine salt state to the emeraldine base state which reduces the hole density and increases the resistance. The sensitivity results of the PANI/AgNP composite show its high sensitivity and good repeatability toward both ammonia and HCl vapors as compared to neat PANI. The high-performance can be attributed to the porous structure due to the incorporation of AgNP nanoparticles. Another conducting polymer, PPy, was used to fabricate the AgNP nanocomposite by electro-polymerization method on Pt substrates. The AgNP affects the electro-polymerization, and the polymerization on composite initial layers is easier than the pure PPy initial layers. Humidity sensors from AgNP/PANI nanocomposite were also reported which showed change in resistance/impedance with water adsorption. Adsorption of water generates ions and leads to efficient directional charge conduction. PANI/AgNP showed three times better performance than the PANI due to the composite porosity.

The photo sensitivity of AgNP-10/PET composites towards different UV power densities were checked and compared with other photodetectors, these materials exhibited faster response/recovery, good orientation, high sensitivity, reproducibility, reliability, and multi-level photoresponse. This flexible sensor proved its high mechanical stability through bending test as well. Chen et al. reported the pressure sensing properties of AgNP nanowire-PMMA composite layers. The interacting surface area of the composite was maintained as $\sim 1\ cm^2$ by keeping

0.1 g weighing plastic cup on the sensor surface. In the absence of external pressure, the dielectric constant and initial capacitance were 6.38 and 90.42 pF, respectively. The electrical and dielectric properties in addition to the capacitance values are influenced by the nature and type of polymer matrices and nanoparticles. Thin films of AgNP–PSS/PVA composites were characterized for their pressure sensing behavior by changing the applied dynamic strain. For the same strain, the voltage generated were compared and correlated to observe the piezoelectric response. With dynamic strain, the voltages generated were enhanced and the main reason for the piezoelectricity of (AgNP–PSS/PVA) films is the embedment of nanoparticles. The generation of piezoelectric potential across the composite thin film is a result of mechanical deformation occurring because of the periodically varying longitudinal tensile and compressive stress vibrations. The output voltage depends strongly on the vibrations, and the d_{31} piezoelectric coefficient measures the vibration sensing.

Humidity sensing curves for the PANI/AgNP composite showed a decrease in resistance with an increase in AgNP concentration. The sensitivity is calculated as the ratio of resistance in dry condition (20% relative humidity) to the resistance at a particular humidity. In the composite, charge transfer capacity of PANI increases in presence of zinc and gives distinct response to water vapor. Similar humidity sensors from PANI/AgNP composites are also reported. Lao et al. practiced electrochemical polymerization to fabricate PANI/AgNP composites and PANI-AgNP/PVA double layers to be useful in sensing applications.

Photoconductive responses of a device made using AgNP NBs functionalized with different polymers (PSS, PS-co-Mac, PNIPAM, and CMC) indicate interesting results. When the UV was radiated on, the photoconductance of PSS-coated AgNP NB (red line) increased by 75,000 times, differing from the other polymer-coated AgNPs. This can be due to the coupling effect formation between the AgNP particles and PSS polymer. At the time of UV illumination, the non-moving electrons trap photon-generated holes and reduce the rate of electron–hole recombination which in turn enhances the lifetime of the carrier. The UV absorption spectrum of PSS has a peak around 260 nm that is close to the applied UV source wavelength, 280 nm.

8 Conclusion

Although there are a variety of methods for the synthesis of AgNP, the one including MW shows the enhancement in various properties such as electrical, microwave absorption, transport, and antimicrobial. We found that MW synthesis of AgNP is a highly efficient, reliable, high-yielding, and low-cost method. The antibacterial and antimicrobial properties of AgNP and their nanocomposites are a huge interest area for research in present time as they show great potential for reducing infections and hence providing faster healing and better health to the patients.

Acknowledgements This publication was partially made possible by UREP grant 23-116-2-041 from Qatar National Research Fund (a member of Qatar Foundation). The statements made herein are solely the responsibility of the authors.

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Electrospun Polymeric Nanofibers: Fundamental Aspects of Electrospinning Processes, Optimization of Electrospinning Parameters, Properties, and Applications

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Abstract Nanotechnology is a novel interdisciplinary field of science which has captured profound attention in all research areas due to its unique applications. Polymer nanofibers (PNFs) are one-dimensional (1D) fibers having diameters less than 1000 nanometers (nm). Electrospinning (ES) has been recognized as one of the most efficient, simple, versatile, and cost-effective methods for the fabrication of PNFs, among various other techniques such as phase separation, template synthesis, and self-assembly. The electrospun PNFs are being increasingly applied to biomedical fields due to its high surface-area-to-volume ratio, high porosity, and easy tuning of their structures, functionalities, and properties. Hence, these electrospun PNFs owing to their high specific surface area create a three-dimensional (3D) porous structure that mimics the native extracellular matrix (ECM), vitally useful in biomedical applications. In this chapter, we briefly discuss the fundamental aspects of the ES process and the properties of electrospun PNFs. This chapter also attempts to highlight the applications and importance of nanofibers in various fields of biomedicine such as tissue engineering, drug delivery, and wound healing.

Keywords Electrospinning processes · Nanofibers · Polymers · Biomedical applications

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K. K. Sadasivuni et al. (eds.), *Polymer Nanocomposites in Biomedical Engineering*, Lecture Notes in Bioengineering,
https://doi.org/10.1007/978-3-030-04741-2_12

1 Introduction

Nanotechnology, an interdisciplinary field, prompts scientist and engineers to fabricate and devise novel, unique, and versatile materials, that can be applied in all vital sectors of life such as agriculture, medicine, transportation, energy production, and information technology (IT) (Ponnamma et al. 2018). In the last few decades, the giant progress in the field of nanoscience and nanotechnology has undoubtedly improved the quality life of humans (Rosic et al. 2013). Polymeric nanofibers (PNFs) are an important class of one-dimensional (1D) nanomaterials which are mainly prepared from electrospinning (ES) method. PNFs are one such new class of material with several especial properties suitable for a wide range of applications (Rosic et al. 2013; Hasan et al. 2014). Nanofibers (NFs), as defined by National Science Foundation (NSF), are fibers having at least 1D lesser than 100 nanometers (nm). On the other hand, the nonwoven industry defines NFs as fibers having diameter lesser than one micron (or 1000 nm) (Hasan et al. 2014). NFs are solid fibers with several unique features such as high specific surface area, high porosity, excellent pore interconnectivity, high flexibility, exceptional mechanical strength, and theoretically unlimited length (Fang et al. 2012; Rosic et al. 2012). These unique properties of NFs make them a potential candidate for a plethora of commercial applications, viz. from medicine to consumer products and from industrial to high-tech applications such as drug delivery systems (DDS), tissue engineering, aerospace, energy storage, fuel cells, and IT (Hasan et al. 2014). NFs produced from natural polymers such as collagen, gelatin, chitin, chitosan, silk fibroin, and alginate or from synthetic polymers such as polyvinyl alcohol (PVA), polycaprolactone (PCL), polyethylene glycol (PEG), polylactic acid (PLA), polyglycolic acid (PGA), and poly (lactic-co-glycolic acid) (PLGA) have captured phenomenal attention for their simple processability and also for the easy tunability of their structural, compositional, and functional properties (Lee et al. 2015).

In recent years, several methods such as drawing, self-assembly, template synthesis, ES, and phase separations have been developed to fabricate PNFs. A schematic diagram of phase separation, self-assembly, and ES methods are depicted in Fig. 1. The drawing method uses a sharp tip to pull single long continuous NFs one by one from the viscoelastic material. This process is viable only for viscoelastic materials that are able to withstand strong deformation and being cohesive enough to support the stress developed during drawing, for producing NFs. In template synthesis, a non-porous membrane is used as a template to fabricate a fibril (solid) or tubular (hollow) NFs with controlled shape and diameter. The insulating polymers, intrinsically conducting polymers (ICPs), metals, carbons, semiconductors, etc., can be used as a raw material for this method. However, this method cannot produce single long continuous fiber. The phase separation technique comprises of five major steps such as polymer dissolution, gelation, solvent extraction, freezing, and freeze-drying to create a porous NFs structure. However, the entire process is relatively time-consuming. In self-assembly method, the individual, preexisting components, i.e., small molecular units, assemble

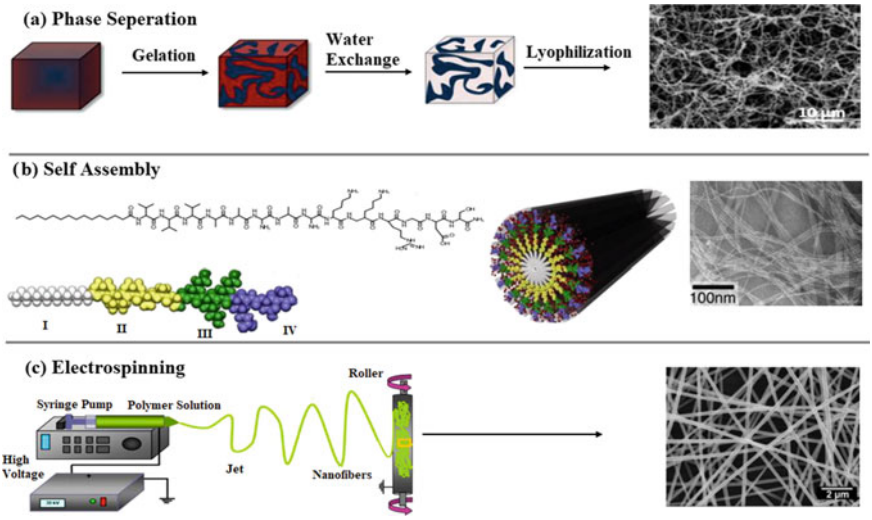

Fig. 1 Schematic diagrams of phase separation, self-assembly, and ES methods for forming PNFs and their corresponding SEM micrographs (Wang et al. 2013). Copyright 2013. Reproduced with permission from Elsevier Ltd.

themselves into appropriate patterns as well as functions. The intermolecular force is responsible for arranging the molecules together and thus decides the shape of the NFs. Similar to phase separation, this method also takes a longer time to form continuous PNFs. Among the aforementioned methods, ES is considered to be the best technique for producing long, continuous PNFs on a larger scale that has excellent control on the fiber dimensions (Huang et al. 2003; Baptista et al. 2013; Wang et al. 2013).

ES is one of the best and appropriate techniques to create pure polymer NFs or polymer composites NFs from the corresponding solution or melt. This technique is much analogous to extrusion spinning which is commonly used in textile industries. On comparing ES technique to extrusion spinning technique, the ES uses electrical force to create PNFs in place of mechanical force. Electrospun NFs membranes own myriads of applications such as scaffolds for biomedical engineering, sensors, organic electronics, fuel cell membranes, and filters (Kanani and Bahrami 2010). Some of the applications of electrospun PNFs are given in Fig. 2 (Huang et al. 2003).

The main driving force for the progress of PNFs is their increasing use in biomedical and biotechnological applications (Zhang et al. 2005; Pawde and Deshmukh 2008a; Venugopal and Ramakrishna 2005; Pawde et al. 2008). PNFs have comparably similar sizes as that of most biological molecules and structures. Hence, they are worthwhile for in vivo as well as in vitro biomedical applications. The unification of NFs and biology has resulted in the advancement of novel diagnostic devices, physical therapy applications, analytical tools, and DDS.

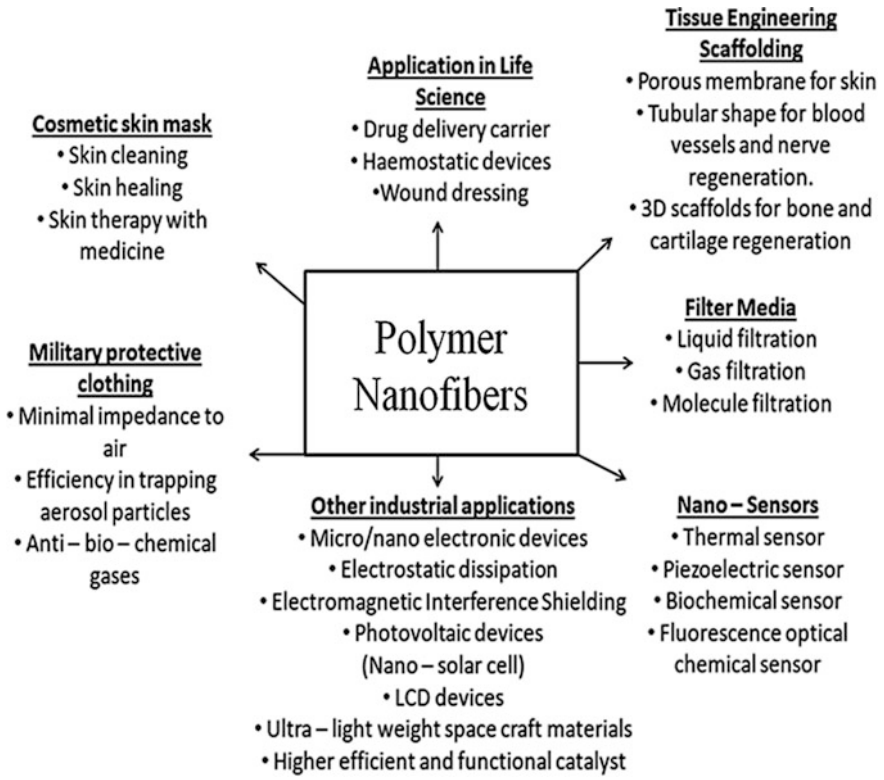

Fig. 2 Potential applications of PNFs (Huang et al. 2003). Copyright 2003. Reproduced with permission from Elsevier Ltd.

Biomedical field is one of the vital application areas that have been best able to trap the maximum potential of ES technique, predominantly for tissue engineering applications, DDS, wound dressing and wound healing, diagnostics, biosensors, etc. (Agarwal et al. 2008; Focarete and Gualandi 2013). Figure 3 represents the transformation of the polymer solution into PNFs using ES process and the potential use of electrospun PNFs for biomedical applications. ES technology is highly competent for fabricating nanofibrous scaffolds (NSs) for culturing tissue cells as well as treating injured and diseased tissues in the portions of skin, blood vessel, tendons, muscles, ligaments, nerves, cartilage, bones etc. (Shin et al. 2012). The usefulness of electrospun NFs produced using biocompatible and biodegradable or non-biodegradable polymers can be recognized from the innumerable research articles that are being published on a regular basis emphasizing its role in biomedical engineering (Deshmukh et al. 2017a; Sridhar et al. 2013).

The electrospun 3D porous membranes possess high surface area that exactly mimics the native extracellular matrix (ECM). The electrospun membranes can be used in composites materials as they have reinforced mechanical properties, biocompatibility, and cellular response. ES technique is a strong tool to fine-tune the

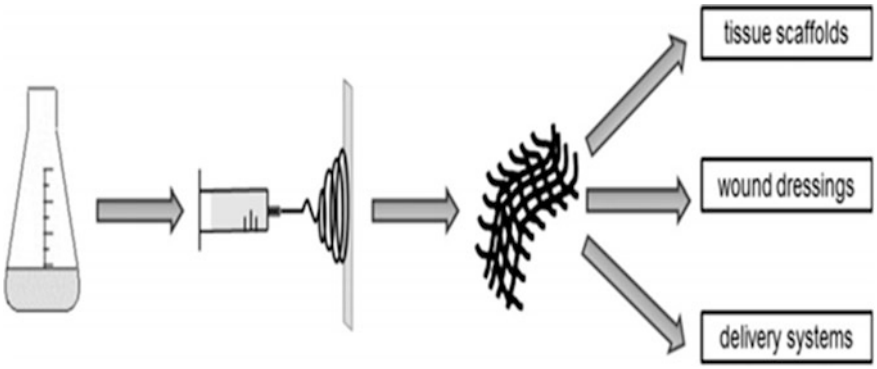

Fig. 3 Schematic diagram depicting the PNFs generated from ES process and their potential use for biomedical applications. Adapted from Rosic et al. (2013)

especial properties of functional materials particularly for biomedical applications, by combining a diverse range of materials with similar morphological characteristics. For example, it is possible to encase biomolecules or bioactive molecules such as enzymes and DNAs into the fibers using conventional or modified ES setups (Ponnamma et al. 2017). Such hybrid NS provides a familiar environment to the cells, leading to their better adhesion, proliferation, migration, alignment, orientation, activation, and differentiation. For instance, collagen fibril enhances the contact between cells and scaffolds. Similarly, electrospun NS is used as a drug delivery carrier (DDC) for carrying drugs to their target sites (Zhang et al. 2005; Haider et al. 2015). The excellent pore interconnectivity of electrospun NFs makes the entire porous structure fully accessible to chemical species (Focarete and Gualandi 2013). Comparing a nanofibrous material to that of a flat surface of a dense material, the NFs have considerably large surface area and directional fiber arrangement that helps cells to discover more sites for adherence and guides them to spread and move in specific directions (Shin et al. 2012). Non-biodegradable polymers have a longer degradation time than biodegradable polymers offering better structural and mechanical support, but it interferes with tissue turnover and remodeling. Hence, they can be effectively used for enzyme immobilization and filtration systems like dialysis etc. Figure 4 depicts the comparison of mechanical, biological, and physicochemical properties of some common polymers. On the contrary, biodegradable polymers due to enzymatic and hydrolytic activities do not interfere with cellular activities and thus permit the cell proliferation. The holes formed by the biodegradable fibers allow ECM to infiltrate and supply nutrition for the proliferating cells. Therefore, these biopolymers can be used in tissue engineering and DDS (Khan et al. 2012; Deshmukh et al. 2015a, b; Pattanashetti et al. 2017). This chapter is an attempt to highlight the basic aspects of the ES technique, the properties, and the potential applications of PNFs in the biomedical field, particularly the use of electrospun PNFs in tissue engineering, DDS, and wound-dressing or healing applications.

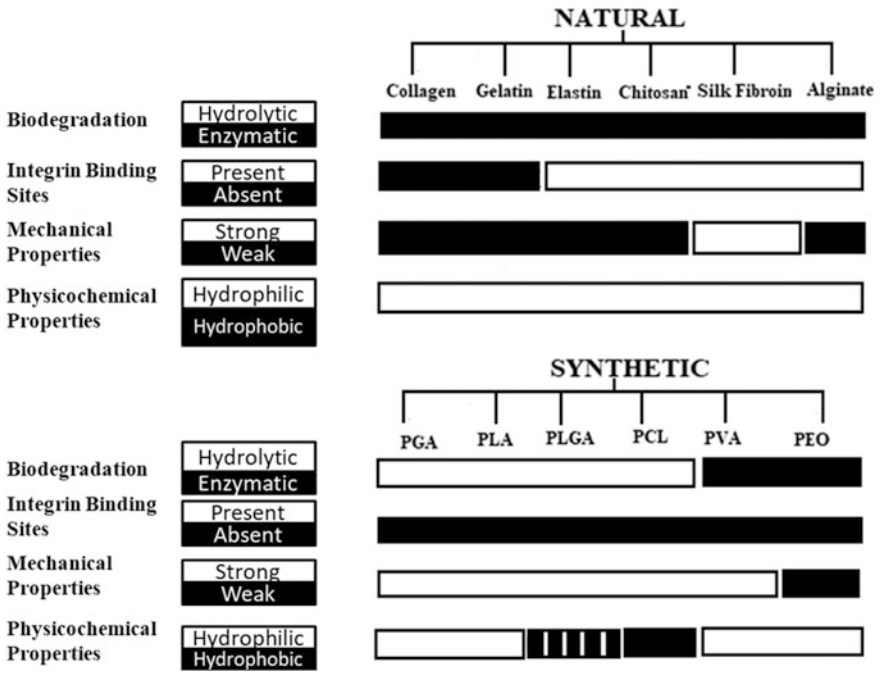

Fig. 4 Flowchart depicting the mechanical, biological, and physicochemical properties of some well-known polymers. Adapted from Rosic et al. (2012)

2 Electrospinning Process

2.1 Fundamental Aspects

ES is a well-known, simple, and versatile technique that utilizes a very high electrical field or high voltage (HV) to accelerate a charged polymer jet into ultrafine NFs. The diameter of the PNFs ranges from 1 μm to 10 nm which is generally 1–3 orders less than the diameter of NFs produced by the other traditional spinning techniques (Fang et al. 2012). A schematic diagram of ES setup in the horizontal direction is shown in Fig. 5 (Huang et al. 2003). Though ES instrument seems to be very simple and easily controllable for producing ultrafine NFs, the physics governing this process is highly complex as it involves the interaction of several physical instabilities (Hasan et al. 2014). The basic ES setup consists of a syringe with metallic needle, HV power supply, and collector. The syringe is loaded with the polymer in solution or melt form, and the tip (or the orifice) of the metallic needle is attached to the positive or the negative terminal of the HV power supply. In most of the cases, the tip of the metallic needle is linked to the positive terminal of the HV power supply. The main function of the syringe pump is to pump the polymeric solution (or the melt) present in the syringe at a steady flow rate (ml/hr)

for producing continuous NFs. The HV for producing an electrically charged jet of polymer solution or melt ranges commonly from 10 to 50 kV. Generally, the negative or the positive terminal of the HV supply is linked to the collector. The collector, in most of the cases, is simply grounded, as displayed in Fig. 5.

On application of HV, the electric field accumulates at the tip of the needle that holds a pendant-shaped droplet of the solution via surface tension. The positive charges get induced on the droplet's surface. The electrostatic force is created against surface tension which may be attributed to the mutual repulsion of induced charges and the nature of the surface charges to move toward the collector (or the counter electrode). On further increasing the HV, the hemispherical surface of the droplet situated at the tip of the metallic needle stretches to produce an inverted cone known as the Taylor cone. Figure 6 illustrates the Taylor cone formation with an increase in applied voltage (Awang et al. 2015). Increasing the HV further, a threshold (or critical) value is reached above which the electrostatic forces overcomes the surface tension and ejects out a fine jet of charged polymer solution from the tip of the inverted cone. This jet emanating out of the inverted cone becomes very thin and long as they reach the collector, as they are further subjected to elongation processes and instabilities. Once the jet reaches the atmosphere, all the low boiling point solvent is evaporated and only charged polymer strands is left behind. Now, the charged polymer strands mutually repel and move away from each other and ultimately get deposited on the collector to form a nonwoven nanofibrous mat, as shown in Fig. 7 (Rosic et al. 2013). Figure 8a–c shows different types of collectors such as flat-type collector, square frame collector, and rotating drum collector that plays a pivotal role in tailoring the structure of PNFs (Khadka and Haynie 2012). Aligned NFs can be fabricated using a controlled deposition technique and also with the help of rotating collector drum. Till now,

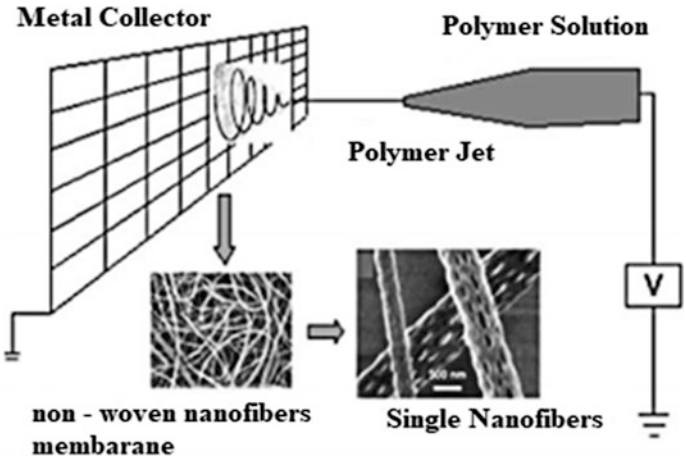

Fig. 5 Schematic diagram representing production of PNFs via ES process in the horizontal position (Huang et al. 2003). Copyright 2003. Reproduced with permission from Elsevier Ltd.

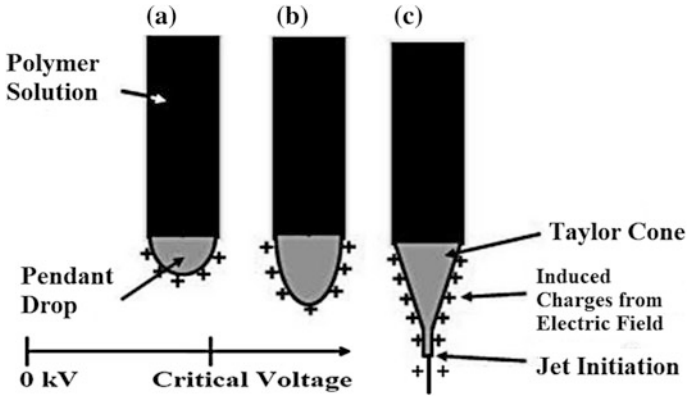

Fig. 6 Schematic illustration of Taylor cone formation with increasing applied voltage (Awang et al. 2015). Copyright 2015. Reproduced with permission from Elsevier Ltd.

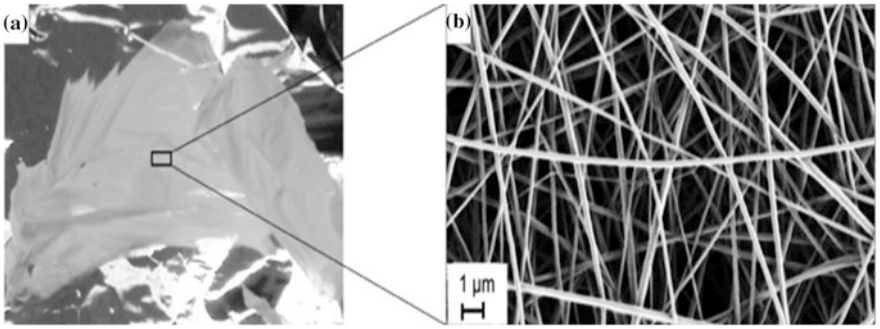

Fig. 7 As-spun nanofibrous mat collected in aluminum foil collector and its SEM micrograph. Adapted from Rosic et al. (2013)

numerous polymers and filler materials have been successfully electrospun into polymer composite NFs. The PNFs can take up different morphological forms such as porous, core-shell, and layer-by-layer structures. Electrospun NFs capture appreciable attention when compared to other techniques because of their distinct properties, simple fabrication, easy functionalization, and adaptability in manipulating the diameter as well as the morphology of the fibers (Deshmukh et al. 2017b). The new improvization in ES technique includes core-shell ES, multi-layered ES, blowing-assisted ES, two-phase ES, and also post-alignment methods (Preethi et al. 2015).

The preparation of polymer solution by dissolution followed by formation of PNFs by ES is mostly performed at room temperature and at atmospheric condition. The ES equipment should be placed in shock-proof chambers and ventilation systems as some polymers radiate unpleasant or even harmful odor. One must avoid

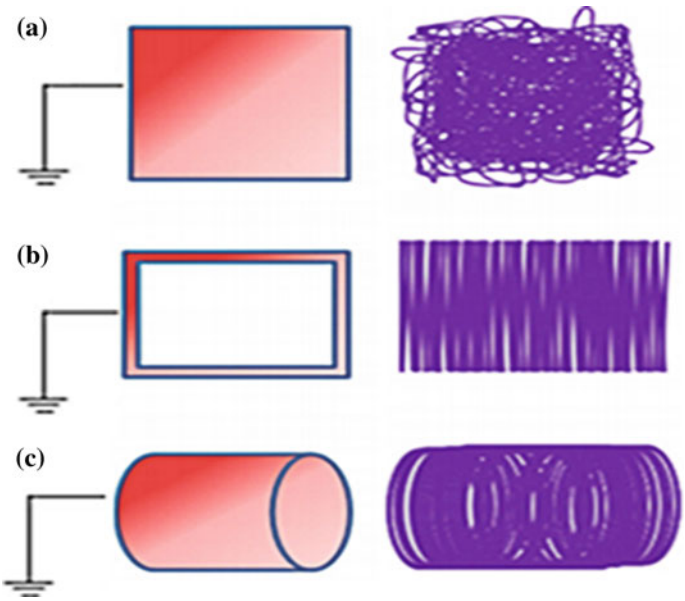

Fig. 8 Deposition of electrospun PNFs in different types of collectors **a** flat plate stationary collector for nonwoven NFs, **b** square frame collector for unidirectional oriented NFs, and **c** rotating cylindrical drum collector for tubular oriented NFs (Khadka and Haynie 2012). Copyright 2012. Reproduced with permission from Elsevier Ltd.

touching the tip of the needle during the formation of NFs. This is because the fabrication of NFs requires a very high applied DC voltage in the order of several tens of kVs. Polymers in molten form at high temperature can also be electrospun into NFs. In the place of a polymer solution, the syringe can be loaded with the polymer melt also. However, the main difference between polymer solution and polymer melt solution is that the ES process for a polymer melt is carried out in a vacuum condition; i.e., the syringe, the accelerating charged melt fluid jet, and the metal collector must be kept in vacuum (Huang et al. 2003).

2.2 *Effect of Optimization Parameters on Electrospinning Process*

The transformation of polymer solutions into ultrafine PNFs through ES is influenced by several optimization parameters, which can be grouped into three main divisions (A) solution parameters such as polymer concentration, solvent, surface tension, conductivity, and solution viscosity; (B) processing parameters such as needle-tip-to-collector distance, needle diameter, applied voltage, flow rate, and type of collectors; and (C) environment parameters such as temperature and relative

humidity. These optimization parameters directly have an effect on the production of smooth as well as bead-free electrospun NFs. Therefore, it is necessary to thoroughly comprehend the effects of these parameters to get a better understanding of the ES mechanisms and fabrication of PNFs (Gupta et al. 2014).

2.2.1 Effect of Solvent

The formation of smooth and beadless electrospun NFs is mainly dependent on the selection of the solvent. Two things must be kept in mind while selecting the appropriate solvent. Firstly, the preferred solvents must be completely miscible with the polymers of interest. Secondly, the solvent must have low to medium boiling point. The boiling point indirectly signifies the volatility of a solvent. High-volatile solvents generally have very low boiling points and high evaporation rates, which results in drying of the jet at the tip of the metallic needle, and hence, solvents of such type are mostly avoided. This drying will arrest the solution in the needle tip and hence will disturb the ES process. The low-volatile solvents are mostly avoided owing to their high boiling points, as they inhibit the drying or evaporation of solvents during the flight of charged polymer jet strands and ultimately lead to NFs with bead formation due to the deposition of solvent on the collector (Haider et al. 2015).

2.2.2 Effect of Polymer Concentration and Solution Viscosity

In ES process, the concentration of polymer solution is one of the key factors in the formation of NFs. The low concentration of polymer solution leads to electrospraying instead of ES since the solution possesses low viscosity and high surface tensions. At slightly higher concentration, the formation of both the beads and fibers is observed. Smooth NFs are generally formed in an ES process at the suitable high concentration. The fiber diameter will eventually increase when solution concentration increases. Furthermore, the solution concentration can be adjusted for obtaining suitable solution viscosity. Figure 9 depicts SEM micrographs of electrospun PNFs with variegated polymer concentration and solution viscosity (Huang et al. 2003).

Solution viscosity is a crucial parameter that determines the fiber morphology. The low-viscous polymer solution is not suitable to yield continuous and smooth fibers; i.e., the dominant surface tension in it yields just beaded fibers. The very high viscosity of the polymer solution will lead to great difficulty in ejecting jets from solution. As mentioned above, the solution concentration helps to adjust the solution viscosity. It is necessary to note that the viscosity, solution concentration, and molecular weight (MW) of the polymer are interlinked to one another. The polymer solution with appropriate viscosity forms continuous, uniform, and smooth fibers (Fong and Reneker 1999). The polymer content present in the jet and the jet sizes decides the fiber diameter, a primary and crucial parameter in ES process.

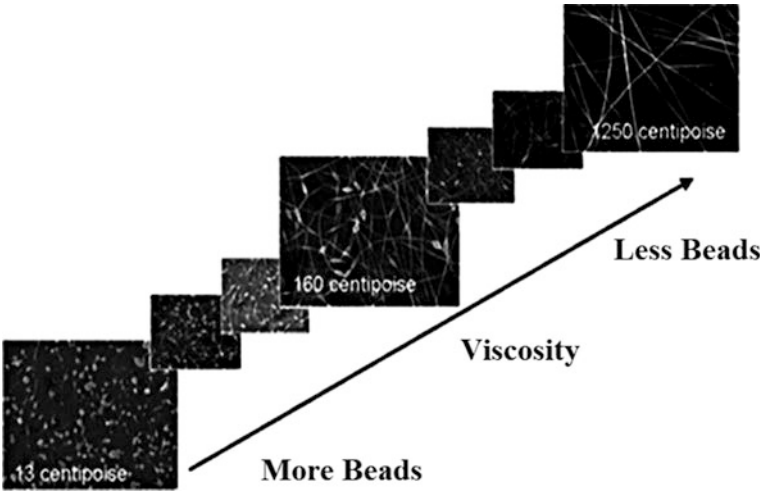

Fig. 9 SEM images of electrospun PNFs with variegated polymer concentration and solution viscosity (Huang et al. 2003) Copyright 2003. Reproduced with permission from Elsevier Ltd.

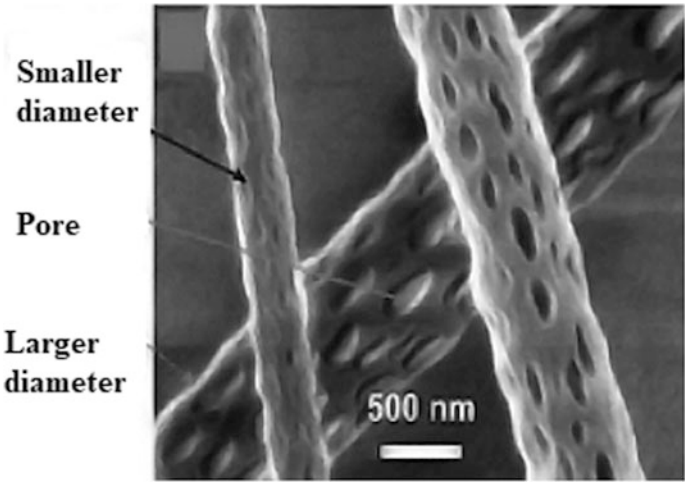

Fig. 10 NFs of PLLA with varying diameter and pore sizes (Huang et al. 2003). Copyright 2003. Reproduced with permission from Elsevier Ltd.

Figure 10 represents poly(L-lactic acid) (PLLA) NFs with varying diameter and pore sizes, wherein the variation in fiber diameter occurs during the polymer jet flight, in between the metallic needle tip and metal collector (Huang et al. 2003).

2.2.3 Effect of Solution Conductivity

The type of polymer, solvent, and the salt are the major factors that decide the solution conductivity. The polyelectrolyte nature of the natural polymers leads to poor fiber formation when compared to synthetic polymers. The conductivity of the solution affects the formation of Taylor cone and also helps in regulating the NFs diameter. A solution with lower conductivity will have deficit charges on the surface of the pendant droplet for producing a Taylor cone, and therefore, ES process will not occur. Further elevating the solution conductivity to a threshold value leads to increase in accumulation of surface charges on the droplet to form Taylor cone, which ultimately decreases the diameter of NFs. Further increasing the conductivity beyond a threshold value will obstruct the Taylor cone formation and ES process.

2.2.4 Effect of Solution Flow Rate

The polymer solution flowing via the tip of the metallic needle decides the morphology of the electrospun NFs. By choosing a proper critical flow rate (in ml/hr) for a polymer solution, uniform beadless electrospun NFs could be well prepared. The threshold value changes with each polymer system. The flow rate of the polymer solution in the syringe is one of the crucial process parameters. The low flow rate is usually considered favorable as the polymer solution acquires more time for polymerization yielding smooth fibers with a thin diameter. In case of higher flow rate, the beaded fibers with the larger diameter will be formed. In case of polystyrene (PS), the bead formation was formed at 0.10 ml/min flow rate and bead-free NFs were witnessed for 0.07 ml/min flow rate. Increase in the flow rate of polymer solution beyond a threshold value results in increased pore size, fiber diameter, and bead formation.

2.2.5 Effect of Applied Voltage

The applied high DC voltage or electric field is an important intrinsic factor for forming ultrafine NFs. It was validated by several research groups that applying higher voltages results in the formation of NFs with thicker diameters. On the contrary, there are several other research groups who proved that the higher voltages lead to narrowing of the fiber diameter, as the electrostatic repulsive force on the charged jet is increased. It can be concluded that the applied electric field has a considerable effect on the diameter of the NFs, in addition to the effect due to other parameters such as solution concentration of the polymer and tip-to-collector distance. Applying HV to a solution via a metallic needle causes the pendent droplet to deform into a Taylor cone and form ultrafine NFs at a critical voltage. This critical voltage is different for every polymer. NFs with a smaller diameter are produced by increasing the applied voltage, which can be mainly attributed to the stretching of the polymer solution and the mutual repulsion of charges in the polymer jet.

Inflating the applied voltage further beyond the critical value leads to the enormous bead formation.

2.2.6 Effect of Needle-Tip-to-Collector Distance and Needle Diameter

The distance between the tip of metallic needle and collector also influences the diameter and morphologies of the fibers. This parameter usually depends on the polymer system selected. The evaporation rate, instability or whipping intervals and deposition time depend on this parameter that affects the morphology of the NFs. A critical distance has to be optimized to prepare smooth and uniform electrospun NFs. When this tip-to-collector distance is kept small, defective and large-diameter NFs are produced whereas when this distance is kept large, the diameter of the NFs is witnessed to be decreased. Sometimes even on changing this distance does not have any influence on the morphology of the NFs. In addition, if the distance between needle tip and the collector is very small, then the fiber jets may not have the proper time for solidification prior to deposition on the collector. If this distance is very large, then there is a high possibility of bead fiber formation. Therefore, to obtain proper dryness from the solvent, it is necessary to maintain the optimum tip-to-collector distance.

2.2.7 Effect of Relative Humidity and Temperature

Environmental factors, viz. relative humidity, temperature, etc., affects the diameter as well as the morphology of the NFs. Humidity affects the diameter of the NFs by regulating the solidification process of the charged polymer jet, which depends on the polymer's chemical nature. The temperature is found to increase the evaporation rate of the solvent and decrease the viscosity of the solution, ultimately leading to decrease in the mean fiber diameter (Li and Wang 2013).

2.3 Properties of Electrospun Nanofibers

PNFs own unique properties such as exceedingly high surface area/unit volume, high porosity, excellent structural as well as mechanical properties, extremely high axial strength and outstanding flexibility, lightweight, cost-effectiveness, etc. (Huang et al. 2003; Baptista et al. 2013). Another promising feature of PNFs is its high feasibility to modify their internal bulk content, a surface structure for carrying diverse functionalities, and, more importantly, morphology. After the synthesis of NFs, they can also be easily functionalized by using processes such as physical vapor deposition (PVD) or chemical vapor deposition (CVD) (Kanani and Bahrami 2010; Zhang et al. 2005). In addition, it is also possible to control the secondary structures of NFs for preparing NFs with porous structures, core-shell structures,

and hollow interiors. These outstanding features make PNFs a potential candidate for the wide range of applications. Electrospun NFs membranes are now being used for sensors, filtration, catalysis, reinforcement for composite materials, protective clothing, biomedical applications including scaffolds for tissue engineering, vascular grafts, bone repair, DDS, wound dressing, implants, etc., space applications, and nano-optoelectronics. Thus, these unique and promising features of electrospun PNFs have been identified and selected as a potential candidate for biomedical applications (Agarwal et al. 2008; Focarete and Gualandi 2013).

3 Biomedical Applications of Electrospun Nanofibers

3.1 Tissue Engineering Applications

Tissue engineering is an interdisciplinary field that unifies knowledge from medicine, material science, biology, and engineering. The damaged cells can be supported by tissue-engineered scaffolds for regenerating new ECM without stimulating an immune response. The natural ECM segregates various tissues, creates a protective meshwork around cells, and also offers anchorage or support to the cells (Agarwal et al. 2008). Tissue engineering scaffolds have the ability to build biological substitutes for restoring, improving, and maintaining the function of human tissues. The designing (or engineering) of polymeric matrices (or scaffolds) plays a crucial role in mimicking the structure as well as the biological functions of the natural ECM. Tissue-engineered scaffolds have been used widely because of its unique features. It has been considered as an alternative field to tissue transplantation of the diseased (or malfunctioned) organs. Every year, millions and millions of people suffer owing to the end-stage organ damage and/or even tissue losses (Kanani and Bahrami 2010). Figure 11 illustrates the basic principle of tissue engineering (Fang et al. 2012). A functional scaffold is said to have high porosity, appropriate distribution of pore size, and also pore interconnectivity. Another requirement is that the scaffold's structural integrity should not collapse the pores during neo-tissue formation. The scaffold should also be non-toxic and biocompatible and is expected to actively communicate with the cells for promoting cell proliferation, cell adhesion, cell migration, etc. (Baptista et al. 2013).

There are two methods that are commonly used for renewing, replacing, maintaining, or healing damaged cells or tissues in the field of regenerative medicine. The first method is to fabricate a carrier from the biomaterials similar to that of the damaged tissue or organ which is first rooted from the analogous cells of the patient, and then, the entire system is implanted into the body. Another method that is currently popular involves preparation of a porous 3D substitute that potentially mimics the natural ECM by itself. Nevertheless, it is very challenging to prepare an effective ECM. A competent analog must mimic the topographical and structural characteristics of the natural ECM, must have the potential to connect with the cells

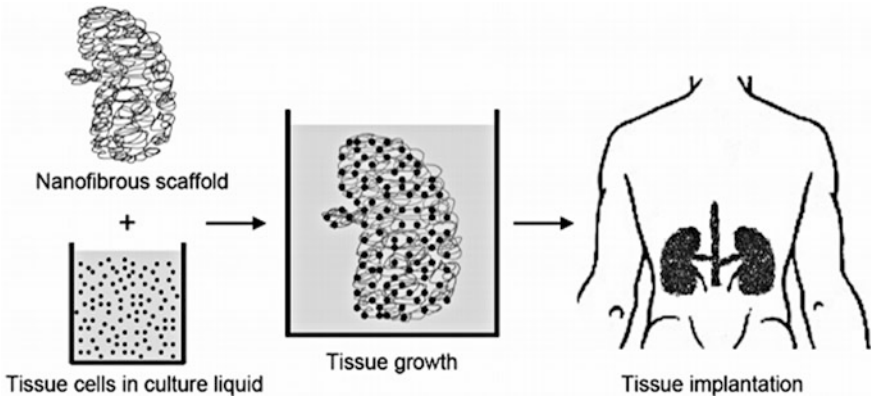

Fig. 11 Illustration of basic principle of tissue engineering. Adapted from Fang et al. (2012)

present in all the 3D, and must also encourage communication between them. Although the physical architecture of the natural ECM is in nm dimensions, it comprises three fundamental groups of macromolecules, viz. (i) filamentary structural proteins (such as collagen, elastin fibers) with 5–500 nm, that offer strength and structure to the matrix or scaffolds, (ii) adhesive glycoprotein that connects the matrix portion to the cells as well as with each other, and (iii) proteoglycans and hyaluronic acid that provide excellent flexibility as well as lubrication to the matrix.

It is a well-known fact that ECM is substantially the most vital part of every tissue as it encases the cells and also generates tissue cells by themselves. ECM, in general, is made up of polymers of fibrous proteins such as collagen and glycosaminoglycans (GAGs) (a form of polymers or proteoglycans made of carbohydrates). ECM usually bestows body support to the tissues/cells (Khan et al. 2012). It plays a greater role rather than merely offering physical supports for the cells; i.e., it regulates cell migration, provides substrates for cell adhesion from specific glands, operates via different bioactive factors, and controls cell growth. At present, the most favorable analogs of ECM are PNFs. This may be attributed to the fact that PNFs can accurately mimic the ECM's fibrillary elements in the most genuine manner. On investigating the human tissues and organs, most of them are in the nm level and are actually hierarchically organized fibrous structures. After embedding the PNFs into the body, it unifies with all those tissues in close proximity to it and bestows efficient cell proliferation, adhesion, differentiation, and migration. They also support neo-vascularization. The PNFs being porous in nature enable the exchange of metabolites and, more importantly, nutrients (Rosic et al. 2013). The electrospun 3D porous NS displays an excellent ability to mimic the structure of natural ECM for providing cell adhesion, movement, invasion, seeding, proliferation, and differentiation and hence becomes a promising candidate to be used in tissue engineering applications (Gupta et al. 2014). The precursor materials used for fabricating scaffolds for tissue engineering should be preferably

biocompatible and biodegradable materials since the incorporated scaffolds should decay with time in the body and restore with newly regenerated tissues. The structure of the scaffolds has a significant impact on the cell binding, and therefore, proper care should be taken to design it. The architecture of fibrous scaffolds, as shown in Fig. 12, is very important and hence affects the cell binding and spreading (Stevens and George 2005; Muzaffar et al. 2018; Asghari et al. 2017; Thangamani et al. 2018; Kishan and Cosgriff-Hernandez 2017; Deshmukh et al. 2017c, d; Turon et al. 2017). The proper selection of the polymer further enhances the biomimetic effects of NFs.

Synthetic polymers such as PCL, PGA, PLA and their polymer blends as well as natural polymers such as collagen and hyaluronic acid can be used to fabricate efficient NFs (Rosic et al. 2013). The biocompatible and biodegradable fibrous scaffolds are prioritized over conventional scaffolds for tissue engineering (Haider et al. 2015). It was validated by several research groups that the usage of pure synthetic or natural polymers alone cannot meet the requisites for creating perfect tissue-engineered scaffolds. Synthetic polymers offer great flexibility during synthesis and fabrication, but they lack cell affinity and surface cell recognition sites and also have low hydrophilicity. On the other hand, the natural polymers are highly biocompatible, but they show poor processability and mechanical properties. It is therefore advantageous to use both synthetic polymers for backbone and natural polymers for cellular attachment so as to fabricate composite NS, which might additionally offer suitable mechanical properties and also bioactive surfaces

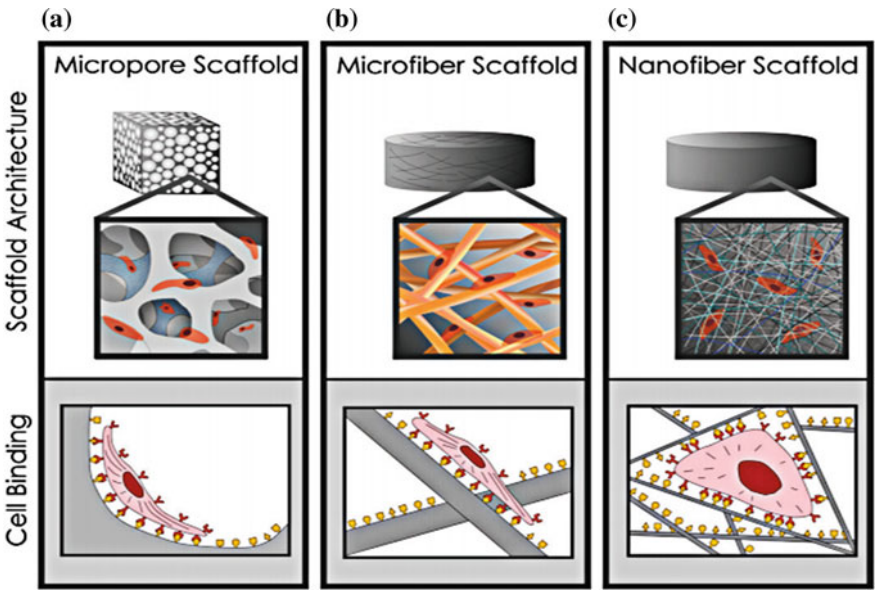

Fig. 12 Pictorial depiction of effect of architecture of NS on cell binding and spreading. Adapted from Stevens and George (2005)

(Wang et al. 2013). There are two types of polymer scaffolds which have been classified based on its degradability for tissue engineering, viz. bioresorbable and non-resorbable polymer scaffolds. Generally, the bioresorbable polymer scaffolds decay with respect to time and the decayed products are found to take part in several other metabolic activities occurring within the body. It functions as a scaffold until the time the new ECM grows and replaces it. These bioresorbable scaffolds are extremely advantageous since their remains need not be surgically removed from the body and hence find a wide range of applications as stents, carriers in controlled drug delivery, surgical sutures, and orthopedic devices. Some common examples are PVA, polyhydroxy butyrate (PHB), aliphatic polyesters, poly (amino acids), or their blends. On the other hand, non-resorbable polymer scaffolds such as polyurethanes (PU), polyethylene terephthalate (PET), and polymethyl methacrylate (PMMA) does not erode within the body as they are inherently strong as well as durable. Hence, these types of scaffolds are observed to be best suitable for permanent encapsulations or supports. In addition, it is mostly utilized in the biomedical field for the permanent or temporary prosthesis (Sharma et al. 2015; Mohanapriya et al. 2015, 2016a, 2017; Pertici 2017; Pasha et al. 2015; Pulapura and Kohn 1992; Zong et al. 2002).

The easy tunability of PNFs via ES process helps to biomimic the natural ECM. A diverse range of heart throbbing natural objects like silver ragwort leaf, lotus leaf, honeycomb, rice leaf, polar bear fur, soap bubble, spider webs, etc., have been depicted in Fig. 13 along with their optical images and the SEM micrographs of electrospun NFs that show similar morphology to these natural phenomena (Wang et al. 2013). The first row in Fig. 13 displays a photograph of the biological structures existing in nature. The next row illustrates optical micrographs of the corresponding micro and nanoscale structures. The third row shows the SEM micrographs of electrospun NFs analogous to the aforementioned natural objects.

The optimization of fiber thickness, alignment, and porosity play a vital role in designing the architecture of microstructure for properly fitting in the appropriate place within the body. For instance, thick-layered NFs offer a good response to the pulsating flow in the artery wall, whereas a structurally oriented NFs better mimic vessels and nerves rather than randomly deposited NFs. The orientation or alignment of NFs appreciably influences the response of the cell, for instance; the cells grown on aligned NFs orient in the same direction of the NFs leading to higher proliferation rate. Another way of upgrading NFs is the surface functionalization, which is either done by adsorption or embedding of compositions such as growth factors and GAGs. The GAGs include hyaluronic acid, chondroitin sulfate, heparin, dermatan sulfate etc. The loading of GAG into the NFs is a perfect way to mimic natural ECM, since GAG can bind various growth factors and also link collagen fibers. In addition, live cells can be included in thicker fibers. Today, PNFs represent a forward-looking approach in tissue engineering for bone, blood vessels, nerves, etc. (Rosic et al. 2013). Xylan can be incorporated with PVA and electrospun to give NFs that are found suitable for skin regeneration (Preethi et al. 2015). The electrospun NS is also used in oral and dental tissues engineering and regeneration as shown in Fig. 14 (Zafar et al. 2016). The functionalization of NFs

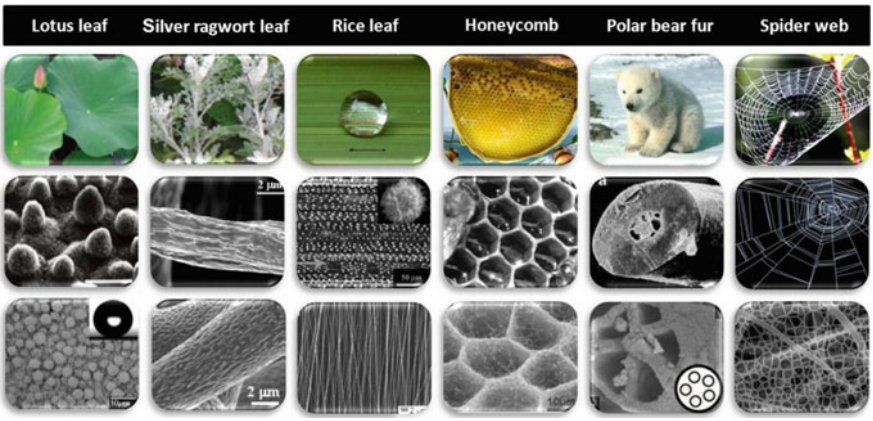

Fig. 13 Biomimetic effect of electrospun nanofibrous structures admired from nature (Wang et al. 2013). Copyright 2013. Reproduced with permission from Elsevier Ltd.

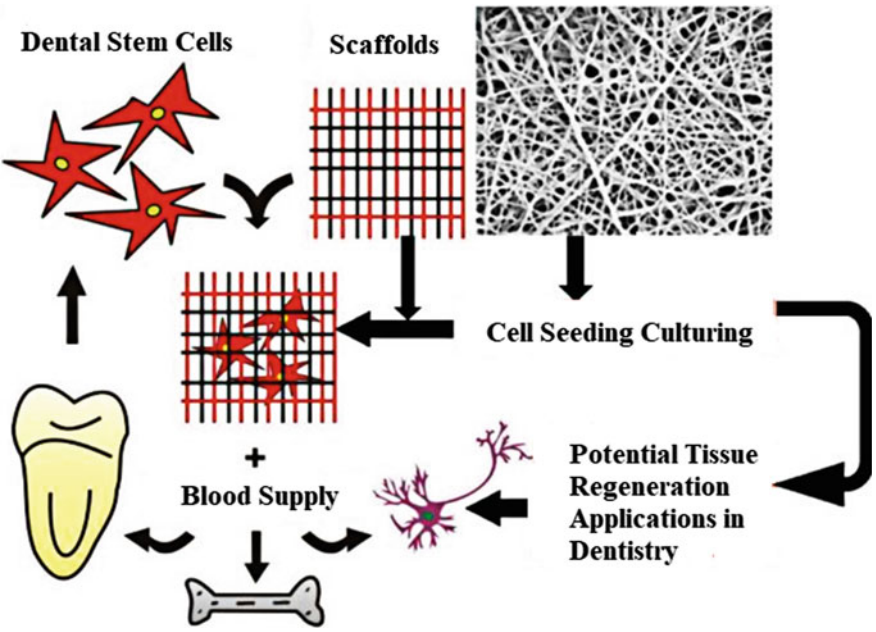

Fig. 14 Pictorial illustration of electrospun NS for tissue engineering of different oral and dental tissues. Adapted from Zafar et al. (2016)

can also be accomplished by incorporating it with bioactive species (e.g., enzymes, DNA, growth factors) that helps to better regulate the cell proliferation as well as cell differentiation that is attached on the scaffolds. These features make electrospun NFs outshining from other processing techniques. Hence, the electrospun NFs are

well-suitable as tissue engineering scaffolds for applications such as nutrient transport, cell communication, and efficient cellular responses (Wang et al. 2013; Liu et al. 2012). There are a number of research studies on core-shell NFs membranes fabricated from coaxial or emulsion type of ES which can be used as scaffolds for tissue engineering applications. Various biomolecules and model proteins have been encapsulated within different polymers to form core-shell configurations. Live cells were also electrospun into fibers using the coaxial ES method (Elahi et al. 2013). A schematic diagram of emulsion-type and coaxial-type ES setup is shown in Fig. 15 (Qu et al. 2013).

In the recent years, Elahi et al. (2013) reported a very simple and alternative setup of coaxial ES instrument as presented in Fig. 16. Here, one capillary is inserted into the other. This setup has two separate syringes with two different capillary sizes. Also, Fig. 17a–c represents the Taylor cone formation as the applied voltage is increased. Figure 17d, e indicates the effect of core diameter on shell thickness. The core-shell NFs seem to be a potential candidate for their simplicity and versatility of encapsulating the biologically appropriate molecules and nanocomposites and also for altering the surfaces of the electrospun NFs. Tailoring the electrical and mechanical properties of NFs plays a pivotal role in tissue engineering (Khan et al. 2012). The biopolymers in the solution or melt form can be normally electrospun using HV in the range of 10–40 kV with an average needle-tip-to-collector distance being about 10–20 cm. Under this processing conditions, the as-spun NF's diameter is about 100–500 nm (Wang et al. 2013).

Even though there is humongous literature on electrospun NFs for tissue engineering applications, there are few limitations of using the electrospun NFs in tissue engineering. One big drawback is the poor infiltration of the cells inside the scaffolds. This is because of the smaller intra-fiber pore size. Various attempts have been made to overcome this hurdle by fabricating scaffolds with a larger intra-fiber pore size that permits the scaffolds to present a 3D environment in place of

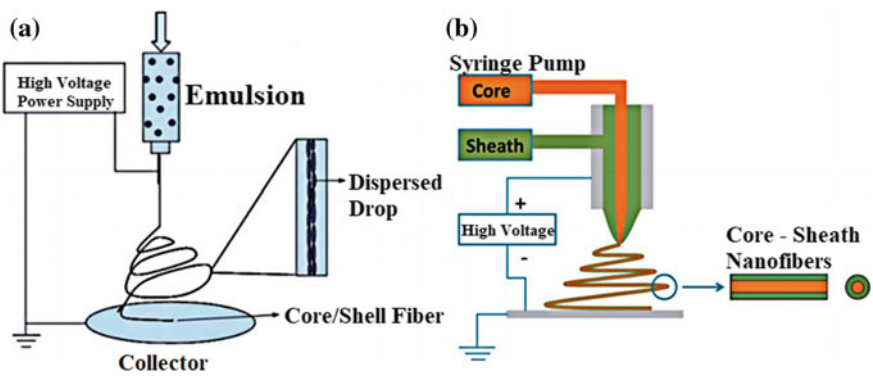

Fig. 15 Schematic diagram for **a** emulsion ES setup and **b** coaxial ES setup; for core–sheath fibers (Qu et al. 2013). Copyright 2013. Reproduced with permission from The Royal Society of Chemistry (RSC)

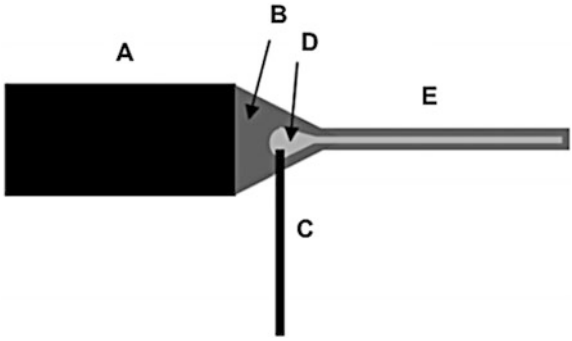

Fig. 16 Alternative and simple setup of coaxial ES process as devised by Wang et al., where **a** a large capillary containing the sheath solution, **b** Taylor cone produced from the sheath solution, **c** a small capillary containing the core solution is directly injected into the Taylor cone formed from the sheath solution, **d** Taylor cone formed coaxially from the core solution within the Taylor cone of the sheath solution, and **e** coaxial jet). Adapted from Elahi et al. (2013)

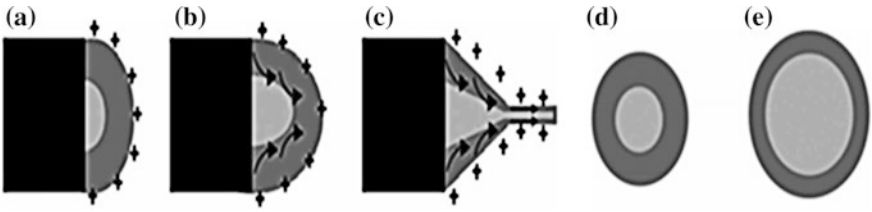

Fig. 17 **a–c** A step-by-step pictorial representation of the production of complex Taylor cone [where **a** formation of surface charges on the sheath solution, **b** formation of viscous force on the core by the distorted sheath droplet, **c** creation of sheath–core complex Taylor cone from the continuous viscous drag]; **d–e** a schematic diagram displaying the effect of core diameter on sheath thickness [where **d** smaller the core diameter implies larger thickness of sheath and **e** larger the core diameter implying smaller thickness of sheath]. Adapted from Elahi et al. (2013)

two-dimensional (2D). The 3D scaffolds have high inner surface area and pore size, thereby exhibiting increased infiltration of cells. The tissue engineering applications such as bone regeneration, vascular grafts, and nerve regeneration require 3D electrospun NS with excellent biocompatibility and physical geometries. Hence, fabricating 3D scaffolds is very important for the scientist and researchers for improving their efficiency in tissue engineering. One of the best ways to produce 3D scaffolds is by fabricating NS with the help of polymer composites. NFs with controlled intra-fiber pore size will be created by combining various polymers that have different solubility and different stretching characteristics (observed at the time of polymer jet flight in between the tip to the metallic collector region). The intra-fiber pore sizes, that are generally controlled and large, help in infiltration of cells. In addition to pores, the usage of wettability of the polymer blends promotes better cell infiltration and adhesion (Haider et al. 2015). Another main challenge is

to design and develop the desired architecture of tissues that are suitable for tissue engineering applications. The natural ECM in terms of the structure contains different interwoven protein fibers having diameters in tens to few hundreds of nm. The practical challenge so far in tissue engineering field is designing the scaffolds that will exactly mimic the tissue architecture at the nanoregime. Additionally, some more issues upon using the electrospun NFs in tissue engineering applications include poor in-depth cell penetration into the NS and poor regulation of pore sizes, solvent toxicity, biomechanical properties, etc., which require immediate attention. In the coming years, the ES approach will undoubtedly stimulate further research in biomimetic scaffold designing for routing out all the limitation witnessed so far in tissue engineering applications (Wang et al. 2013).

3.2 Drug Delivery Applications

Today, the most important concern in medicine is that the therapeutic drug must be given to every individual patient in the most physiologically agreeable fashion. The drug will be absorbed better by the human beings if the geometry of the drug and the coating material desired for encapsulation is smaller. The basic principle on which the PNFs are used for drug delivery applications is that the increase in surface area of the drug and the drug carrier elevates the rate of dissolution of a particulate drug. Figure 18 shows various preparation methods and applications of electrospun drug-loaded PNFs (Yu et al. 2009). Although the development of NFs for drug delivery applications is still in the onset stage of research, a smart as well as real delivery mode must be determined in the future to improve its production and efficiency (Huang et al. 2003; Yu et al. 2009). Controlling the release rate of the drug is a very important requirement in drug delivery applications. In a controlled release DDS, the carrier is loaded with an active substance or the drug and then discharged at a predictable rate. The electrospun NFs that generally possess high surface-area-to-volume ratio is said to provide a convenient pathway for delivering the drug. The release profile in electrospun NFs should be skillfully regulated by tailoring the NF's compositions, morphology, and porosity. The facile nature of ES technique permits the encapsulation of therapeutic compounds within the PNFs. There are several methods to load the drug into the electrospun NFs, such as embedding, encapsulating, and coating, using the coaxial or emulsion ES techniques. In the coating method, the drug molecules will be either absorbed or cross-linked to the surface of the electrospun NFs by physical or chemical means as shown in Fig. 19 (Rosic et al. 2012). The alternative way to produce drug-loaded NFs is by ES a polymer solution containing the therapeutic compound. The major requirement of this method is that both the polymer solution and the drug must be miscible with each other; i.e., the drug particulates in solid state should well disperse into the host polymer solution. The embedding method is highly challenging for loading the bioactive drugs into the electrospun NFs. The highly preferred approach to encapsulate the drug into PNFs is by coaxial and emulsion type of ES.

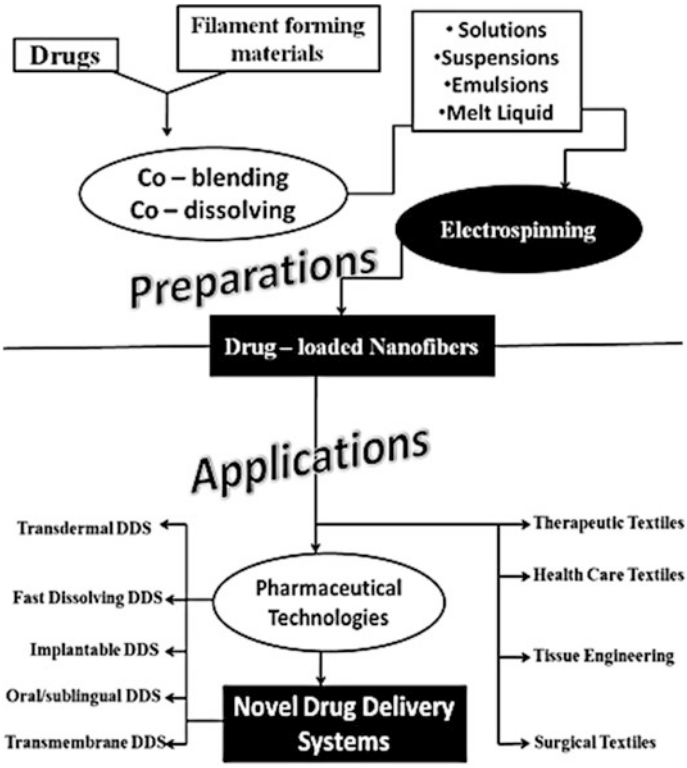

Fig. 18 A flowchart representing the production and applications of drug-incorporated NFs using ES process. Adapted from Yu et al. (2009)

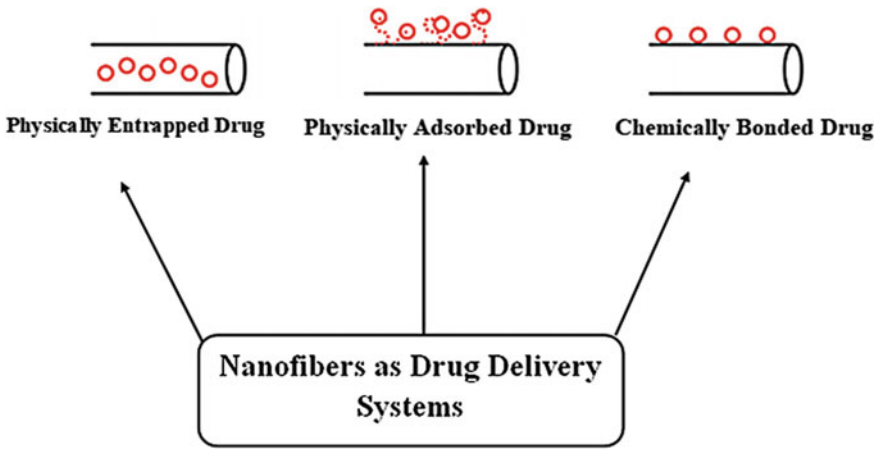

Fig. 19 Schematic representations of various possibilities of incorporating drug in or on electrospun NFs. Adapted from Rosic et al. (2012)

The ES of core-shell and hollow-structured fibers is an easy way to prepare DDS for larger molecules (Baptista et al. 2013).

Currently, the most promising method for producing controlled (or sustained) drug release systems is by coaxial ES technique, wherein the polymer and the drug solution are kept in isolation until they leave the nozzles, and subsequently, the drug gets encased or encapsulated at the central portion of the NFs protected by the polymeric shell. In this process, the burst release is completely evaded as the drug release occurs only through diffusion across a barrier. Figure 20 illustrates the microencapsulation of additives and its controlled release in core-shell NFs (Elahi et al. 2013). The drug reservoirs (shell portion) are mostly biodegradable polymers that permit the regulation of drug release kinetics along with a drug-driven mechanism and a degradation-driven mechanism (Focarete and Gualandi 2013). Even though the electrospun NFs serve as an excellent drug carrier, there are still some serious issues posed by them. The incorporation of voluminous drugs into the PNFs via traditional ES technique leads to poor regulation of the drug release, which can be attributed to the agglomeration and adsorption of drugs at the surface of the NFs. However, the coaxial and emulsion ES process has generated NFs with reduced initial burst/bulk release (Gupta et al. 2014). Many investigations have proved that the surfactant aids in reducing the surface tensions and diameter of the NFs and enhances the drug uniformity, resulting in subdued burst effect (Yu et al. 2009; Deshmukh et al. 2016a, b, c; Zeng et al. 2003; Sill and Recum 2008).

Till date, several drugs such as anticancer agents, proteins, and antibiotics have been loaded successfully into electrospun NFs for drug delivery applications. Besides monitoring the controlled release of a drug, the ES technique also boosts the therapeutic efficacy and reduces the toxicity to a greater extent. The electrospun NFs can be loaded with multiple drugs which can act as a perfect DDC. Figure 21 illustrates the role of polysulfane (PSU) NFs as DDC for bovine serum albumin (BSA) proteins (Haider et al. 2015). The influence of biodegradable and non-biodegradable polymers on controlled and sustained drug release using electrospun NFs has also been evaluated. The PNF drug membranes can be synthesized from both the natural and synthetic polymers. The natural polymers are best suited

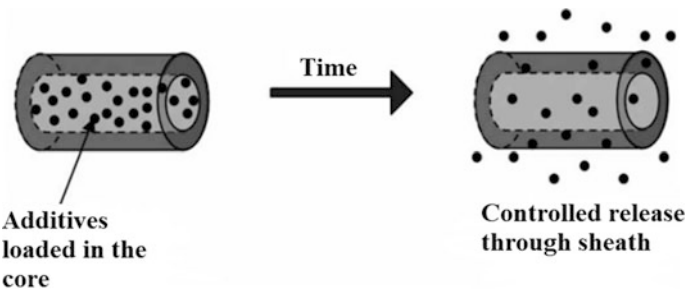

Fig. 20 Pictorial illustration of microencasing of additives and its controlled release rate in the electrospun NFs. Adapted from Elahi et al. (2013)

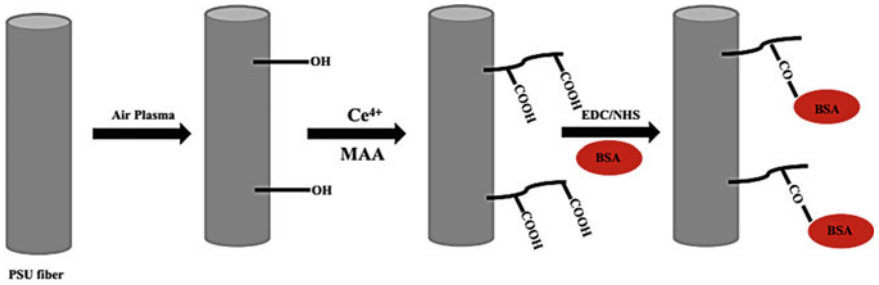

Fig. 21 Illustration of PSU NFs acting as DDC for BSA proteins (*Note* MAA—Methacrylic acid, EDAC—Carbodiimide hydrochloride and NHS—N hydroxysuccinimide). Adapted from Haider et al. (2015)

for biomimicking ECM in tissue engineering, whereas the synthetic polymers incorporated into drugs are useful in drug delivery applications (Sharma et al. 2015; Ma et al. 2006; Deshmukh et al. 2017e; Dhandayuthapani et al. 2011; Sathapathy et al. 2017). In comparison with conventional casting techniques, the drug release profiles of the electrospun NFs displayed better results (Haider et al. 2015).

The factors such as drug loading, drug localization, and drug release highly rely upon the physicochemical attributes of the carrier matrix and the drug. Hence, the loading mechanism of the NFs is controlled by two prime factors (i) the drug solubility in the polymer solution and (ii) the interaction of polymer and drug in the solid state. The amorphous drug having higher solubility is desirable due to the limitation of time available for the recrystallization of a drug during ES. It has also been validated by various characterization studies such as X-ray diffraction (XRD), Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and proton nuclear magnetic resonance (H–NMR) that the application of HV during the ES does not modify the structural, biological, and chemical integrity of the loaded drug (Rosic et al. 2012; Illa et al. 2018; Deshmukh et al. 2017f). PNFs are best suitable for drug delivery and targeted therapies. The drug release profile of PNFs loaded with drug functions on the concept that increase in NF's surface area increases the rate of drug release. The preferable features of polymers used for drug delivery include (i) potential to hold the desirable drug and discharge the same drug in the targeted (diseased or morbid or pathological) tissues, (ii) steady release of drug in the targeted areas for a prolonged period, and (iii) maintain maximum drug loading capacity for releasing the drug for a prolonged duration. The sustained drug release is attained by regulating the porosity of NFs, fiber thickness, and time (biodegradability).

The electrospun PNFs as DDS have numerous advantages. Firstly, PNFs exhibit useful characteristics for delivering a huge number of insoluble drugs as they possess high surface-to-volume ratio. Solid dispersion seems to be one of the good options to improve dissolution rates and bioactivity of the poor water miscible drug. The practical drawback that still limits the use of solid dispersion systems includes complication in traditional preparation methods, insufficient or poor reproducibility

of physiochemical properties, low dosage formation, and poor viability for scaling them up at production (or manufacturing) level. The electrospun NFs have been upgraded with improved dissolution rate for a very poorly miscible compound. Secondly, the modulation of the composition, morphology, processing, and microstructure of the NF mats can help in tailoring the drug release profile easily. Thirdly, various dosage forms can be flexibly designed by using NFs for obtaining maximum bioavailability of a drug moiety for variegated drug delivery routes. Usually, the electrospun NFs incorporated with drugs are mostly considered as mid-dosage forms. Fourthly, the drug encapsulation efficiency of electrospun NFs is higher compared to other nanotechnologies. Few more benefits of drug-loaded NFs include short diffusion passage length due to the small diameter of the NFs, effective drug release, and facilitating mass transfer because of the high surface area of NFs. The 1D structure of electrospun PNFs loaded with drugs is bestowed with many key benefits. One such is that the PNF mat containing DDS in nm scale alters the biopharmacokinetic and biopharmaceutic features of the drug molecule for the desired clinical outcomes. The other benefits of 1D electrospun PNFs include easy processability, excellent drug stability, simplicity in packaging, and freight. To date, in vitro culturing has only been experimented to understand the release profiles of drug-loaded electrospun NFs (Yu et al. 2009). The drawn conclusion from all the foregoing outcomes certainly displays the appropriateness and uniqueness of PNFs as a DDS, which not only keeps a proper check on the desired drug release profile of the specifically loaded drugs but also offers a biomimetic environment in view of commercial applications (Rosic et al. 2012).

3.3 Wound-Dressing Applications

Health is a crucial aspect of human sustenance. The unique characteristics of polymer materials have attracted tremendous attention in a number of biomedical applications. The fundamental objective of wound management is to boost speedy healing and obtaining both functional and cosmetic results. A wound is simply a bruise, cut, or break in the path of any tissues caused due to injury or surgery. Until the mid-1900s, people strongly believed that the wound heals rapidly if it was kept dry and uncovered. But, medically it is proven that keeping a moist environment hugely helps the wound to heal by stopping additional tissue losses from desiccation and boost the activity of lytic enzymes that remove the residual debris in the initial stage of wound healing itself.

Wound healing is a natural body mechanism for restoring the wounded tissues to a normal or quasi-normal state found prior to the wound injury, by regenerating dermal and epidermal tissues via several sequences of complex events. The sequence of complex events involved in wound healing is classified into four phases, namely (i) hemostasis; (ii) inflammation; (iii) formation of granulation tissue; and (iv) remodeling. The intensity and duration of these four phases on the wounds varies from individual to individual depending on their age, nutritional

status, behavior, systemic diseases, medication, and also the depth, size, etiology, and causation of the wounds. Wound dressings are generally divided into three types, namely passive, bioactive, and interactive wound dressings. Generally, passive wound dressings (such as gauze) simply act as a cover to the wounded area. Interactive wound dressings (such as polymer dressings) are permeable in nature. Bioactive wound dressings that usually comprise of antimicrobial drugs, nanosilver, growth promoting factors, and other bioactive ingredients trigger the growth of tissues in the wounded sites (Gupta et al. 2010; Winter 1962).

Winter (1962) studied the effect of polymer film dressing on the wounds of a pig and observed that the wounds healed two times faster with a decent growth of epithelial tissues when compared to air-exposed wounds. The wound care sectors, in the current scenario, are one among the best profitable as well as expanding medical sectors for both wholesalers and retailers. The two methods of wound dressing include wet and dry methods. In the olden days, the dry method of wound dressing was considered as the best practice of healing wounds. Until the 1970s, the common commercial wound-dressing or healing methods included nonwoven rayon and fiber such as polyester and cotton blends, woven cotton gauze, etc. These conventional wound-dressing methods perform several functions such as remove exudates, cushion the wound site, permit drying, hide the view of the wound, and provide a shield from contamination. These dressings are removed very easily for accelerating further drying of the wounded sites. It was proved by Winter (1965) that the air-exposed wound forms a scab that covers the wound, in turn reducing the rate of epithelialization. Hence, the wound healing occurs at a faster rate in a wet environment than a dry one. This is because of the fact that the renewed skins are created without the formation of scab during healing in a wet environment. The moist wound dressing replicates the skin ideally with 85% water content and inherent permeability (Gupta et al. 2010).

Undoubtedly, PNFs can be employed for treating the wounds or burns of all the human skins. The fine NFs formed from biodegradable polymers using electric field can be directly spun onto the wounded or burnt part of the skin, forming a fibrous membrane or mat dressing as shown in Fig. 22 (Huang et al. 2003). Such direct way of forming a fibrous membrane dressing on the wounded sites lets the wound to heal via the growth of normal skin or tissues and eradicates the formation of scar tissue which is usually witnessed in the conventional wound treatment. The pore sizes of the nonwoven NFs membranes for wound dressing are very small (between 500 nm and 1 μm) and therefore can defend the wound from penetration of bacteria via the aerosol particle trapping mechanisms. High surface area (5–100 m^2/g) is mandatorily required for efficacious fluid absorption dermal delivery (Hasan et al. 2014). A comparative study of collagen NS fabricated using freeze-drying and an ES technique was conducted by Powell and his coworkers (2008). The conclusion drawn from their study was that the electrospun NS is alternatives for the scaffolds generated from the freeze-drying method. SEM micrographs of freeze-dried NFs and electrospun NFs of collagen scaffolds are shown in Fig. 23 (Powell et al. 2008).

The selection of ideal polymer is a vital factor to obtain a good electrospun PNF that would be suitable for wound-healing applications. Polysaccharides such as

Fig. 22 Handy ES machine generating NFs for dressing the wound (Huang et al. 2003) Copyright 2003. Reproduced with permission from Elsevier Ltd.

cellulose, chitosan, and hyaluronic acid and proteins such as silk and collagen are electrospun for promoting wound healing. Among which, the chitosan is said to possess both hemostatic and antibacterial properties and is best-suited natural polymer for preparing scaffolds meant for wound-healing applications. Synthetic polymers such as PEO, PLA, PVA, and PCL are also being commonly used for wound-healing applications. The synthetic polymers used for fabricating electrospun NS have good mechanical strength when compared to natural polymers. In addition, these synthetic polymers are soluble in numerous solvents, which further increase its preference to be used in ES process. The wound-healing electrospun NS can be generated by blending natural and synthetic polymer by fine-tuning their morphological, mechanical, and degradation properties for gratifying the needs of individual patients (Ahmad et al. 2014; Sadeghi-Avalshahr et al. 2017;

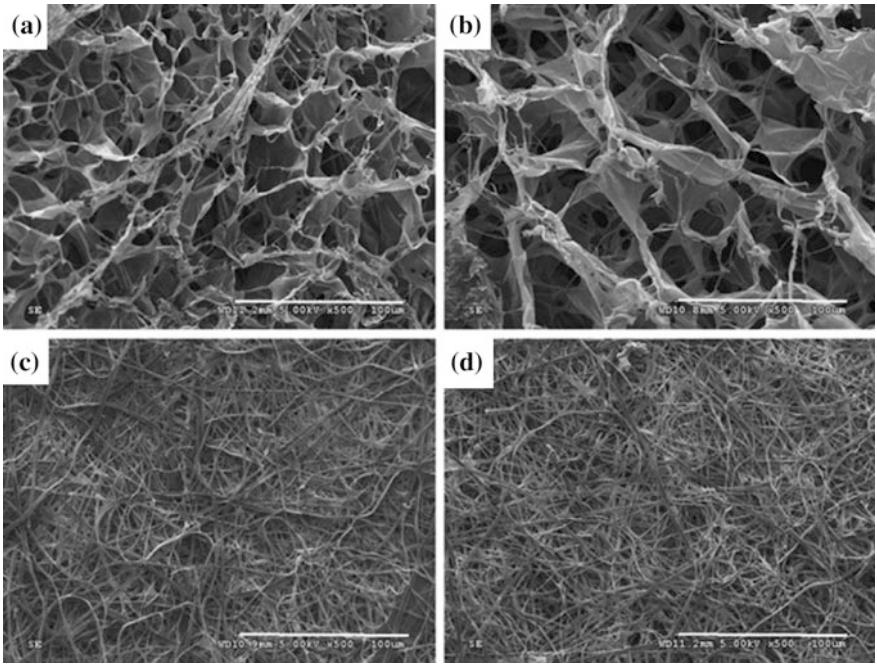

Fig. 23 SEM micrographs of **a**, **b** freeze-dried collagen scaffolds and **c**, **d** electrospun collagen scaffolds (Powell et al. 2008). Copyright 2008. Reproduced with permission from Elsevier Ltd.

Ahmad et al. 2013; Sundaramurthi et al. 2014; Pawde and Deshmukh 2009). Electrospun NS can be used for oxygen permeation, protection of wound from contamination (or infection), and as wound-dressing materials for dehydration. Several synthetic and natural polymers such as collagen, chitosan, carboxymethyl chitosan, silk fibroin, PU, and PEG have been successfully electrospun for wound-healing or dressing applications (Abrigo et al. 2014; Pawde and Deshmukh 2008b; Uttayarat et al. 2012; Deshmukh et al. 2014).

Chronic wounds can be delineated as the delay or disruption in the natural healing of all treated wounds over a period of eight weeks. The chronic wound does not heal easily because of two major reasons: (i) the imbalance occurring between the construction and degradation processes of the tissues in the wounded region and (ii) insufficient or poor formation of a functional ECM. The normal ECM usually functions to encourage, direct, and organize the healing. Thus, fabricating modern wound-dressing materials and methods that exactly mimic the missing tissues is the most intelligible means of treating non-healing/chronic wounds. Therefore, NFs can be used for mimicking ECM efficiently. After dressing the wound with NFs, the cells assume NFs as ECM and stimulate cell growth, cell adhesion, cell differentiation, oriented chemotaxis, re-epithelialization, growth, and deposition of provisional matrices. The addition of NFs as an integrant in the modern wound dressing includes numerous advantages (Gao et al. 2014). NFs can replace natural elastin

and collagen as they have analogous mechanical properties, size, and shape. NFs also discharge the wound exudates out, since they are gas permeable and also, prohibit wound infection. One additional advantage is that if NFs are made of hydrophilic materials, they provide a moist wound environment which seals the epithelial cell migration from the edge to the center of the wound and ameliorates healing (Rosic et al. 2013). Also, the biomimicking property of the nanofibrous membrane promotes wound healing and limits scar formation (Focarete and Gualandi 2013).

Active substances can be loaded into NFs either by physical absorption or by chemical bonding on the surface. The physical entrapment is currently the most common loading techniques among the other loading possibilities, as the drug in the NFs is well shielded against the adverse environmental conditions and also has the ability to regulate drug release in a sustained manner (Mohanapriya et al. 2016b; Rath et al. 2016; Deshmukh et al. 2016d; Aytimur and Uslu 2014). Furthermore, incorporating the drug into the fiber is relatively easy and practical. In this method, the drug to be loaded is simply homogeneously dispersed in the polymer solution before the onset of ES process. Since there is very short time for recrystallization of the drug during the fiber formation, the amorphous drugs are mostly preferred. The ideal drug release profile of such NFs displays a burst effect initially and then succeeded with nearly linear and sustained release. The core-shell NFs can be fabricated, as it provides a drug reservoir system that shields the loaded drug and also regulates the drug diffusion rate. The drug that was first loaded into NFs was antibiotic tetracycline, which was encased within the blends of PLA and copolymer of polyethylene and vinyl acetate. Since then, various other antiseptics, antibiotics, antifungals, non-steroidal, anticancer drugs, biomolecules, anti-inflammatory agents, nucleic acids, etc., have been loaded into or absorbed on NFs. The latest approach that is adapted to control bacterial infections in chronic wounds is by embedding silver nanoparticles into NFs, as it serves as effective antimicrobial agents (Rosic et al. 2013).

The special features of electrospun NFs are the fiber pores and the high surface area which provokes the fibroblastic cell response by swiftly activating the cell signaling pathway. The electrospun NFs also have greater potential to be used in the fabrication of cosmetic mask for skin cleaning and healing. The skin mask prepared from ES has a high surface area which promotes the to-and-fro movement of additives to the skin. These skin masks are highly flexible and hence can easily be applied and removed from the skin effortlessly without causing pain (Kim et al. 2009; Deshmukh et al. 2017g; Pillai and Sharma 2009). The treatment of skin can be further improved by incorporating various factors into the electrospun NF matrix. Some schemes for preparing a suitable wound dressing with antibacterial properties are depicted in Fig. 24 (Haider et al. 2015). Moreover, these scaffolds have the tendency of alluring cells to the dermal layer, which excretes the vital ECM that aids in the repair of injured tissues such as cytokines, collagen, and growth factors. Nonwoven NFs serve as the most appropriate candidate for wound-dressing agents. Therefore, the ES technique can be employed to generate various NSs from raw materials that include hydrophilic polymers and polyesters

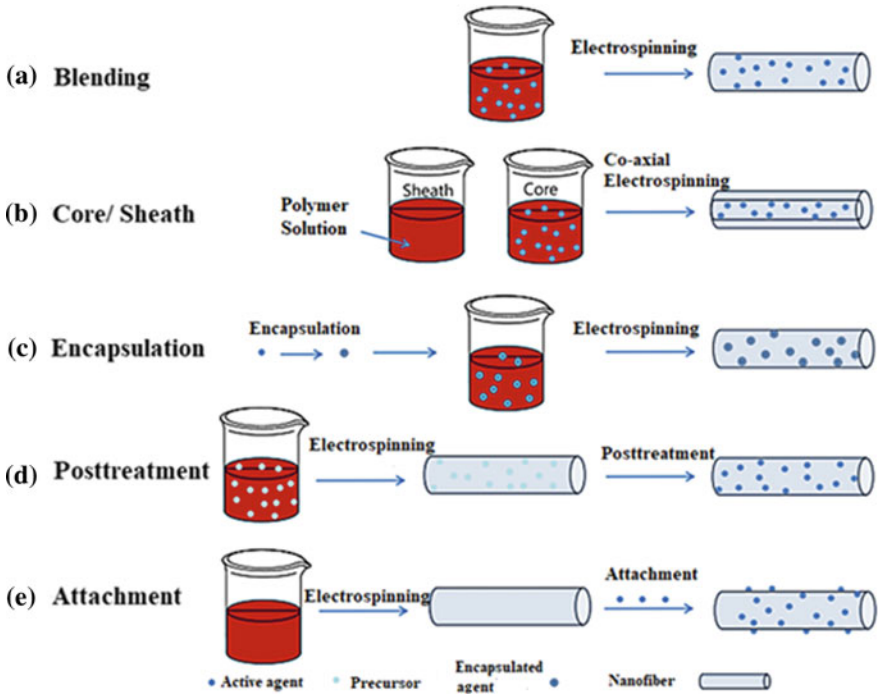

Fig. 24 Different methods adapted for the preparation of suitable wound-dressing materials. Adapted from Haider et al. (2015)

that act as a wound-dressing agents (Haider et al. 2015; Yuan et al. 2016; Kumar et al. 2018; Zhang et al. 2017; Azuma et al. 2015). The properties such as excellent hemostasis, absorbing ability of water exudates, semi-permeability conformability, and functionality must be considered for fabricating electrospun NFs for wound-healing and dressing applications (Zhang et al. 2005).

4 Conclusions

In the current scenario, the field of nanoscience and nanotechnology is highly reliable as it bestows outstanding solutions to the technological problems in comparison with any other conventional systems. ES technique is a well-known, facile, versatile, cost-effective, and simple process for creating highly functional and high-performance PNFs from a diverse range of polymers. These polymers can be used in pure or blended form along with the incorporation of bioactive materials for forming polymer composite NFs. The electrospun PNFs bear especial advantages such as lightweight, high surface area, ultrafine diameter, small pore size, superior mechanical properties, and easy functionalization. Today, the NFs have become

very popular as they offer a pool of opportunities in biomedical applications, viz. tissue engineering, DDS, wound dressings, enzyme immobilization, infiltration, etc. The morphology, topography, and structures of the electrospun NFs can be easily tailored for desired biomedical applications by tuning their properties and processing parameters such as polymer concentration, viscosity, MW, applied voltage, tip-to-collector distance, and solvent. The recent advancement in ES techniques such as emulsion ES and coaxial ES can be a promising solution to the unsolvable problems faced in the biomedical field. Although the number of literatures on the application of ES process in the biomedical applications is humongous, it is highly necessary to assimilate that the research and practical application achieved in this fields is still in its infancy. The research, scientific, academic, and industrial community must start to think about the limitless potential of the ES method and biomedical field and also find infinite ways to interlink the use of electrospun PNFs for biomedical applications, which will undoubtedly uplift the well-being of the humanity.

This chapter has attempted to outline the fundamental aspects of ES mechanisms, the effect of various optimization parameters on the ES process, its properties, and finally, the importance of electrospun PNFs for biomedical applications, namely in tissue engineering, drug delivery, and wound-dressing sectors. The aim of this chapter is to give a better understanding of the all the key control mechanisms of ES that will help to bring progress in smart medicine. Moreover, it will be possible to fabricate multifunctional scaffolds by compiling the knowledge of electrospun NFs for tissue regeneration, drug delivery, and wound dressings, which will lead to the utilization of the full potential of electrospun PNFs for biomedical applications.

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Correction to: Polymer Nanocomposites in Biomedical Engineering

Kishor Kumar Sadasivuni, Deepalekshmi Ponnamma, Mariappan Rajan, M. Basheer Ahamed and Mariam Ali S A Al-Maadeed

Correction to:
K. K. Sadasivuni et al. (eds.), *Polymer Nanocomposites in Biomedical Engineering,* Lecture Notes in Bioengineering, https://doi.org/10.1007/978-3-030-04741-2

In the original version of the book, the following belated corrections have been incorporated:

The co-editor names "Basheer Ahmed" has been changed to "M. Basheer Ahamed" and "Al-Maadeed Mariam Ali S A" has been changed to "Mariam Ali S A Al-Maadeed".

In chapter "Silver Nanoparticles and Its Polymer Nanocomposites—Synthesis, Optimization, Biomedical Usage, and Its Various Applications", the author name "Snehal Kargirwar Bramhe" has been changed to "Snehal Kargirwar Brahme" and the affiliations of authors "Snehal Kargirwar Brahme" and "Subhash Kondawar" were swapped.

The correction book has been updated with the changes.

The updated version of the book can be found at
https://doi.org/10.1007/978-3-030-04741-2_11
https://doi.org/10.1007/978-3-030-04741-2

K. K. Sadasivuni et al. (eds.), *Polymer Nanocomposites in Biomedical Engineering*, Lecture Notes in Bioengineering,
https://doi.org/10.1007/978-3-030-04741-2_13