# Polymers, Blends and Nanocomposites for Implants, Scaffolds and Controlled Drug Release Applications

**Kumar Abhinav Dubey, Chandrashekhar V. Chaudhari, Yatendra Kumar Bhardwaj and Lalit Varshney**

**Abstract** Polymer blends and nanocomposites are widely explored for different biomedical applications such as biodegradable scaffolds, biosensors, implants and controlled drug release. Both, synthetic and semi-synthetic polymers are used in medical applications and have their inherent advantages and disadvantages. Synthetic polymers offer flexibility of varying monomer unit, molecular weight, branching and thus offer a diverse set of physico-mechanical properties, whereas natural polymers offer superior biocompatibility and biodegradation profile. Availability of polymer blending techniques adds another dimension to the property set that polymers can offer, and therefore polymer blending is often used to tailor biodegradability and physico-mechanical properties. Polymers, in general, have poor mechanical properties when compared to metals and ceramics, putting a load bearing limit on polymer-based medical implants. The addition of reinforcing/functional filler is expected to overcome such disadvantages of polymers. Polymers composites are heterogeneous systems wherein polymers are compounded with micron or nano-size particles to render high strength, electrical conductivity or any other functional attribute. This chapter describes the technological aspects of polymer blends and nanocomposites with a specific reference to synthesis, characteristics and applications of multi-phasic polymer systems as implants, scaffolds, and controlled drug release matrices. A detailed account of synthetic and natural polymer nanocomposites along with a brief discussion on important nano-fillers used in medical applications and interface modification techniques is presented. Few examples of recently explored novel polymer blends and composites that displayed promising properties as implants, scaffolds, biosensors and control release matrices have also been discussed.

**Keywords** Polymers · Implants · Tissue engineering · Drug delivery

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## Abbreviations

| | |
|---|---|
| ABS | Acrylonitrile butadiene styrene |
| AFM | Atomic force microscopy |
| $Bi_2O_3$ | Bismuth oxide |
| BN | Boron nitride |
| BNT | Born nitride tubes |
| DMF | Dimethyl formamide |
| CNTs | Carbon nanotubes |
| CTAB | Cetyl trimethylammonium bromide |
| CVD | Chemical vapour deposition |
| EG | Exfoliated graphene |
| EVA | Ethylene-vinyl acetate |
| EPDM | Ethylene propylene diene monomer |
| GIC | Graphene intercalated compound |
| GO | Graphene oxide |
| HDPE | High-density polyethylene |
| HEMA | 2-Hydroxyethyl methacrylate |
| HUVEC | Human umbilical vein endothelial cells |
| LDPE | Low density polyethylene |
| LDS | Lauryl dodecyl sulfonate |
| $MoS_2$ | Molybdenum disulfide |
| MWNT | Multi walled nanotube |
| NCB | Nano carbon black |
| NP | Nanoparticle |
| NCC | Nanocrystalline cellulose |
| NMP | N-Methylpyrrolidone |
| PC | Polycarbonates |
| PCL | Polycaprolactone |
| PDMS | Polydimethylsiloxane |
| PET | Polyethylene terephthalate |
| PEG | Polyethylene glycol |
| PEEK | Polyether ether ketone |
| PEI | Polyethylenimine |
| pHEMA | Polyhydroxyethylmethacrylate |
| PLA | Polylactic acid |
| PLGA | Poly(lactic-co-glycolic acid) |
| PMMA | Poly methylmethacrylate |
| PTFE | Polytetrafluoroethylene |
| PU | Polyurethane |
| PVA | Poly vinyl alcohol |
| PVC | Polyvinyl chloride |
| PVDF | Polyvinylidene fluoride |
| ROS | Reactive oxygen species |
| SC | Sodium cholate |

| | |
|---|---|
| SDBS | Sodium dodecylbenzenesulfonate |
| SDS | Sodium dodecyl sulphonate |
| SEM | Scanning electron microscopy |
| SPR | Surface plasmon resonance |
| STM | Scanning tunnelling microscopy |
| SWNT | Single walled nanotube |
| TDOC | Sodium taurodeoxycholate |
| TEOS | Tetraethoxysilane |
| THF | Tetrahydrofuran |
| TPU | Thermoplastic polyurethane |
| TTAB | Tetradecyltrimethylammonium bromide |
| UHMWPE | Ultra-high-molecular-weight polyethylene |
| VEGF | Vascular endothelial growth factor |
| WS2 | Tungsten sulphide |
| XRD | X-ray diffraction |
| Nd:YAG | Neodymium-doped yttrium aluminium garnet |

## 1 Introduction

Polymers are natural or synthetic macromolecules composed of many repeating units. They offer a variety of properties that make them amicable to different biomedical applications. The earliest use of polymers can be traced back to Mayan civilization though the modern era is believed to be heralded with the discovery of rubber vulcanization by Charles Goodyear in the nineteenth century (Bergström 2015). Today, polymers are among the most widely used materials, surpassing steel, aluminum and ceramics. In medicine, natural polymers are used since long time but synthetic polymers gained significance only in the last few decades. The application domain of polymers is as wide as the property set they offer, ranging from regenerative medicine to orthopedics (Aguilar 2013; Baran et al. 2014; Fabian and Wulff 2014; Hall 2015; Han 2015; Ivanova et al. 2014; Pruitt and Chakravartula 2011; Yang 2015).

Polymers are light, relatively inexpensive and closely mimic biological tissue. Indeed, macromolecules of biological origin were among the first explored for biological application such as sutures. Synthetic polymers though initially thought to have issues of biocompatibility and biodegradability, now play a major role in medicine, due to advancement in polymer synthesis, modification, blending and composite formation techniques. Synthetic biodegradable and biocompatible polymers are also now available and bio-functionalization techniques have been developed to improve interaction between polymers and cells or tissue, through surface modification. Such endeavor felicitates development of highly specialized polymers that serve the desired function, stay in the body only as long as they are

needed and then degrade, avoiding surgical intervention for the removal. Drug delivery systems, orthopedic fixation, ligament augmentation, vascular stents are among the most important medical functions of polymers.

Natural polymers are abundant in nature and are derived from plant or animal resources. Animal horn, a natural thermoplastic protein that is primarily composed of keratin, is reported to be used by medieval craftsmen to make lantern windows and moulded impressions. Cellulose, the most abundant natural polymer was isolated from plant cell wall and its chemical formula was determined in 1838. Cellulose, because of its high crystallinity and strength, can be converted into fiber and can be used for diverse set of applications. Oxidized cellulose suture was patented in 1951, to replace sheep intestines derived absorbable sutures and are still being explored for corporal body grafting and suture-less correction of severe penile chordee (El-Assmy et al. 2007). Chitosan, the second most abundant natural polymer has recently gained considerable attention due to its biodegradability, biocompatibility, antibacterial activity, haemostatic properties and ability to bind lipids. It is linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine and N-acetyl-D-glucosamine, derived from shrimp and other crustacean shells. Alginate, carrageenan and pectin are other promising natural polymers for different biomedical applications. Natural rubber, vulcanization of which is considered an important step in the modern era, is also a plant based polymer, and is used for many surgical and medical applications (Feneley et al. 2015; Teo et al. 2016).

Synthetic and semi-synthetic polymers have their own advantages. They offer flexibility of varying monomer units, molecular weight, branching and thus offer a diverse set of physico-mechanical properties. The first semi-synthetic polymer synthesized was celluloid, a thermoplastic obtained by nitration of cellulose. World's first synthetic plastic claimed is Bakelite; today, a wide range of polymers with extremely high stretchability and strength are available. These polymers can be processed in different shapes, are light weight and meet structural and mechanical characteristics demanded by several medical applications. Polymers are also being extensively researched for the development of new applications, and many polymers are currently used in drug delivery devices, vascular stents, sutures, plastic surgery, orthopedics and orthodontic therapy.

Synthetic polymers can be broadly classified into biodegradable and non-biodegradable polymers, considering the application profile for biomedical applications. Non-biodegradable polymers are the one resistant to enzymatic, microbial or hydrolytic degradation during their application life. Accordingly such polymers are used as implants that are long lasting, in surgical applications or in conditions where in vivo application is desired. For ligament and tendon defects, polypropylene, ePTFE, PET/Dacron and nylon are preferred as they provide better mechanical stability than mammalian collagen scaffolds. Mammalian scaffolds contain type I collagen, type III collagen and elastin; though these biopolymers offers good interaction with the host tissue, their mechanical properties are very poor, leading to poor surgical outcome. Conversely, synthetic polymers mentioned above are durable though they have issues of biocompatibility. Implants, especially

orthopedic and regenerative surgery are increasing employing synthetic polymer based procedures. Biodegradable polymers, as the name suggests, degrade in the biological environment and are supposed to have good cyto-compatibility. Apart from naturally occurring biopolymers mentioned above, synthetically produced biodegradable polymers have also shown promising properties for medical applications. Poly lactic acid, polycaprolactone, poly (lactide-co-glycolide) and polyurethane-urea are widely researched for medical applications including implants and drug delivery (Teo et al. 2016; Ruys 2013).

Availability of polymer blending techniques provides another dimension to the property set that polymers can offer. Polymer blends can be a homogeneous or heterogeneous mixture of two or more polymers that can offer different combinatorial or novel properties (Dubey et al. 2012). One of the major objectives of polymer blending is overcoming the functional deficits of a polymer by adding another polymer. If a polymer is very brittle, it can be made tough by mixing it with a soft polymer; similarly, the biodegradability of polymer matrices can be tuned by making a blend of biodegradable and non-biodegradable polymers and varying the composition. pH stability, temperature stability and other properties can also be tuned by polymer blending. However, the thermodynamics of the polymer blends is generally unstable, leading to phase separation and poor physico-mechanical properties. Efforts are therefore needed to stabilize the morphology of polymer mixtures by tailoring the interface. A more recent development in the blending technology is the stimuli sensitive switching by making shape memory polymers, which are expected to be highly useful in medical applications. Examples of polymer blending include the blending of HDPE and LDPE to achieve intermediate flexibility, or nylon and urethane to achieve a balance of lubricity and elasticity. Additionally, polymers for medical use may be blended with specialized additives for enhancing properties to achieve specific functional requirements. Polymer blends of PC/ABS have been used for housing surgical instruments, PC/PET in surgical instruments and PVC/EVA bags and films for blood storage (Modjarrad 2014; McKeen 2014).

Polymers, in general, are insulators with mechanical properties poorer than metals and ceramics, putting a load bearing limit for polymer based medical implants. Polymers composites are heterogeneous systems wherein polymers are compounded with micron to nanosize particles with high strength, electrical conductivity or any other functional attribute. Nanosize particles have considerably higher surface area than their micro counterparts and have markedly different optical, magnetic and biological properties, allowing a profound increase in the polymer-nanoparticle interfacial area and associated interactions and development of formulations that are high strength, antibacterial or conducting can be realized. Silver nanoparticles based composites are the most notable example wherein antibacterial properties are imparted to the polymer matrices by nanofiller. Efficient interactions between filler and polymer matrix facilitate efficient load transfer and leads to high reinforcement at much lower filler loading. However, as the size of filler decreases, the dispersion and distribution of filler in the polymer matrix becomes difficult; moreover, intrinsic properties of polymer and of nanoparticle

play a crucial role in limiting the micromechanics of the nanocomposites for medical applications.

In following sections, properties of polymers, blends and fillers commonly used in medical applications are discussed with reference to reinforcement, conductivity, magnetic properties, biostability and other functional requirements. A brief introduction to the theoretical aspects of polymer blending, composites, conductivity and interface modification is also made. Finally, few recent examples of polymer blends and composites in regenerative medicine, dentistry and drug release are discussed.

## 2 Fillers for Reinforcement, Conduction, Antibacterial and Other Functionalities

### *2.1 Carbon Nanotubes*

Carbon nanotubes (CNTs) are allotropes of carbon, having tubular structure with exceptional mechanical and electrical properties. High surface area of nanotubes, resistance to metabolism, aromatic structure, tubular geometry and nanosize diameter offers an opportunity of delivering therapeutic or diagnostic molecules drugs directly to targeted cells and tissues. CNTs diameters are of the order of few nanometer and length can be up to several millimeter, translating in extremely high aspect ratio. High intrinsic strength together with high aspect ratio makes CNTs as one of the most promising material for structural applications. CNTs can be visualized as seamlessly rolled graphene sheets. They are commonly categorized as single walled, double walled and multiwalled carbon nanotubes. The mechanical properties of CNTs are considerably higher than conventionally used structural materials. Several theoretical and indirect experimental estimates have been made for the mechanical characteristics of CNTs; however recently mechanical properties of MWNTs were measured directly through stress-strain measurements using an electron microscope. The elastic modulus was reported to be as 0.27–0.95 TPa, strength 10–52 GPa, elongation at break $\sim 5\%$ and toughness of $\sim 770$ J/g. Modulus of 1 TPa and strength of 100 GPa are now commonly accepted for MWNTs. SWNTs have higher strength than MWNTs due to the shear induced sliding of concentric cylinders present in the MWNTs. Though SWNTs have superior mechanical properties, but their dispersion in polymers is generally more difficult than the dispersion of MWNTs. Arc discharge, laser ablation and chemical vapour deposition are frequently used for the synthesis of nanotubes. The arc discharge procedure used for CNT synthesis is similar to the one used for fullerene synthesis. The procedure involves production of arc discharge between two high purity graphite electrodes in an inert atmosphere. After arc discharge for optimum time, nanotubes get deposited on the cathode. This process generally leads to formation of MWNTs but SWNT can also be produced if metal catalysts such as

Fe, Co, Ni, Y or Mo are used. The characteristics of nanotubes formed depend on various processing conditions such as the type of gas, catalyst used and system and plasma configurations. In the laser ablation technique, a high power laser is used to vaporize carbon from a graphite target at high temperature. Almost all lasers are used for the ablation though Nd:YAG (Neodymium-doped yttrium aluminium garnet) and $CO_2$ are most common. Both MWNTs and SWNTs can be produced by this technique. In order to generate SWNTs, metal particles as catalysts must be added to the graphite targets. Carbon nanotubes produced by laser ablation are purer, crystalline and have a narrow distribution of diameters. Chemical vapour deposition (CVD) is presently considered to be the most economically viable process for large scale synthesis of CNTs. In CVD, thermal decomposition of a hydrocarbon vapour is achieved in the presence of a metal catalyst. The process is easy to control and yields high purity nanotubes.

As CNTs can absorb or conjugate with variety of drugs, proteins and genes, they were investigated for drug delivery, gene therapy, immunotherapy, tissue regeneration and bio-sensing in several medical conditions (Gulati and Gupta 2012; Varkouhi et al. 2011; Foldvari and Bagonluri 2008). Functionalizing nanotube surface with polar groups increases the potency of CNTs to deliver therapeutic agents across the cytoplasmic membrane and nuclear membrane. The functionalization also improves CNTs chemical and biocompatibility with cellular components and facilitates cellular interaction. Figure 1 demonstrates the intensity of the free siRNA bands on the gel containing CNT-PEI reduced gradually with an increase of the CNT-polymer ratios (Varkouhi et al. 2011). CNT based drug delivery offers possibility of delivering drug directly inside the cells or tissue, via

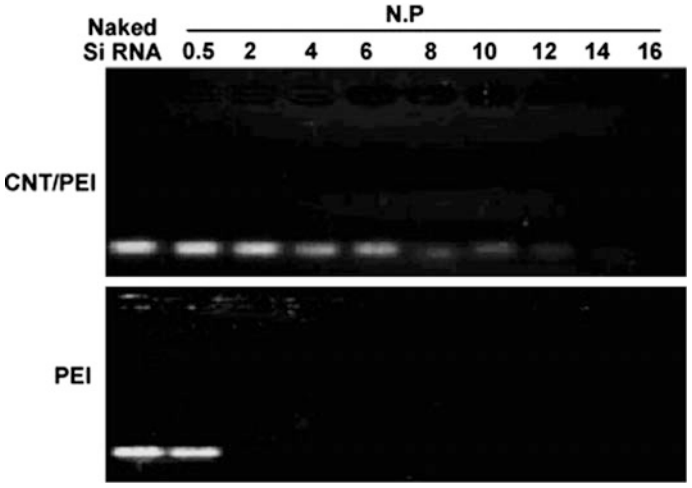


**Fig. 1** Complex formation of CNT-PEI 25 kDa and PEI with siRNA as function of CNT/polymer ratio as studied by agarose gel electrophoresis (Varkouhi et al. 2011). Reproduced with the permission from Elsevier

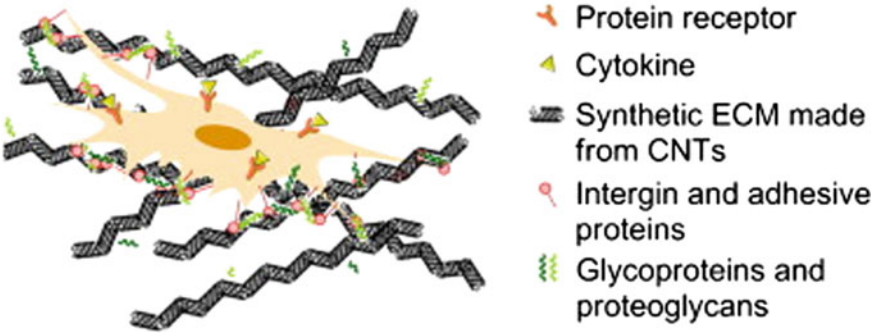


**Fig. 2** Shows the adhesion of cells to CNTs. The adhesive properties of such substrates may have an indirect mechanism, where binding between CNTs first adhere to cell adhesion mediators which in turn adhere to cells (Newman et al. 2013). Reproduced with the permission from Elsevier

endocytosis pathway or via the insertion and diffusion pathway (Maruyama et al. 2015). CNTs have also been reported to enhance the bone tissue regenerations and neural differentiation in murine model (Newman et al. 2013; Park et al. 2013). It has been proposed that CNT first adhere to the cells via cell adhesion mediators (Fig. 2) (Newman et al. 2013). Notably, CNTs are also good free-radical scavengers and therefore are envisaged in alleviating chronic ailments (Nymark et al. 2014; Galano 2008).

## *2.2 Graphene*

Graphene is a two dimensional one atom thick (<1 nm) sheet of carbon with a hexagonal conjugated structure. Due to presence of in plane δ-bonds and out of plane π-bonds, the graphene sheet has exceptionally high mechanical strength, making it strongest material ever discovered. Single-layered graphene exhibits Young's modulus of $\sim$1100 GPa and the tensile strength of 130 GPa. The presence of delocalized electrons in completely conjugated two dimensional network makes the thermal and electrical in-plane conductivity of graphene remarkable.

Graphene can be synthesized both by top-down and bottom up approaches. CVD and epitaxial growth have been extensively used to synthesize graphene; though up-scalability and cost effectiveness of these processes are lower in comparison to top down approach. The epitaxial growth of graphene has been used to grow graphene films on a single-crystal substrate under ultrahigh vacuum at high temperature. Unzipping of CNTs and arc discharge has also been explored extensively for production of graphene. In top down approach, graphene is generated from natural graphite through mechanical peeling, exfoliation or delamination. Graphene intercalated compounds (GIC) or expandable graphene (EG) are also available; in which graphite is intercalated using different reagents.

Graphene based biosensors for glucose, dopamine, DNA and proteins are reported recently. Drug delivery, medical imaging and photo thermal therapy in graphene based systems have also shown promising results. It was demonstrated that graphene oxide (GO) sheets that are soluble in buffers and serum without agglomeration. via π-stacking can be used for loading doxorubicin, a widely used cancer drug onto GO functionalized with antibody for selective killing of cancer cells in vitro (Fig. 3) (Sun et al. 2008). It was also established that dsDNA can bind to GO forming complexes (dsDNA/GO) in the presence of salts, which protects dsDNA from being enzymatically digested, by hindering the access of DNA enzymes (Liu et al. 2008). Graphene has shown increased therapeutic efficacy in phototherapy, as it has strong adsorption in the near-infrared region (Liu et al. 2015). It can be used not only for targeted delivery of molecules but also for ablation of malignant tumours, combining benefits of chemotherapy and phototherapy. The pH or other stimuli sensitive drug release behaviour has also been demonstrated by graphene polymer composites (Karimi et al. 2016). Biosensing applications of graphene and its polymer conjugates are enormous (Pumera 2011). GO has also exhibited high gene transfection efficiency and graphene/chitosan composites produced by solution casting method have also been investigated as scaffold materials in tissue engineering (Fan et al. 2010; Yang et al. 2010).

## 2.3 *Inorganic Fillers*

Inorganic nanoparticles possess unique electronic, optical, magnetic and mechanical properties and can be synthesized by physical or chemical methods. Physical methods involve vapour deposition and mechanical milling whereas chemical routes can be hydrothermal, sono-chemical, solvo-thermal, reverse-micelles, sol-gel, flame spray pyrolysis, organometallic synthesis, microwave method, thermal evaporation and mechano-chemical synthesis. In terms of mechanical reinforcement, silica, $MoS_2$, boron nitride and nanoclays are of special importance. Nanoclays are generally derived from naturally occurring clays such as montmorillonite, bentonite, kaolinite, hectorite, and halloysite. Among them, plate-like montmorillonite and tubular halloysite are the common nanoclays used for polymer nanocomposite synthesis. Like graphene, montmorillonite nanoclays are also nanosize sheets, having lateral dimensions varying from few nanometer to several microns. Though unlike graphene, interlayer interaction is electrostatic. Isomorphic substitution of an atom within the layer by other metal atom leads to generation of negative charge that is counter balanced by hydrated alkali or alkaline earth cations. Presence of week forces between clay layers makes their separation possible with action of suitable surfactant or polymer. Halloysite is also a naturally occurring aluminosilicate that is used for polymer nanocomposite synthesis. Boron nitride nanotubes (BNTs) are also promising filler for polymer reinforcement owing to their high elastic modulus that is comparable to CNT. BNTs are structural analogues of CNTs where C atoms are substituted by alternating B and N atoms.

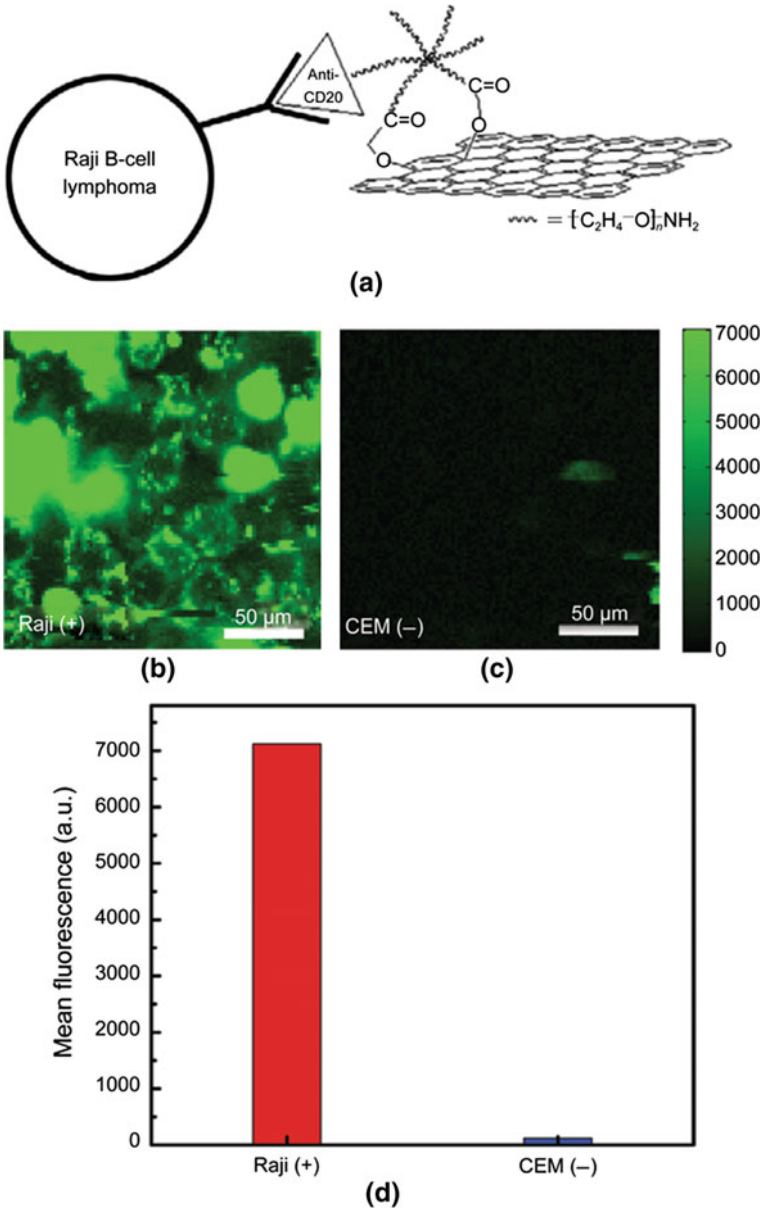


**Fig. 3** Nano-graphene for targeted NIR imaging of live cells. **a** A schematic drawing illustrating the selective binding and cellular imaging of NGO–PEG conjugated with anti-CD20 antibody, Rituxan. **b** NIR fluorescence image of CD20 positive Raji B-cells treated with the NGO–PEG–Rituxan conjugate. The scale bar shows the intensity of total NIR emission (in the range 1100–2200 nm). Images are *false-colored green*. **c** NIR fluorescence image of CD20 negative CEM T-Cells treated with NGO–PEG-Rituxan conjugate. **d** Mean NIR fluorescence intensities in the image area for the both the positive (Raji) and negative (CEM) cells treated by NGO–PEG–Rituxan conjugate (Liu et al. 2008)

$MoS_2$ and the related $WS_2$ nanotubes have also been explored and they offer combination of strength and flexibility.

Metal oxides have been explored for diagnostic applications, and for imparting antibacterial, antifungal properties to polymer matrices (Bhattacharyya et al. 2011; McCarthy et al. 2007). Iron oxide nanoparticles show exceedingly good contrast in MRI; they have high sensitivity and follow metabolic pathways of cellular iron, making them very attractive for clinical applications (Liu et al. 2007). Gadolinium (Gd) is used due to their strong and stable photoluminescence properties (Maalej et al. 2015; McCarthy et al. 2007). Metal nanoparticle preparations have been developed for angiogenesis, cancer staging, tracking of immune cells and cellular targeting (Conniot et al. 2014; Sanna et al. 2014; Weissleder et al. 2014). Figure 4 presents organs and cell type distribution of injected nanomaterials (Weissleder et al. 2014; Keliher et al. 2011). Gold nanoparticles can bind to many different biological ligands as they have affinity for thiols, disulfides, phosphine, and amines (Giljohann et al. 2010). PEG conjugated gold nanoparticle was demonstrated to target the factor receptor (FR) on various cancer cells. The SPR band of the Au NPs can be used to generate heat at the tumour site (El-Sayed et al. 2006). $Fe_3O_4$, gamma phase nanoparticles can also used in hyperthermia treatment, due to their magnetic properties (Gupta et al. 2007). Under magnetic field such nanoparticles and their composites can produce, heat in a controlled fashion due to magnetic hysteresis loss. Au-based nanoparticles are also used as sensitizer in photo-thermal

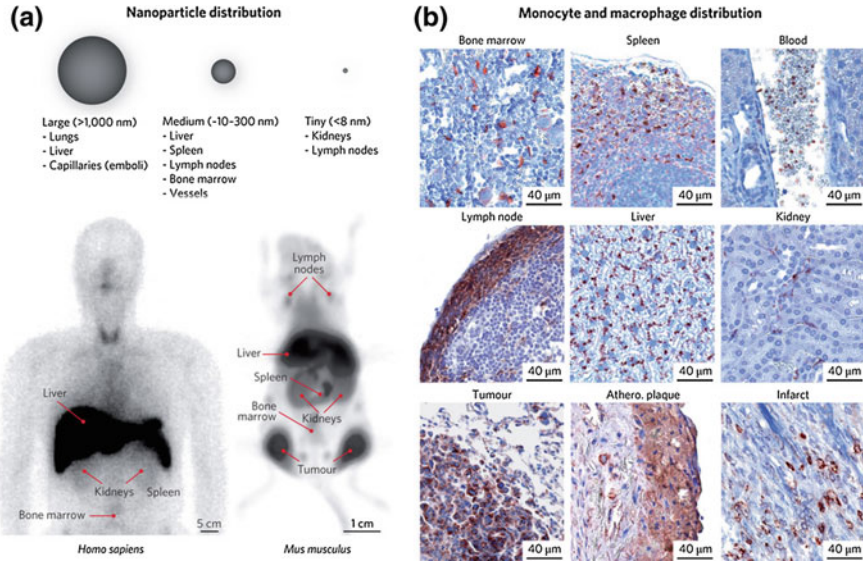


**Fig. 4** Organ and cell type distribution of systemically injected nanomaterials. Most nanoparticles for in-vivo use fall into the intermediate category (10–300 nm), where distribution to liver, spleen, lymph nodes and bone marrow is common (Weissleder et al. 2014). Reproduced with the permission from Nature Publishing Group

therapies. Gd and $CeO_2$ nanoparticles are reported to quench ROS and reduce of mitochondrial damage (Yin et al. 2008). Antibacterial properties are reported in different types of metallic nanoparticles and their oxides. Silver nanoparticles have received highest attention as antimicrobial agent and their several commercial applications have emerged. Silver nanoparticle/polymer based composites are also extensively reported. Aluminium nanoparticles, Aluminium oxide NPs have wide-range of applications in industrial and personal care products. $TiO_2$ nanoparticles show accelerated antibacterial effect under UV light, via production of hydroxyl radicals. Zinc oxide nanoparticles have been found to exert selective toxicity to bacteria (Agren et al. 1991).

### *2.4 Natural Fillers*

Flax, sisal, cotton, coir, ramie, jute and bamboo fibres are widely used in reinforcing polymer composites. Their availability, good mechanical properties, easy processability, low cost, low density, and biodegradability make them attractive choice. However, because of their natural origin their mechanical characteristics and density varies significantly with the source of origin. These fibres are generally of micro scale diameter, and therefore do not show high surface area effect on the polymer reinforcement, as shown by nanosize fillers. Nanocrystalline cellulose (NCC) is a recent development that possesses advantages because of nanoscale dimensions. NCC is generally synthesized by acid hydrolysis of native cellulose and the properties of final product markedly depend upon reaction time, temperature and acid concentration (George and Sabapathi 2015). NCCs are rigid rod-like crystals with diameter in the range of 10–20 nm and lengths of a few hundred nanometres. It has high specific strength and modulus making it a promising reinforcing agent for polymers. Furthermore, natural polymers are attractive for biomedical applications since they are of natural origin, they offer better biocompatibility than synthetic fillers.

## 3 Polymers for Biomedical Applications

Polymers are considered to be exciting matrices for structural applications, by virtue of their light weight, easy processability and long term stability. Large variety of polymers is used for medical applications and can be broadly classified as elastomers, thermoplastics and thermosets. An elastomeric polymer offers high toughness and excellent elongation at break along with good tensile strength. Such matrices are widely used in automobile, space, wire and cable, sports and nuclear industry. Elastomers have high molecular weight, amorphous structure and weak inter and intermolecular forces, translating in low elastic modulus but high elongation. Their glass transition temperature is considerably below room temperature;

therefore at room temperature segmental motions are possible, making them soft and flexible. However, reversibility of deformation demands covalent or ionic linkages between polymer chains. This can be achieved by using peroxides, metal oxides, sulphur, and ionic moieties or by radiation crosslinking. Elastomers are saturated or unsaturated and are used for variety of applications such as tyres, conveyor belts, vibration dampeners and insulating structures. Due to weak intermolecular bonding, elastomers need further reinforcement even after crosslinking to attain desired mechanical properties. Carbon black, fumed silica, clay, talc and mica are commonly used fillers for elastomer reinforcement. However conventional fillers demand high loading, increasing weight, hysteresis and processability. Therefore, there has been considerable interest in using nanofillers for their reinforcement. Elastomers and their composites are used for several biomedical applications. Natural rubber (poly isoprene), polyurethanes, silicones rubbers and thermoplastic elastomers are among the most commonly used elastomers for medical applications such as catheters, vascular access, prosthetic devices, transdermal drug delivery patches and urological aids (Yoda 1998).

Thermoplastics polymers have unique virtue of reprocess ability. These polymers become soft or melt over a specified temperature range and solidify again on cooling. Unlike elastomers, these polymers do not require crosslinking due to the presence of crystalline domain or polar intermolecular interactions. The presence of crystalline and amorphous domains allows a wide range of thermal and mechanical properties, opacity and permeability. The glass transition of thermoplastic can be above or below room temperature. These polymers can be extruded, injection moulded, compression moulded and transfer moulded reversibly. Nanoparticle additions have been reported to significantly improve properties like flame retardancy, durability and elastic modulus of thermoplastics such as acrylic ABS, nylon, polybenzimidazole, polyethylene, polystyrene, polyvinyl chloride and Teflon.

Thermosetting polymers, are highly crosslinked polymers and cannot be recycled or reprocessed. Prior to crosslinking they can be monomers/oligomer (liquid) or molten polymer filled in a mould of predefined shape and size, where in situ crosslinking takes place. Using suitable initiator, sensitizer or radiation, monomers/oligomer (liquid)/molten polymer transform into a highly rigid three dimensional structure. Epoxy, polyurethane and acrylate resins are widely used as thermosetting polymers. They contain un-saturation or highly strained groups that can be crosslinked at room temperature or at high temperature by aromatic/aliphatic amines or anhydrides or by high energy or UV radiation. Generally, high temperature cured thermosets have superior physico-mechanical properties than room temperature cured systems. A variety of fillers are used to improve modulus of thermosetting polymers. Glass fibre, carbon fibre, natural fibres are traditional choice and several commercial applications have been developed using them. Recently there has been a considerable interest in using nanofillers as reinforcing agents for thermosets. Due to their high strength and flexibility thin, yet strong structural objects can be made by using suitable thermosets-filler compositions. However, unlike thermoplastic nanocomposites, thermosets nanocomposites cannot be recycled, involves toxic solvents and are less chemical resistant. Corrosion

resistance, structural integrity, low cost, thermal insulation, and dielectric strength of thermosets make them useful for several medical applications such as medical instrumentation, tools and prosthetics.

# 4 Common Polymers for Biomedical Applications

## *4.1 Synthetic Biodegradable and Non Biodegradable Polymers*

### 4.1.1 Polyolefins

Polyolefins are polymers made of repeating unit of olefin or alkenes. Polyethylene (HDPE, LDPE, and UHMWPE) and polypropylene are two most commonly used polyolefins. They are non biodegradable, hydrophobic, chemical and bacterial resistant thermoplastics. Polyolefins offer different crystallinity, branching and molecular weight options which in turns offers wide property domains to suit different applications. They are low cost, have good environmental stress-cracking resistance and are therefore used for wide range of medical applications including dilators, disposable hypodermic syringes, suture materials, meshes, packaging, medical vials, diagnostic devices, petridishes and surgical components. In cardiovascular applications, polyolefins are utilized as tubing and housings for blood supply. They are also utilized in production of blood bags to store blood. Metallocene PP is one of the polyolefins which has shown great potential in medical applications; UHMWPE is another highly used polyolefin. It has very high molecular weight ($\sim$2 M amu), abrasion resistance, impact strength and a low coefficient of friction and has been used as sliding surfaces of artificial joints in total joint arthroplasty. It is used as artificial hips, knees, as well as in shoulders, elbows, wrists, ankles and spinal disks. The alterative material for such applications is titanium, which offers disadvantages such as cytotoxicity, corrosion and release of metal ions over long term use. UHMWPE is therefore usually used for the replacement of total hip, knee, shoulder, ankle, elbows and spinal disk. It has good stability in radiation field, and is often crosslinked by high energy radiation to improve mechanical properties. UHMWPE based non absorbable sutures are also used for surgical applications as it offers good knot security and precise knot placement. Polyolefin elastomers are also gaining applications for medical applications. Propylene-based elastomers are reported to offer softness of elastomers and drape ability and abrasion resistance of propylene. For outdoor applications polyolefin-based elastomer showed better performance than thermoplastic polyurethane (TPU) material (Patel et al. 2009). In another interesting work, liquid blowout force results demonstrated that polyolefin elastomer offers better properties than silica filled PP (Brostow et al. 2007). In a recent review, titanized polypropylene meshes were compared with polypropylene, polyester and ePTFE

meshes for hernia surgery. For inguinal hernias, titanium-coated polypropylene mesh was associated with less post-operative pain in the short term, lower analgesic consumption and a quicker return to everyday activities (Kockerling and Schug-Pass 2014).

### 4.1.2 Fluropolymers

PTFE and PVDF are two most common synthetic fluorocarbon polymers used in medical applications. They are biocompatible, inert thermoplastic and have a low coefficient of friction. PTFE is used in vascular grafts and heart valves and PTFE sutures are used for repair of mitral valve for myxomatous implantable prosthetic heart valve rings. Elongated-PTFE (e-PTFE) is used in smaller arteries. Another type of PTFE, dense polytetrafluoroethylene (d-PTFE), results in lower levels of early infection following surgical procedures. d-PTFE has been identified as barrier membrane for guided tissue regeneration and guided bone regeneration around teeth and implants. PTFE is also used to deliver coronary stents and other devices as the guiding catheter. PTFE and PVDF membranes are used as filters for biological fluids. Both PTFE and PVDF can be made hydrophilic or oliophilic by surface modification. PTFE has been used in otorhinolaryngology, urology and in the treatment of vesicorneal reflux (Laustriat et al. 1990). ePTFE valve patches/conduits are recognized as excellent material for right ventricular outflow tract reconstruction due to biocompatibility and low antigenicity of ePTFE, and also due to the fluid dynamics of the valve. e-PTFE covered stents have significantly improved two-year transjugular intrahepatic portosystemic shunt patency (Saad 2014). Prosthetic graft PTFE has also been used in above-knee femoropopliteal arterial bypass.

### 4.1.3 Poly(Vinyl Chloride)

PVC is a polymer with an ethylene backbone with one covalently bound electronegative chlorine atom. It is among the most extensively used polymers for biomedical applications. However, for better stability and processability, PVC needs to be compounded with stabilizers and plasticizers, which raises medical concerns. Stabilizers are added to avoid autocatalytic dehydrochlorination and thermal degradation of the PVC chains during thermal processing. Plasticizers are used to enhance the flexibility of PVC, making it suitable for applications such as extracorporeal tubings, sheets and blood storage bags. It has shown direct cytotoxicity mainly due to the presence of stabilizers and plasticizers. Plasticizer di(2-ethylhexyl) phthalate (DEHP) was found to release from the PVC matrix and diffuse into the lipid bilayers of cells. Hormonal imbalance, birth defects and infertility have been reported for DEHP in rodent models. It is however important to note that these toxic effects are not reported upon parenteral administration. Blood storage bags are mostly made of PVC and therefore any leaching of plasticizers or of stabilizers, may

affect the blood component separation and storage. There are developments in the area of DEHP-free PVC bags for platelet storage and plasma storage. However there is no major breakthrough on the storage bags for RBC and still DEHP-plasticized PVC are in use (Prowse et al. 2014; Sampson and de Korte 2011).

### 4.1.4 Silicones

Unlike most of the polymers, which have carbon backbone, silicone based polymers consist of –Si–O– backbone. Silicone polymers are used as oils (oligomers) and elastomers (high molecular weight) in medical applications. The most common silicone polymer is PDMS which contains methyl as side group. Silicones are highly flexible biostable elastomers which present biocompatible, adhesion, hydrophobic, aesthetics, nonirritating and nonsensitizing behaviour. They are used in ophthalmology as tamponade, personal care, cosmetic surgery, topical/transdermal drug delivery and implants (Aliyar and Schalau 2015). PDMS has low surface energy and thus shows limited interfacial interactions with different substrates. Moreover, PDMS do not require stabilizers or plasticizers because of their intrinsic flexibility (low $T_g$) and stability, making them more hemo-compatibile and preferable over PVC. To make PDMS medical grade, impurities, such as catalysts, oligomers can be removed easily. Due to its low surface tension, minimal interfacial interaction, softness and elasticity, PDMS is expected to be associated with low risk of trauma if applied in biological applications. They are permeable to oxygen, carbon dioxide, water vapor and various small molecules, making transdermal drug delivery and wound management applications feasible. PDMS based subcutaneous contraceptive implant based drug delivery systems are used in vaginal ring for treatment of menopause associated urinary problems. PDMS based drug delivery systems are explored for angina pectoris, hormone replacement and pain management. PDMS is also very stable in terms of temperature and radiation sterilization.

### 4.1.5 Polyurethanes

Polyurethanes (PU) contain –NH–(C = O)–O– linkages and come in diverse variety including elastomers, thermoplastics and thermosets. The synthetic chemistry of PU allows offering variable hard and soft segments, aromatic or non aromatic or ester, ether or carbonate based. They are typically synthesized by reacting polyisocyanate with polyols (functionality greater or equal to 2). However non-isocynate based polyurethanes have also been developed (Usman et al. 2016). Aromatic and silicone based PUs shows better biostability, lower cost, high chemical resistance and more toughness, and are promising for long-term implants. In general PUs are biocompatible and hemocompatible, moreover, they do not need plasticizers and have low residual monomers impurities. Different extent of elasticities can be obtained by varying the hard and soft segments ratio in PU. Hard PUs have better biostability

while, soft polyether based polyurethanes, provide better patient comfort due to their soft feel. PUs are used in faecal incontinence as anal plugs (Deutekom and Dobben 2015). Collagen/PU bio-composites have also been used to explore biomedical applications (Zuber et al. 2015). PU is also used as biological adhesive and sealant (Scognamiglio et al. 2016). Elastomeric PU is also used in spinal surgery as disc replacement and stabilization of spinal movement to relieve nerve root compression. The main advantage of PU in such applications is its efficacy in closely matching the mechanical properties of spinal disk and maintaining motion between spinal segments (St John 2014). In a recent study, comparison was made between complications in silicone and polyurethane lines in peripherally inserted central catheters (PICC) in cancer and other patients. It was found that both lines have similar overall average post insertion complication rates; however polyurethane PICC lines were found to provide lower rates of infection, dislodgment, and thrombus and rupture complications (Seckold et al. 2015). Polyurethane coatings are also used in different medical applications, and can be used to impart variety of attributes such as hydrophilicity, non-thrombogenicity, drug release, or lubrication (Associates 2016). Polyurethanes are used in catheters; due to their excellent mechanical properties, very low thickness can be maintained allowing the maximum number of lumens at low outer diameter. PU building blocks can be tailored to offer different property combinations in PU (Aslam and Darouiche 2010); however, the design of polyurethanes for catheter relies on biocompatibility, toughness, good column strength and minimal kinking.

### 4.1.6 Poly Methylmethacrylate

PMMA is a hard polymer which is used in dentistry, ophthalmology, arthroplasty and other orthopedic applications. Its monomer rapidly polymerizes allowing onsite polymerization. It is biocompatible, tough and transparent. PMMA is harmless, however, since in situ polymerization is often used, exposure to methylmethacrylate (MMA) vapours puts a challenge to its use in medical applications (Leggat et al. 2009). In dental applications, use of PMMA is known since long time and was used for fabrication of denture bases. In orthopedics, it is used as bone cements, filler for bone cavities and defects, osteomyelitis and or vertebrae stabilization in osteoporosis (Frazer et al. 2005). Antibacterial agents are often added to MMA based formulations avoid implant related complications (Inzana et al. 2016). Figure 5 shows one interesting applications of PMMA for control drug release applications, wherein PMMA powder, carboxymethylcellulose hydrogel and PLGA microspheres composites were loaded with colistin and demonstrated to show continuous colistin release for 5 weeks (Shi et al. 2010). PMMA is used in non-metal clasp dentures; though other thermoplastics are increasingly explored to avoid the MMA associated complications, PMMA still offers better abrasion and functional properties (Fueki et al. 2014). PMMA is also used as cosmetic filling agent in dentistry and for orofacial medicine (Vargas et al. 2012). In orthopedics, PMMA can serve as a spacer and as a delivery vehicle for antibiotics (Jaeblon 2010; Cancienne et al. 2015).

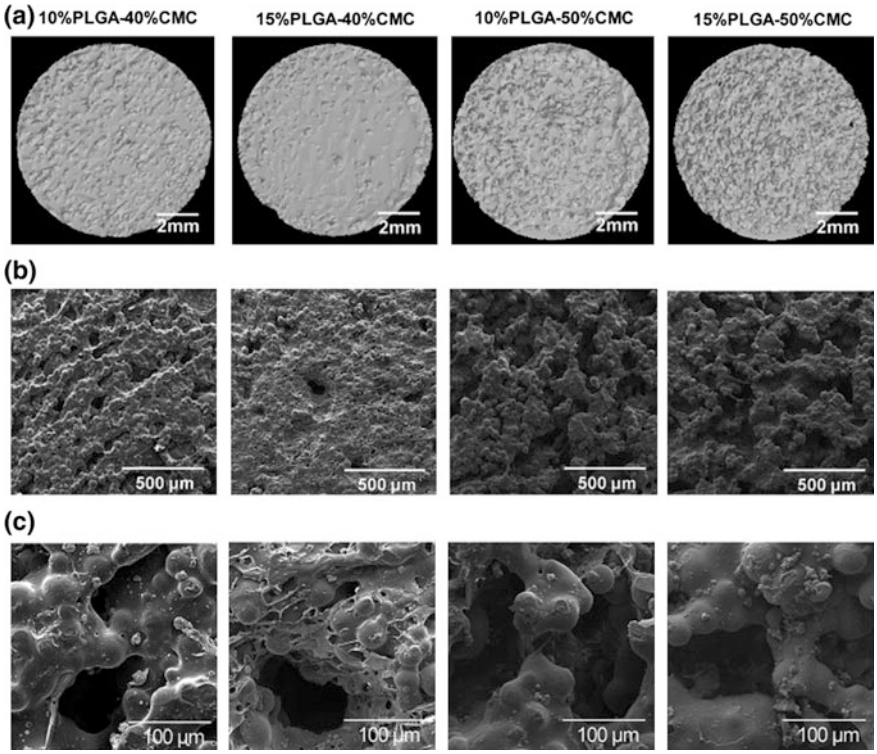


**Fig. 5** Surface morphologies of PLGA microsphere-incorporating porous constructs characterized by **a** micro CT (size bars represent 2 mm); **b** SEM (lower magnification, size bars represent 500 µm); and **c** SEM (higher magnification, size bars represent 100 µm): surface porosity was created by incorporation of CMC hydrogel, and higher percentages of CMC incorporation led to greater surface roughness (Shi et al. 2010). Reproduced with the permission from Elsevier

Another common methacrylate in medical applications is poly-HEMA (pHEMA) made of 2-hydroxyethyl methacrylate monomer. Because of presence of one hydroxyl group per monomer unit, pHEMA is hydrophilic and shows good anti-fouling properties and thus used in hemocompatible coatings or to coat contact lenses (Kluin et al. 2013; Gautam et al. 2012).

### 4.1.7 Polyesters, Polycarbonates and Polyethers

Polyester as the name suggests contains ester linkage and can be of natural or of synthetic origin. Synthetic polyesters are generally non biodegradable and can be thermoplastic or thermosets. Aromatic polyesters are generally bio-stable and are used in membranes, filaments and meshes. Two main synthetic biodegradable polymers are poly (glycolic acid) and poly (lactic acid). The biodegradation of these

polyesters depends on the monomer, molecular weight and crystallinity. The main driving force of using these biodegradable polymers in medical applications is that their degradation involves natural metabolism. These polymers are thermoplastics and can be converted into different shapes to suit different applications ranging from coating to drug eluting stents. Modification of polyesters fibres have also been extensively investigated to make them suitable for different biomedical applications. Sericin-treated polyester fabrics was recently used as medical textile for potential applications in atopic dermatitis, pressure ulcers and rashes (Gupta et al. 2015). Polyesters contain ether linkages and polyacetal, polyether sulfone, polyethylene oxide (PEO) and polyether ether ketone (PEEK) are three major examples of such polymers. Polyether is used in orthopaedic bandages, plasters, in artificial tendon and other implant applications. PEEK is one of the most extensively studied polymer material for medical implants due to its superior biostability, creep resistance and also mechanical and wear properties Polycarbonates are highly rigid plastics; they have been explored for renal dialysis cartridge, heart-lung machine, trocars, tubing interconnector; however, the presence of hazardous ingredients puts a limit to the medical applications of polycarbonates.

### 4.1.8 Polyamides, PVA and EVOH

Polyamides are polymers that contain amide links therefore they represent a wide class of natural and synthetic polymers. Common naturally occurring polyamides are silk and wool whereas common synthetic amides are nylons, aramids, and sodium poly (aspartate). Nylon non-allergenic and resistant to chemicals is used for sutures in applications demanding high strength. Nylons are considered for balloon of catheters for angioplasty and transfusion lines and fittings, due to their excellent burst strength and flexibility.

PVA is derived from poly vinyl acetate by full hydroxylation. It has low protein adsorption, biocompatibility and bio-stability. It is used in soft contact lenses, tissue adhesion barriers, and as artificial cartilage (Baker et al. 2012). Ethylene vinyl alcohol is a copolymer of ethylene and vinyl alcohol. It has exceptional barrier properties making it highly suitable for stormy pouching system and dialysis bags. It has also gain prominence in drug delivery devices and implants.

## 5 Natural Polymers and Their Derivatives for Medical Use

The varieties of chemical structures existing in the natural polymers present precise molecular architecture and rationalize their numerous applications as biomaterials in high technological and biomedical fields. In general, biopolymers are the degradable class of polymers which are the part of or produced by living organisms. In principal, biopolymers are safe materials which can be obtained by processing of monomers or polymers found in nature following the good manufacturing practices

(GMP) and relevant regulations. Presently, biopolymers are used in food, pharmaceuticals, cosmetics, animal feed and other industrial applications. The inherited properties of biopolymers attract its applications as a biomimetic component for biomedical applications, however, some concerns are also associated like undesired active components within natural polymers may provoke immune responses. The most commonly used natural polymers in biomedical applications are described in this section.

## 5.1 Collagen

Collagen is the most abundant structural animal protein accounting for 25–35% of total body proteins in mammals. It is found in connective tissues, skin and in extracellular space and is synthesized mostly by fibroblast cells. It has good tensile strength, molecular weight ~3000 D and tissue dependent rigidity. It has been used in prosthetic heart valves and vascular prosthesis. Compared to the synthetic analogues discussed above; collagen has lesser rejection rate and higher biocompatibility. Collagen based drug delivery systems have been explored to treat infected corneal tissue or liver cancer and bone formation promotion, both as injectable and as oral drug carrier (Khan and Khan 2013). Collagen sponges are used in the severe burns and wound healing and collagen nanoparticles are also used as a sustained release formulation. Collagen based implants have been widely used as vehicles for transportation of cultured skin cells or drug carriers for skin replacement and burn wounds. Collagen has been used as bone substitute due to its osteoinductive activity. Collagen has been used as implantable carriers for bone inducing proteins, such as bone morphogenetic protein 2 (rhBMP-2) (Barboza et al. 2004). Collagen achieves rapid coagulation of blood through its interaction with the platelets providing temporary framework while the host cells regenerate their own fibrous stroma (Yadav et al. 2015). The use of collagen based haemostats has been proposed for reducing blood loss in generalized bleeding in a wide number of tissues and management of wounds to cellular organs such as liver or spleen (Lewis et al. 2016). The various types of collagen (so far 28 types are identified) are different in their structures (Sherman et al. 2015). Due to various types of collagens and their different immunological activity, its partial hydrolyzed form called 'Gelatin' has been extensively studied as a supportive biomaterial (Singh et al. 2011; Tripathi et al. 2009, 2013).

## 5.2 Cellulose, Hemicelluloses and Derivatives

Cellulose is the most abundant naturally occurring polymer. It is the main constituent of plants and natural fibbers. It is a polysaccharide having a linear chain of several hundred to over ten thousand β (1 → 4) linked D-glucose units. Cellulose and its

derivatives are extensively used for different medical applications since several decades. Cellulose ether is used in drug delivery formulations which allow swelling-driven release of drugs. The swelling behaviour can be designed to match the release requirement, as swelling proceeds from the surface to the glassy core of the tablet, the drug progressively dissolves in water and diffuses out from the polymer network. Due to the excellent biocompatibility of cellulose and its good mechanical properties the use of cellulose and its derivatives as biomaterials for the design of tissue engineering scaffolds has been increasing (Müller et al. 2006). Figure 6 represents different type of cellulose scaffolds seeded with primary bovine chondrocytes (Müller et al. 2006). Bacterial cellulose has been widely investigated for wound healing due to its purity and high water retention capacity. Hemicelluloses are the second most abundant polysaccharide after cellulose. Xylans are the main hemicelluloses in hardwood and they also predominate in annual plants and cereals making up to 30% of the cell wall material and one of the major constituents (25–35%) of lignocelluloses materials. Xylan has been considered as a suitable raw material to produce colonic drug delivery systems as it is biodegraded by enzymes produced by the colonic micro flora (Hamady 2013). It is known to induce faecal bulking effect and lowering of blood cholesterol and decrease of postprandial glucose and insulin responses. Some of xylans also show anti-phlogistic effect (Oliveira et al. 2010). Xylan rich hemi-celluloses have been reported to inhibit the growth rate of sarcoma 180 and other tumours, probably due to the indirect stimulation of the non-specific immunological host defence (Zhuang et al. 1993).

## *5.3 Chitin and Chitosan*

Chitin is the second most abundant biopolymer in the world. It is the main component of the exoskeleton of crustaceans and insects, it also occurs, in nematodes and in the cell wall of yeast and fungi. However it is difficult to process as it is not soluble in most of the solvents under room conditions. Generally it is deacetylated to chitosan for practical applications. Chitosan has excellent biocompatibility, bioactivity and biodegradability. It has been known to have antibacterial and anti acid effect (Raafat and Sahl 2009). Chitosan shows antimicrobial action in against great variety of microorganisms, including algae, fungi and bacteria. It has also been found to be a preventive material for dental caries (Chen and Chung 2012). Chitosan has been explored as drug carrier for controlled release, bacterial plaque formation inhibition, decalcification of dental enamel promoting osteogenesis, fat absorbent action and the healing of ulcers and wounds. Chitosan has an in vivo stimulatory effect on both nitric oxide production and modulates peroxide production (Park and Kim 2010). Chitosan has potential to improve drug absorption and stabilization of drug components to increase drug targeting (Ahmed and Aljaeid 2016). In addition, chitosan can protect DNA and increase the expression period of genes (Bozkir and Saka 2004). Chitin or chitosan derivatives, which were conjugated with some kinds of anticancer agents, can execute better anticancer effects

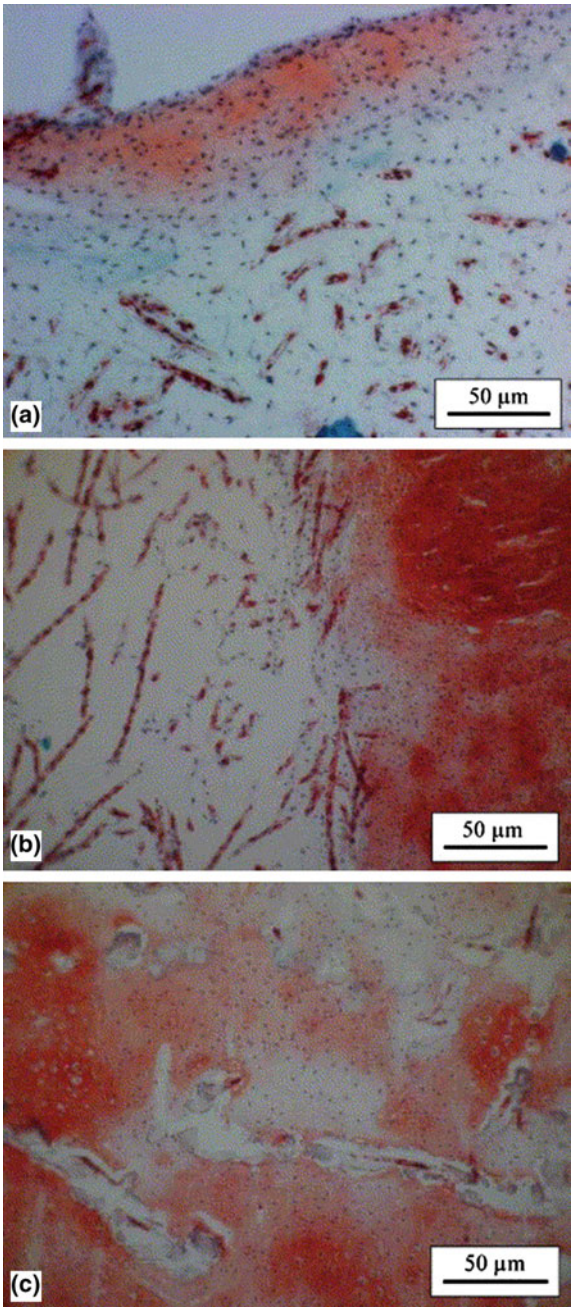


**Fig. 6** Safranine-O staining of cellulose scaffolds seeded with primary bovine chondrocytes, in-vitro cultured for 6 weeks: **a** untreated, **b** $Ca(OH)_2$-treated and **c** CaP-coated samples (Müller et al. 2006). Reproduced with the permission from Elsevier

with gradual release of free drug in the cancer tissues. Chitosan is confirmed to partially inhibit the secretion of both interleukin-8 and tumornecrosis factor-α from mast cells, demonstrating that water-soluble chitosan has the potential to reduce the allergic inflammatory response (Kim et al. 2004). Chitosan promotes phagocytises and production of osteopontin and leukotriene by polymorphnuclear leukocytes, production of interleukin-1, transforming growth factor β1 and platelet-derived growth factor by macrophages, and production of interleukin-8 by fibroblasts, enhancing immune responses (Ueno et al. 2001). Chitosan and hydroxyapatite are among the highly researched bioactive biomaterials in cartilage and bone tissue engineering (Venkatesan and Kim 2010; Bhat et al. 2011; Kathuria et al. 2009).

## 5.4 Alginate and Carrageenan

Alginates are extracted from brown seaweed. Because of its biocompatibility, biodegradability, non-antigenicity and chelating ability (Tripathi et al. 2013), alginate is widely used in a variety of biomedical applications including tissue engineering, drug delivery and in some formulations preventing gastric reflux (Lee and Mooney 2012). Alginates are also widely used for impression making in the dental clinic because of its ease in handling. Carrageenan is a generic name for a family of gel-forming and viscosifying polysaccharides. Carrageenan is a sulphated polygalactan with 15–40% of ester-sulfate content. The anticoagulant activity of carrageenan makes it useful in anti-thrombic applications (Sokolova et al. 2014; Dore et al. 2013). The mechanism underlying the anticoagulant activity of carrageenan involves thrombin inhibition. Carrageenan is a selective inhibitor of several enveloped viruses, including such human pathogens as human immunodeficiency virus, herpes simplex virus (HSV), human cytomegalovirus, human rhinoviruses and others. Carrageenan acts primarily by preventing the binding or the entry of viruses into cells (Grassauer et al. 2008).

## 5.5 Silk

Silk is a natural protein fiber. Silk has been considered biocompatible and used for medical applications for centuries. It has been demonstrated that some of the wild silks have unique properties and are preferred for medical applications. For example spider silk has gained considerable attention in tissue engineering, regenerative medicine and other medical applications due to good elasticity and tensile strength. It showed good attachment and spreading of mouse fibroblast cells suggesting potential for medical applications (Reddy et al. 2013a, b). Recent studies with well-defined silkworm silk fibres and films suggest that the core silk fibroin fibre

exhibits biocompatibility under in vitro and in vivo conditions comparable with other commonly used biomaterials such as polylactic acid and collagen. The ability to genetically tailor the protein in silk provides additional advantages of silk based fibrous proteins. In scaffolds for tissue engineering of bone and ligaments, silk based scaffolds have shown encouraging results (Altman et al. 2003).

# 6 Polymer Blends and Composites for Medical Applications

## *6.1 Theory*

### 6.1.1 Polymer Blending

Blending of two amorphous polymers can produce either a homogeneous mixture at the molecular level or a heterogeneous phase-separated blend. Separation of polymer chains produces two totally separated phases, and hence leads to macro-phase separation in polymer blends. The miscible polymer blend is a blend of two or more polymers that is homogeneous to the molecular level and fulfills the thermodynamic conditions for a miscible multicomponent system. Whereas, an immiscible polymer blend is the blend that does not comply with the thermodynamic conditions of phase stability. Equilibrium phase behavior of polymer blends complies with the general thermodynamic rules.

$$\Delta G_{mix} = \Delta H_{mix} - T\Delta S_{mix} < 0 \tag{1}$$

and

$$\mu_i^{'} = \mu_i^{''} \tag{2}$$

where $\Delta G_{mix}$, $\Delta H_{mix}$, and $\Delta S_{mix}$ are the Gibbs energy, enthalpy, and entropy of mixing of a system consisting of i components, respectively, $\mu'_i$ and $\mu''_i$ are the chemical potentials of the component i in the phase $\mu'$ and $\mu''$. Whether polymers are miscible or not depends on a balance of interactions among all components in a system.

### 6.1.2 Micromechanics of Composites

Mechanical properties of polymer micro, meso or nano composites mainly depend on the polymer matrix, aspect ratio of filler, orientation and packaging density. Polymer-filler interface plays a critical role in determining mechanical properties of the composites. Due to the additive nature of the properties, several models have been proposed to predict mechanical properties of polymer composites. Most of the

work however is confined to fibre-reinforced composites, and the reinforcement theory for nanofillers is not yet fully established. Still, it is proposed that established micromechanical models can be applied to nanocomposites with a great deal of success. Among several models, rule of mixture, Halpin-Tsai and Neilsen's model are most frequently used.

Elastic modulus of the polymer composites in the simplest form can be described by following equation.

$$E_c = E_m V_m + E_f V_f \tag{3}$$

where $E_m$ and $E_f$ are the modulus of the matrix and filler respectively and $V_m$ and $V_f$ are their respective volume fractions. It is assumed that the filler distribution is isotropic and the filler covers full length of the matrix. It is also assumed that the bonding between filler and polymer matrix is strong and under applied stress, filler and polymer are equally strained. However, in practice, most of the composites depart from these ideal conditions and therefore different efficiency factors have been incorporated in the above equation. If reinforcement length and orientation efficiency factors are considered the Eq. (3) is modified as.

$$E_c = E_m V_m + E_f \eta_l \eta_o V_f \tag{4}$$

where $\eta_l$, $\eta_o$ are length (for asymmetric fillers) and orientation efficiency factors. $\eta_l$ can be defined using Cox's shear lag model as follows

$$\eta_l = 1 - \left[\frac{Tanh(\alpha \cdot l/d)}{\alpha \cdot l/d}\right] \tag{5}$$

where $\alpha$ is defined as

$$\alpha = \sqrt{-3E_m/2E_f \ln V_f} \tag{6}$$

Another important concept in determining length efficiency factor is the critical length of the filler which is essential for the stress transfer from the matrix to the filler. Stress transfer is expected to increase as the length to diameter ratio (l/d) of the filler increases, since the surface area is expected to increase with an increase in the length for a fixed diameter. It is therefore possible that at a particular length, transferred stress would be higher than the tensile strength of the filler and may lead to the breakage of the filler. This length is generally defined as a critical length ($l_c$) for a matrix-filler system. Subcritical length will lead to inefficient stress transfer and reinforcement and efficiency factor approaches to 1 as l/d increases. A porosity and filler area (dimension) correction factor can also be introduced in the above equation to take care of porosity generated during composite formation and to take in consideration the fact that dimension of all fillers are not equal. The modified equation can be presented as

$$E_c = [E_m V_m + E_f \eta_l \eta_o k V_f] \cdot (1 - V_p)^2 \tag{7}$$

where k and $V_p$ are dimensional and porosity factors respectively.

Halpin-Tsai model predicts modulus of a polymer composite with oriented filler using following relation (Affdl and Kardos 1976)

$$E_c = E_m \frac{[1 + (2l/d)\eta V_f]}{1 - \eta V_f} \tag{8}$$

where η is defined as

$$\eta = \frac{E_f/E_m - 1}{E_f/E_m + 1} \tag{9}$$

For random orientation, the efficiency factors $\eta_l$ and $\eta_t$ are introduced. The model can be further refined as

$$E_c = E_m \left[\frac{3}{8} \cdot \frac{1 + (2l/d)\eta_l V_f}{1 - \eta_l V_f} + \frac{5}{8} \cdot \frac{1 + 2\eta_t V_f}{1 - \eta_t V_f}\right] \tag{10}$$

where

$$\eta_l = \frac{E_f/E_m - 1}{E_f/E_m + 2l/d} \tag{11}$$

and

$$\eta_t = \frac{E_f/E_m - 1}{E_f/E_m + 2} \tag{12}$$

These models consider aspect ratio as well as filler volume fractions and predict almost linear increase in the modulus whereas some models such as Guth have power functions. In case of symmetrical particles Nielsen's model is generally employed, which has been described as

$$\frac{E_c}{E_m} = \frac{1 + ABV_f}{1 - \psi BV_f} \tag{13}$$

$$A = k_E - 1 \tag{14}$$

$$B = \frac{\frac{E_f}{E_m} - 1}{\frac{E_f}{E_m} + A} \tag{15}$$

$$\psi \cong 1 + \frac{1 - \phi_m}{\phi_m^2} V_f \tag{16}$$

where $E_f$, $E_C$ and $E_m$ are the elastic modulus of the filler, polymer composite and polymer matrix respectively, $k_E$ is the Einstein's coefficient. The constant A takes care of the aspect ratio and orientation of the filler and the factor B addresses relative difference in the modulus of the two components. $\phi_m$ is related to the packing density of the filler and $\psi$ is associated with the filler volume fraction. In case of binary polymer blends, the elastic modulus varies substantially with the variation in the blend composition. Parallel and series model are often used to predict the elastic modulus data of blends. Parallel model which represents the upper bound of modulus values of a binary system can be described as

$$E = E_1\phi_1 + E_2\phi_2 \tag{17}$$

where E is the modulus of blend predicted by the model and $E_1$ and $E_2$ are the modulus of two polymers respectively and $f_1$ and $f_2$ are their respective volume fraction (Dubey et al. 2011). Series model, on the other hand predicts the lower boundary of modulus, as it assumes the components are arranged in series with the applied stress. It can be described as

$$\frac{1}{E} = \frac{\phi_1}{E_1} + \frac{\phi_2}{E_2} \tag{18}$$

### 6.1.3 Electrical Conductivity of Composites

The conductivity behavior of the composites is often governed by a power law:

$$\sigma = \sigma_t(V_f - V_c)^t \tag{19}$$

where $V_f$ is the volume fraction of the filler, $V_c$ is the percolation threshold, $\sigma_f$ is the filler conductivity and t is the critical exponent. For different composites, t and $V_c$ is expected to have different values. To get further insight into the conductivity behavior, additive model and modified Mamunya model can also be employed (Mamunya et al. 1996; Via et al. 2011; McLachlan 1986, 1987, 1988; Michels 1992). Additive model can be described as

$$\log(\sigma) = \log(\sigma_p) + H(V_f - V_C)^{\frac{G}{(V_f - V_C)^n}} + E \tag{20}$$

where σ is the conductivity of the composite, $\sigma_p$ is the conductivity of the polymer and E, G, H and n are adjustable parameters related with the percolation, structure of the filler and surface energy.

## 7 Preparation of Polymer Nanocomposites and Interfacial Compatibility

Solvent mixing, melt mixing, shear mixing and in situ polymerization are some of the most common routes for nanocomposite synthesis. In solvent mixing, fillers are dispersed in a polymer solution and sonication assisted dispersion is generally used to disaggregate fillers. In melt mixing, the fillers are incorporated into molten polymer and distributive and dispersive mixing can be achieved. Another method of nanocomposite synthesis is dispersing nanofiller in monomer and polymerizing the dispersion. Polymer-filler interfacial interactions play an important role in mechanical and electrical properties. Stress transfer from the matrix to filler is necessary for reinforcement. A careful optimization of electrostatic interactions, hydrogen bonding, van der Waals interactions is needed to achieve good dispersion. Covalent or/and non covalent functionalization of the filler surface can be used to improve the interaction between the filler and the surface. In covalent approaches, a functional group or grafting of a suitable polymer is used; whereas, the non-covalent functionalization involves surfactants. Non-covalent modification is easier; though it leads to reduction in the yield strength. Physical modification involving plasma, heat or mechanical treatment can also be used. Chemical treatment using silanes and isocyanates is traditionally used to modify the filler surface.

## 8 Recent Research on Polymer Blends and Composites for Medical Applications

Polymer blending is extensively used to tailor biodegradability, hydrophilicity, mechanical properties, stimuli response, electrical and magnetic properties. Polylactic acid, a biodegradable aliphatic polyester, is among the most promising biomedical polymers; it has been blended with other polymers and reinforced with fillers for different medical applications. Bamboo charcoal particles have been recently used to reinforce PLA and reported 99% enhancement in the flexural strength (Fig. 7) (Ho et al. 2015). On the other hand, blending technology was used to develop PLA based shape polymer alloys which has potential of lifting 50 g of weight and thus claimed to have potential applications in the development of artificial muscles (Song et al. 2015). It has been recently reported that PLA/chitosan/keratin composites have better hardness than pristine PLA and

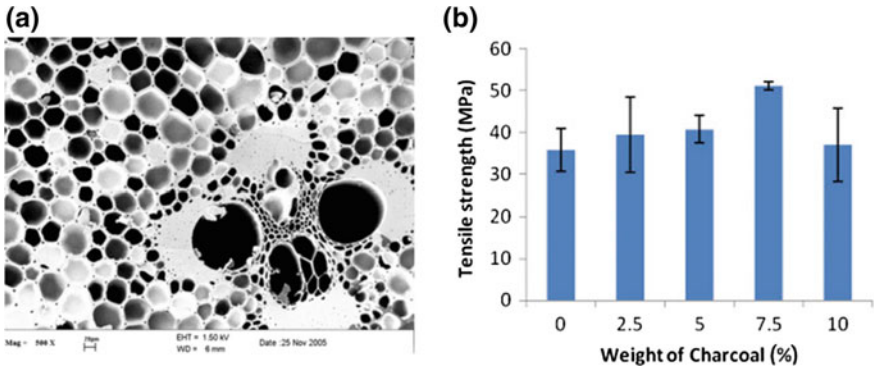


**Fig. 7** **a** The porous structure of bamboo charcoal. **b** The tensile strength of pure PLA sample and BC/PLA composite with different BC contents (Ho et al. 2015). Reproduced with the permission from Elsevier

showed good viability/proliferation outcome in osteosarcoma cell line (Tanase and Spiridon 2014). Large porous PLA/calcium phosphate composite scaffolds were synthesized and cell seeding efficiencies of up to 50% have been reported (Koch et al. 2010; Charles-Harris et al. 2008). Combinatorial advantages of polymer composites were demonstrated in three dimensional porous composite of polylactide-co-glycoside and 45s5 bioactive glass; these composites offer significantly improved mechanical properties and osteointegrative potential than the matrix polymer (Lu et al. 2003). PLGA/alginate composite microspheres have been recently used for hydrophilic protein delivery (Zhai et al. 2015). Notably, cartilage-like tissue formation was reported in PLGA/alginate blends and in alginates, but not in PLGA, clearly indicating advantages of blending PLGA with alginate (Jin et al. 2007). Ulvan, a polysaccharide from green seaweeds (Lahaye and Robic 2007), was blended with polyethylene oxide and polycaprolactone; the blends were able to be electrospun and were proposed for applications in tissue engineering scaffolds, wound dressings, or drug delivery systems (Kikionis et al. 2015). Fucoidan/PCL composite mats were demonstrated to have more widely distributed osteoblast-like cells compared with pure PCL mats (Lee et al. 2012). Polymer blends are also used for the development of effective artificial nerve guide conduit to connect detached peripheral nerve ends (Chiono et al. 2009a, b). PCL guides have been shown to be successful in repairing small and medium size nerve defects by bio-mimetic coatings (Chiono et al. 2009a). Chitosan/gelatin natural blends combined the benefits of protein phase and polysaccharides phase; in in vitro neuroblast adhesion tests. Chitosan/gelatin films showed promising results as artificial nerve guides for peripheral nerve regeneration (Ciardelli and Chiono 2006). Chitosan/gelatin blends were found to show affinity towards neuroblastoma cells adhesion and proliferation at 80 wt% gelatin (Pulieri et al. 2008).

Dental implants are used to support dental crowns and bridges; a ring like implantable device was prepared from a composite of calcium-alginate

hydrogels/polycaprolactone for the localized delivery of metronidazole at the implant location to check bacterial growth (Lan et al. 2013). Hydrophilic polysaccharide and hydrophobic polycaprolactone have been blended for several applications (Garcia Cruz et al. 2008; Ciardelli et al. 2005). Composite polymeric scaffold with topographical cues and sustained biochemical release were also prepared and demonstrated to have synergistic effects on cell behaviour (Cutiongco et al. 2015). Polyvinyl alcohol/dextran blends were used in acute myocardial infarction model. These blends were used for the topical delivery of basic-fibroblast growth factor to promote angiogenesis in ischemic heart disease (Fathi et al. 2013). Polyurethane containing aniline pentamer (AP-PU) was blended with PCL to develop a platform substrate for investigating the effect of electrical signals on cell activities (Baheiraei et al. 2014). Poly(epsilon-caprolactone) scaffold modified by chitosan PCL scaffold were used to explore applications in heart valve and blood vessel tissue engineering (Mei et al. 2005). Figure 8 shows morphology of

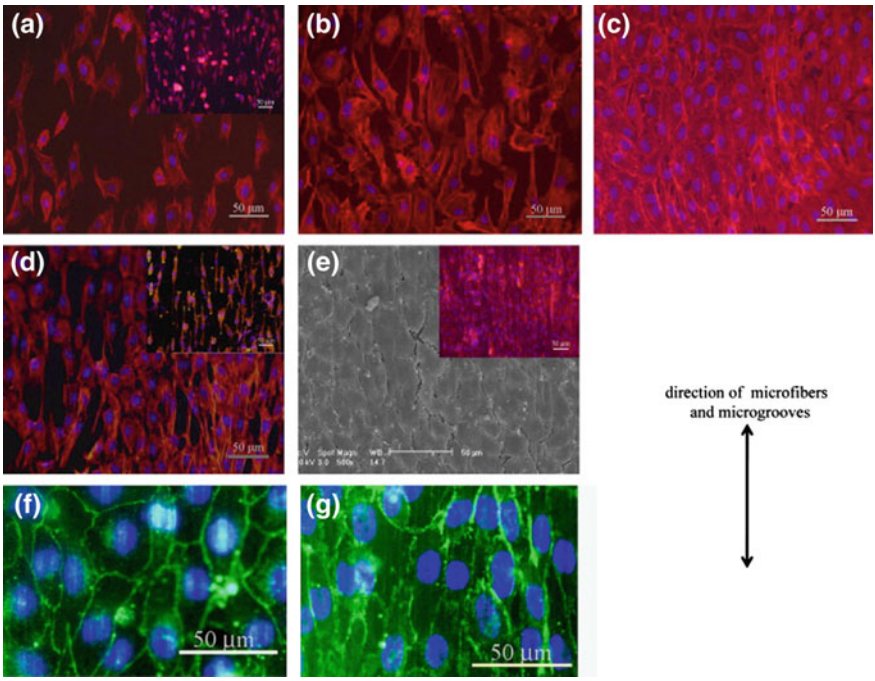


**Fig. 8** Morphology of endothelial cells lining micropatterned grafts. **a–c** Cells cultured inside electrospun grafts patterned with microfibers. Overlays of fluorescently stained actin filaments (*red*) and cell nuclei (*blue*) of BAECs or EA.hy926 endothelial cells (*inset*) at **a** 2 h, **b** day 3 and **c** day 5 post-seeding. **d**, **e** Cells cultured inside hybrid grafts patterned with microgrooves. **d** Overlaid fluorescence image of BAECs or EA.hy926 endothelial cells (*inset*) at day 3 post-seeding. **e** SEM image of a BAEC monolayer at confluence and overlaid fluorescence image of a EA.hy926 endothelial cell monolayer (*inset*). **f**, **g** VE-cadherin staining (*green*) of (**f**) BAEC and (**g**) EA.hy926 monolayers on microgrooves at day 7 post-seeding. Double-headed arrows indicate the direction of microfibers and microgrooves (Uttayarat et al. 2010)

endothelial cells lining micro patterned grafts of three-dimensional electrospun polyurethane vascular grafts (Uttayarat et al. 2010).

Polymer blends and composites are extensively explored for bone repair and regeneration. Chitosan/calcium phosphate (CaP) composites were investigated as a potential implant candidate for bone defect repair. The composite containing the 5 mass/vol.% CaP lasted 40 min in vitro fatigue test until failure occurred (Ding 2006). Collagen/chitosan blend porous scaffolds were found to demonstrate improved biostability for skin tissue engineering. In vivo animal tests of these blend based scaffold revealed that they support and accelerate the fibroblasts infiltration from the surrounding tissue (Ma et al. 2003). Chitosan hydrogels/nano ZnO composite based bandages were prepared for wound dressing. These porous and flexible blends showed enhanced swelling, blood clotting, and antibacterial activity. In vivo evaluations of these bandages in Sprague–Dawley rats revealed faster reepithelialization and collagen deposition, suggesting the use of these bandages for burn wounds, chronic wounds, and diabetic foot ulcers (Sudheesh Kumar et al. 2012). Microspheres made of carboxymethyl chitosan, sodium alginate, and collagen blends showed platelet adherence, platelet aggregation, and platelet activation in vitro (Shi et al. 2016). Chitosan/gelatin blend based sponge has been show to work as an absorbable surgical haemostatic agent with good blood-clotting index at chitosan/gelatin sponge blend ratio of 5/5 (W/W). Blend based sponges showed haemostatic effect in rabbit artery bleeding and liver model tests compared to the two individual components (Fig. 9). No differences were observed in thrombin generation and cell toxicity tests with L929 cells were negative. Most importantly, on subcutaneous transplantation onto rabbits, a complete degradation of blends based sponges was observed along with vascular generation and proliferation (Lan et al. 2015). Chitosan-hyaluronic acid/VEGF loaded fibrin nanoparticles composite sponges were also reported to promote angiogenesis; 60% of the loaded VEGF was reported to be released in three days and Human umbilical vein endothelial cells (HUVECs) seeded on VEGF containing sponges showed tubule formation (Mohandas et al. 2015). Bioactive glass/chitosan/carboxymethyl cellulose blends were also showed potential for bone regeneration and hemostasis in critical-sized bone defects (Chen et al. 2015). Chitosan-hyaluronic acid/nano silver composite porous sponges were developed for drug resistant bacteria infected diabetic wounds and showed sliver nanoparticle dependent antibacterial activity against *Staphylococcus aureus* (Anisha et al. 2013a). Chitosan/PVA composite sponges showed higher haemostatic activity than pure chitosan sponges and erythrocytes cells were found to bind first to the surface of chitosan polymer in the sponges and then promote the binding with other cells in the solution (Chen et al. 2013). Chitosan-hyaluronan/nano chondroitin sulfate ternary composite sponges showed good cytocompatibility, proliferation and cell adhesion studies on human dermal fibroblast (Anisha et al. 2013b). Tranexamic acid-loaded chitosan/alginate composite microparticles were found to achieve hemostasis in $2.48 \pm 0.88$ min and stopped the bleeding in $1.90 \pm 0.75$ min in a liver transfection bleeding model (Li et al. 2012).

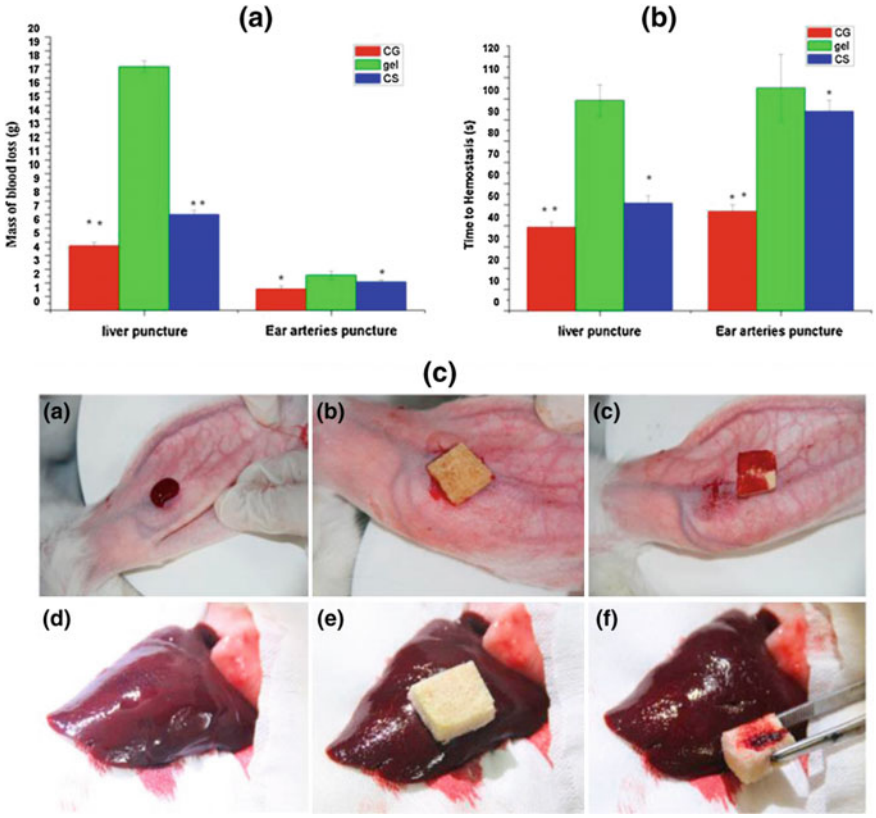


**Fig. 9** **(a)** Blood loss in rabbit liver and ear artery injury; **(b)** Time to hemostasis in rabbit liver and ear artery injury; **(c)** hemostasis for CG composite hemostatic material in rabbit ear artery and liver hemostasis models. *a* Bleeding in freshly cut ear artery; *b* Using a CG composite hemostatic material on ear artery bleeding; *c* Ear artery bleeding stopped by the CG composite hemostatic material. *d* Bleeding when cutting the liver; *e* Using a CG composite hemostatic material on the liver; *f* Liver bleeding stopped by the CG composite hemostatic material. *P < 0.05, **P < 0.01 compared to the negative control analyzed by one way ANOVA with post hoc Scheffe test, N = 6 (Lan et al. 2015). Reproduced with the permission from Elsevier

Polymer/bioactive glass composite containing magnetic nanoparticles were develop for potential applications in the magnetic hyperthermia treatment and drug delivery (Jayalekshmi et al. 2013). Chitosan blended with heparin has shown lower platelet adhesion, significant thromboresistivity and lower haemolysis rate (Wang et al. 2012). Wet chemical synthesis of chitosan hydrogel-hydroxyapatite (HAp) composite membranes was done and biocompatibility studies and cytotoxicity studies on MG-63 osteosarcoma cells suggested that chitosan hydrogel-HAp composite membranes can be useful for tissue-engineering applications (Madhumathi et al. 2009). Chitosan dressings containing polyphosphate and silver nanoparticles were developed for the treatment of haemorrhage and infectious

complications. Procoagulant (polyphosphate) and an antimicrobial (silver) were loaded onto different amount in chitosan; these blends were found to accelerate blood clotting, increased platelet adhesion, generated thrombin faster, and absorbed more blood than chitosan. These composites also exhibited significantly greater bactericidal activity than chitosan (Ong et al. 2008).

Carbon nanotubes and graphene can be used to improve both, mechanical reinforcement and electrical conductivity of the polymers, therefore yielding biomaterials for a wide range of regenerative medicine applications. Dispersion of nanofillers in a polymer matrix is a challenge and as mentioned in the earlier sections, various approaches can be used to improve the filler dispersions. In a recent study, the dispersibility of MWCNTs in polyprolactone and polycarbonate polyurethane (PCU) with an incorporated polyhedral oligomeric silsesquioxane (POSS) was investigated and a computational model that can visualise MWCNTs and predict the chemical concentration for ideal nanocomposites was developed (Antoniadou et al. 2010). Nanocomposites based on poly L lactic acid (PLLA) and MWCNTs showed electrical percolation threshold within a range of 0.21–0.33 wt% MWCNTs and six orders of magnitude increase in conductivity of PLLA by optimal loading of MWNTs. It was found that PLLA/MWCNTS nanocomposites could be suitable substrates for primary stem cell culture (Lizundia et al. 2012). In an interesting work, PLGA/MWCNTs nanocomposites were synthesized via solvent casting technique and rat bone marrow-derived mesenchymal stem cells (MSCs) were employed to assess the biocompatibility of the nanocomposites in vitro. It was shown that the MWCNTs accelerated the hydrolytic degradation of PLGA and the cells could adhere to and spread on composite films via cytoplasmic processes. Furthermore, MSCs cultured onto PLGA/MWCNTS nanocomposites showed improved adhesion, viability and higher production of alkaline phosphates. The authors claimed that these results reflect the potential of thee composite matrices for the development of 3-D scaffolds for bone tissue engineering (Lin et al. 2011).

Designing biodegradable scaffolds with bone-compatible mechanical properties has been a significant challenge in the field of bone tissue engineering and regenerative engineering. PLGA/MWNT composites containing pristine and modified with hydroxyl (OH), carboxylic acid (COOH)) multi-walled carbon nanotubes (MWCNTs), were synthesized as three-dimensional porous scaffolds. It was shown that on adding just 3% MWCNTs, the compressive strength and modulus were significantly increased compared to pure PLGA scaffolds. These composites showed excellent cell adhesion, proliferation and mineralization. On implantation for 12 weeks, carbon nanotube functionalization indicated differences in inflammatory response, OH-modified MWCNTs showed the least response, and COOH-modified CNT showed the highest response (Mikael et al. 2014).

Conducting polymer composites have special significance in context of conducting tissues; however, the use of exogenous electrical stimulation to promote nerve regeneration has achieved only limited success. The design of biocompatible implants for neuron repair/regeneration ideally requires high cell adhesion as well as good electrical conductivity. Conditions impeding optimized outgrowth may arise from inadequate stimulus presentation due to differences in injury geometry or

signal attenuation. Implantation of an electrically-conductive biomaterial may mitigate this attenuation and provide a more reproducible signal. In a recent study, SWNT was selected as one possible material to impart electrical conductivity to a collagen type hydrogel. Neurite outgrowth within hydrogels increased 3.3 folds in 20-μg/mL SWCNT loaded biomaterials relative to the nanofiller-free control. Notably, electrical stimulation promoted greater outgrowth within SWCNT-free control; while combination of electrical stimulation and SWCNT-loading resulted in a markedly enhanced increase in outgrowth (Fig. 10) (Koppes et al. 2016). Recently, surface modified CNT and polymer composites have gained special attention. It was shown that plasma-treated chitin carbon nanotube composite scaffolds offers good neuron adhesion and supports of synaptic function and was claimed to have potential applications as an implantable electrode for stimulation and repair of neurons (Singh et al. 2016).

Magnetic field stimulation through polymer/magnetic filler composites can be useful in several therapeutic and diagnostic applications. Compounding of magnetic filler with a polymer matrix is a very common technique to achieve this. Core-shell particles can be made wherein, the polymer outer layer will stabilize the magnetic shell, that can add stimuli response or target the delivery and also tune the magnetic properties (Rodriguez-Arco et al. 2016). The development of a soft and multiple-environment-adaptive robotic platform with ferromagnetic particles impregnated in silicon-based polymer was recently reported; this flexible platform of human skin-like material was found to have controllability which can be operated like a human finger to manipulate biological objects (Gao et al. 2016). For molecular imaging novel core-shell magnetic microsphere for dual modal magnetic resonance imaging (MRI) and optical imaging was produced by one-pot emulsifier-free emulsion polymerization, which could provide high resolution rate of histologic structure information and realize high sensitive detection at the same time. The synthesized magnetic microspheres composed of cores containing oleic acid (OA) and sodium undecylenate (NaUA) modified $Fe_3O_4$ nanoparticles and styrene (St), Glycidyl methacrylate (GMA), and polymerizable lanthanide complexes (Gd(AA)3Phen and Eu(AA)3Phen) polymerized on the surface for outer shells. In vitro and in vivo MRI studies exhibited high signal enhancement on both T1- and T2-weighted MR images. These fascinating multifunctional properties suggest that the polymer microspheres have large clinical potential as multi-modal MRI/optical probes (Zhang et al. 2016). Chemically synthesized magnetic nanoparticles containing polyethyleneglycol-lactate polymer (PEG-LAC), chitosan, and polyethyleneimine were used as a gene delivery vehicle for enhanced siRNA delivery into cells has been explored (Arami et al. 2016). Notably, a series of pH and temperature-responsive polymer grafted iron oxide nanoparticles were prepared in a recent study, by simple coupling of aminated iron oxide nanoparticle with poly (N-isopropylacrylamide-ran-poly(ethylene glycol) methyl ether acryl ate)-block-poly(acrylic acid) (Dutta et al. 2016).

Nano-hydroxyapatite/gelatin nanocomposite scaffold were demonstrated to support cell adhesion and to heal the critical size bone defect created on rat calvarium (Samadikuchaksaraei et al. 2016). Polyvinyl alcohol and

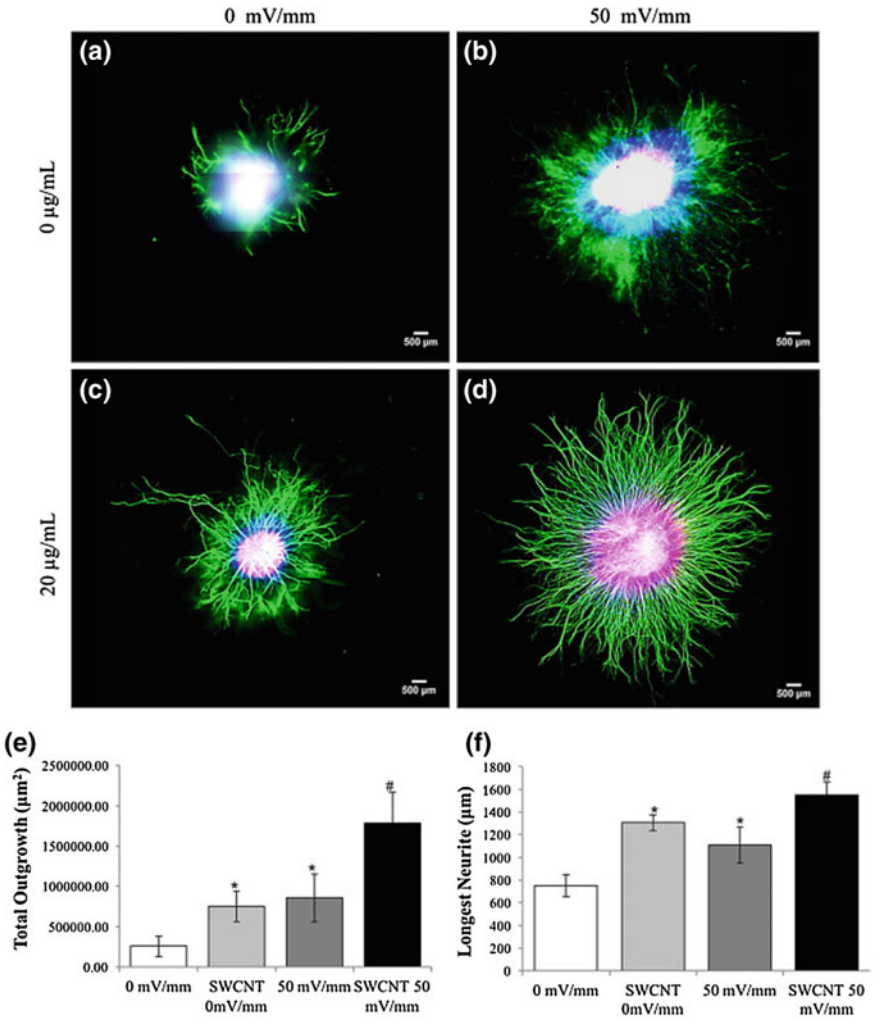


**Fig. 10** Electrical stimulation enhances neurite outgrowth in SWCNT composite hydrogels. Neurite outgrowth is promoted by either electrical stimulation with 50 mV/mm (DC 8 h, 1 mA) (**b**) or inclusion of 20 µg/mL SWCNT within hydrogels (**c**) compared to control (0 µg/mL) hydrogels (**a**) with significant increases in outgrowth (**e**) and neurite length (**f**). When SWCNT are combined with 50 mV/mm, a robust increase of neurite outgrowth is observed compared to either singular cue alone (**d**) and significant increases are observed in both total neurite outgrowth (**e**) and neurite persistence length (**f**). *Green* = β-III-Tubulin neurites, *Red* = Phalloidin actin, *Blue* = DAPI nuclei, Bar = 500 µm, 20 ×. ∗ = $p < 0.05$ compared to all conditions, n = 3, standard error shown (Koppes et al. 2016). Reproduced with the permission from Elsevier

polyvinylpyrrolidone blend containing different concentrations of bioactive nanohydroxyapatite (nHAp) demonstrated higher effective conductivity and effective dielectric constant than those of PVA, PVP or nHAp. Enhancement of

electrical conductivity was reported to result in the increased biocompatibility of the fibrous scaffold (Chaudhuri et al. 2016). As stated above, the addition of graphene and graphene oxide nanosheets to bioactive polymers could enhance their electrical conductivity. Polyaniline and polyacrylonitrile composites with graphene and graphene oxide nanosheets were demonstrated to have a higher proliferation and differentiation of satellite cells (Mahmoudifard et al. 2016). Li et al. recently, reported three-dimensional nanocomposite scaffolds by mixing type I collagen extracted from porcine skin and polyvinyl pyrrolidone coated titanium dioxide ($TiO_2$) nanoparticles. These PVP-containing scaffolds have four times higher strength than that of scaffold without PVP, therefore degradation resistance was enhanced however, ultimate percentage of elongation decreased (Li et al. 2016). In general, for bionics and tissue engineering applications, the nano-composite films with highest electrical conductivity and moderate roughness showed highest cell attachment and proliferation (Gopinathan et al. 2016).

## 9 Future Scenario

Polymer nanocomposites and blends offer tremendous opportunity and their applications covers almost entire domain of medicine and surgery. Tissue culture, biosensing, surgical implants, drug delivery are among major areas wherein polymers are extensively used. Polymers can be biodegradable or non-biodegradable and hence can be used for diverse set of medical applications, depending on the functional requirement. With the advent of conducting fillers, a new era has emerged for the development of conducting scaffolds for applications such as nerve cell regeneration. Plastic and reconstructive surgery is increasingly using polymer nanocomposites and blends, for wound healing and regeneration. Many polymer based drug delivery systems have achieved commercial success and many are in developmental stage. However, the concerns related to toxicity of plasticizers and residual monomers in polymers used for medical use still needs to be further addressed. Efforts are needed to produce medical grade polymers with high reliability. In case of hybrid systems, especially for nanofiller based composites; a careful cytotoxicity analysis is needed to weigh all possible risks. Feasibility of sterilization of the polymer based formulations should also be kept in mind for the products to be used for medical applications.

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