Chapter 6
Fabrication of Stimuli-Responsive Polymers and their Composites: Candidates for Resorbable Sutures

Deepshikha Das, Neha Mulchandani, Amit Kumar and Vimal Katiyar

Abstract Sutures are known to facilitate wound healing and recently, a significant attention has been laid on the development of different classes of materials, their properties to enhance tissue approximation and wound closure. The advancements in the suture technology have introduced different types of sutures such as barbed sutures, antimicrobial sutures, drug-eluting sutures. The biostable and bioresorbable materials have received importance in augmentation and proper growth of the tissues due to their extraordinary characteristics. Furthermore, the biodegradable polymeric sutures have been explored for suture applications due to their efficiency, both in terms of property and application. In this regard, the current chapter highlights the various biodegradable polymers as possible candidates for sutures along with their essential properties and applications. Moreover, the utilization of different biofillers for fabricating sutures along with various fabrication techniques is discussed. Additionally, an impact is laid on the development of 'stimuli-responsive sutures' in order to tailor the behavior of the suture for subjected applications by using external agents or stimulus. These materials respond to small changes that can be both physical and chemical environment. Electric field, magnetic field, radiation are some of the stimulants that can be used based on the polymer used and nature of the application (cell adhesion, nerve regeneration, drug delivery, degradation control, antimicrobial, etc.) of suture. Magnetic responsive composite materials possess fine tuning properties which find their potential in biomedical, cell guidance and controlled drug release study (hyperthermia effect). A good understanding in terms of application and physical phenomena is portrayed which would help in developing the stimuli-responsive materials and devices in the biomedical field.

Keywords Biodegradable polymers · Composites · Bioresorbable · Stimuli-responsive sutures

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1 Introduction

The development of biomaterials in today's era is one of the significant research challenges evolving in the areas of medicine and tissue engineering. Based on their behavior in the living tissue, these materials are divided into biodegradable and bio-absorbable materials. Biodegradable polymer-based materials are nowadays becoming an obvious choice for preparation of biomaterials for their degradable behavior, compatibility with living system and non-toxic nature. The biodegradable polymers degrade into the host and are removed thereafter, whereas the importance of the resorbable biopolymers eliminates this process and gets metabolized therein. Biodegradable polymers are in use for various versatile applications such as packaging, cosmetics, textile applications and one of the most prominent emerging fields is biomedical. Till date, a number of polymers have been explored for their biodegradable nature and compatibility with most of the living tissues. The most important among these are polyglycolic acid (PGA), polylactic acid (PLA), poly (ε-caprolactone) (PCL) and copolymers of different biodegradable polymers [1].

The biodegradable and bio-absorbable polymers used for the biomedical applications must possess essential properties for their safe medical use. The removal of the implant post-healing often requires re-surgery which may be painful. The materials used as implants must therefore absorb inside the body, possess good mechanical strength, easy processability, controllable surface nature and retention of strength during in vivo and in vitro analysis. Such properties have therefore promoted these classes of materials as one of the prime replacement for the conventional orthopaedics transplants, tissue engineering substance, drug delivery application, surgical applications, etc. [2].

Recently, the use of biodegradable polymers as surgical sutures has been commercially increased. These materials are replacing the conventional suture materials almost in all the different surgical cases. However, different modifications have been carried out by different groups in order to improve the properties of suture apart from only the mechanical support such as fabrication of composites, variation in the spinning technique, coating the surface of the suture. In order to get the controllable performance of suture under external fields and tailor the properties like antibacterial activity, cell adhesion stimuli-responsive materials are studied in the form of matrix or filler. Electric field, magnetic field, pH, chemical environment are the stimulus studied majorly. In this chapter, a detailed survey of biodegradable polymeric materials as sutures and the scope of stimuli-responsive sutures and their fabrication are discussed [3].

2 Suture

Suture is a biomedical device which is used to ligate blood vessels by upholding tissues together to expedite wound healing. It has both natural and synthetic origins.

Physicians have used suture to close wounds for at least 4000 years [4]. The wound closure implies eradication of dead space, evenly distributed tension along deep suture lines, maintenance of tissue tensile strength and approximation of the closure. Although there are various developed materials for wound closure management such as staples, screws, tape, and adhesive, sutures are found to be the most widely used ones. Sutures have witnessed enormous growth since the past two decades. Sutures are considered to be the largest group of biomaterials which constitute a huge market exceeding $1.3 billion annually [5]. A significant growth of surgical sutures features in the case of healthcare industry, for both absorbable and non-absorbable suture-based products. Since the early times, different plant- (cotton, silk) and animal-based (animal gut, horse hair), metal- and steel-based sutures have been utilized. Recently, various synthetic biomaterials such as polydioxanone, polyglycolic acid (PGA) are being used as suture materials. Sutures provide the flexibility and stability during wound management which are usually the shortcomings observed in other wound healing products. Different kinds of sutures may be fabricated such as absorbable, antimicrobial, barbed, coated sutures based on the targeted applications [6]. Roberts et al. in the year 1983 reported a comparative study between PGA sutures and traditional catgut in 190 patients undergoing episiotomy. They found edema disease was significantly reduced in case of PGA-based suture compared to the catgut suture [7]. In the year 1988, Singhal et al. reviewed emerging trends on sutures and its biodegradability based on PGA and its copolymers [8]. In the year 2006, Li and Yuan studied about the progress on synthetic-based absorbable polymeric sutures [9]. A general comparative study was made upon closure materials for vascular devices by Hon et al. in the year 2009. They focused on the mechanism of sutures and their potential in serving homeostasis [10].

2.1 Characteristics of Suture

The ideal properties of suture for fulfilling the increasing demands of wound-closure issues are described below:

- It must be biocompatible, biodegradable and bioresorbable.
- It must have adequate mechanical strength and impart flexibility.
- It must have knot-pull strength and straight-pull strength and knot security [11].
- It must evoke inflammatory response.
- It must have an acceptable shelf life.
- It must have permeability and help in healing process.
- It should be non-toxic and should not support bacterial growth.
- It should be easily handled.
- It must have slow absorption rate with the healing of the wound.

3 Classification of Suture Materials

Sutures are originally made from natural and synthetic polymers. It can be classified into different categories based on their nature of degradation, size, texture and structure, and commercial surgery notation.

Filament Structure	Texture	Degradation	Size
Monofilament Multifilament Pseudo-filament	Smooth Barbed	Absorbable Non-absorbable	US Pharmacopeia (USP), European Pharmacopeia (EP)

On the basis of the structure and number of strands, sutures may be classified as monofilament, multifilament, and pseudo-filament [12].

Monofilament sutures: These are single-stranded materials. These impart less resistance while passing through tissues and are also less prone to infection. These are easily tied down and must be handled carefully. Because of their simple structure, these can lead to breakage of the suture strand.

Multifilament sutures: These are comprised of many strands of filaments twisted and braided together. The multifilament sutures render much higher mechanical property with appropriate flexibility and pliability than the monofilament ones. These are sometimes coated to enhance handling properties and are applicable in intestinal procedures. These are called as *pseudo-filament sutures*.

The sutures for wound closures may further be categorized on the basis of their texture and surface design as follows:

Barbed sutures: These sutures generally contain spikes on their surfaces for deep wound closures and possess sharp projections or barbs which help in anchoring of the sutures to tissues in a linear fashion, thereby eliminating the need to knot. The barbed sutures have widened their applications in complex reconstructive surgical procedures.

Smooth sutures: The smooth sutures are tightly knotted around the tissues of bones. These correspond to the response to inflammation and bacterial growth. These are not recommended for minimally invasive surgeries.

On the basis of nature of degradation, sutures may be classified as:

Absorbable sutures: These sutures undergo rapid degradation in tensile strength within 60 days. These are used to hold wound edges temporarily. These are prepared from animal origin and synthetic polymers. These can also be coated for easy handling and visibility in the tissue. The natural-based sutures are absorbed by body enzymes, and the synthetic polymers are hydrolyzed by breaking the polymer chains.

Non-absorbable sutures: These sutures are not digested by enzymes or hydrolyzed into the living tissue. These are made up of non-biodegradable materials which remain repressed within the host tissue. There is a need for postoperative removal. These comprises of single or multiple filaments. The fiber strand conforms to the USP for

its size and composition. These are of different types, coated or uncoated, dyed, etc., to enhance visibility.

There are different standards to select size of suture for surgery. One of such standard is 'US Pharmacopeia' (USP), according which the size of the suture indicates the diameter denoted by the number of zeroes. The number of zeroes is inversely proportional to the strand diameter. The smaller the diameter, the lesser is the strength of the suture [5].

Sr. No.	Size	Use	Diameter (mm) (natural)
1.	7-0 or smaller	Opthalmology	0.070–0.099
2.	6-0	Blood vessels	0.100–0.149
3.	5-0	Face, neck, blood vessels	0.150–0.199
4.	4-0	Mucosa, neck, hands, limbs, tendons, blood vessels	0.200–0.249
5.	3-0	Limbs, trunk, gut, blood vessels	0.300–0.339
6.	2-0	Trunk, fascia, viscera, blood vessels	0.400–0.399
7.	0 or larger	Orthopedics	0.400–0.499

3.1 Selection of Suture

The ability of the sutures to facilitate wound healing directly correlates to the size and tensile property of the suturing material. The tensile strength of any suture material should also balance the tensile strength of the healing tissues. The tensile strength of the knot denotes the force in pounds which the suture strand resists before it breaks when tied a knot. The size of the suture signifies the diameter, which is denoted by the number of zeroes. The number of zero's is inversely proportional to the diameter of the suture. For example, size 5-0 or 00000 is smaller in diameter than size 4-0 or 0000. The smaller the diameter, the lesser is the strength of the suture. The selection of any suture material takes into account the layers of wound closure, tension around the wound and location of the suture [4].

- Suture must be selected on the basis of strength retention and finely structured material which also correspond to the strength of tissue.
- In case of slow healing tissues, non-absorbable sutures and in the case of fast healing tissues, absorbable sutures must be used.
- When the foreign bodies prevail in the contaminated tissues, multifilament sutures must be avoided and monofilament should be used.
- In the case of cosmetic surgeries, monofilament materials such as polypropylene, PP, and nylon are used for the proper closure and recovery of tissues.

- In the presence of fluids such as in urinary tracts, monofilament materials are used to prevent from causing stone formation and precipitation.

3.2 Fabrication of Sutures

The suture material can be synthesized by fiber spinning process. The ingredient can be directly from nature (cotton, catgut etc.), synthesized polymers (degradable, non-degradable), or metallic. The spinning process involves two steps, i.e., conversion of polymers into fibers such as extrusion or spinning of fibers and further post-spinning, i.e., drawing of fibers and heat treatment. Different spinning methods are selected based on the nature of material and thermal stability of materials. Post-treatments are conducted in order to achieve better properties or tailored surface nature [13].

The major steps involved in the fiber production are:

- Spinning
- Drawing
- Post-treatment.

The spinning techniques may be classified as:

- Melt spinning
- Solvent spinning
  - Dry spinning
  - Wet spinning
  - Dry-jet wet spinning
- Electrospinning.

Melt spinning technique:

The *melt spinning process* is the primitive method used for the production of fibers which is a solvent-free process and based on simple extrusion process. It is the most eco-friendly route used for the fiber fabrication. The schematic of the melt spinneret is shown in Fig. 1. The polymers having degradation temperature much higher than their melting temperature may be subjected to melt spinning in order to be spun into fibers. The production speeds are normally high. The polymer melting point and its solubility in organic/inorganic solvents are to be known when using this technique. This method is mainly used for the polymers such as polyesters, polyamides, polyolefins. After melting at higher temperatures, the melt is forced to pass through the spinneret at high pressure around 10–20 MPa and temperature. The molten strands are then cooled while it solidifies. One of the characteristic of the melt spinning is that the strands are extruded from the melt which are solidified by exchange of heat within the medium. Eling et al. 1982 fabricated poly (L-lactic acid), PLLA-based melt spun fiber at 185 °C and used hot furnace for the thermal

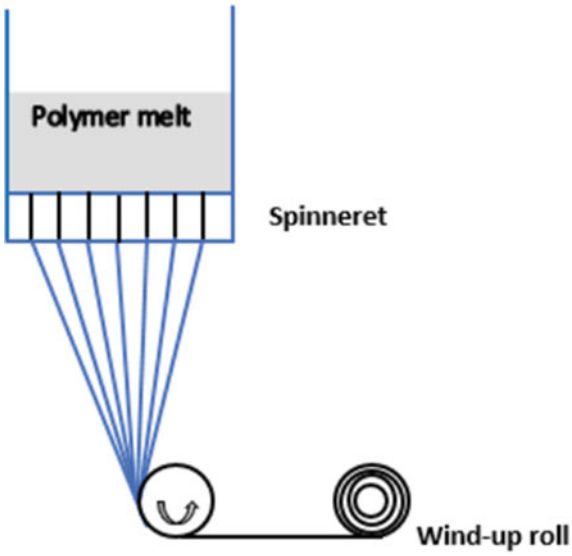

Fig. 1 Schematic of melt spinneret

treatment which led to the production of PLLA fiber with 0.5 GPa tensile strength was achieved [14]. Charuchinda et al. studied the effect of spinning temperature, drawing speed, polymer properties on the melt spinning of PCL. Increase in the drawing ratio, spinning temperature led to the reduction of the fiber diameter, whereas increase in the drawing ratio led to the increase the strength of melt spun fiber [15].

Solvent spinning technique:

The solution spinning, although complex, is suitable for the polymers which do not meet the requirements for melt spinning and such polymers may be spun if they are dissolved in a suitable solvent. The polymer then dissolved, swells, and forms a completely homogeneous solution. The polymers prepared by this process can be directly spun without intermediate processing such as polyacrylonitrile (PAN). The spinning pressures are usually 0.5–4 MPa, which is less than that in melt. The polymers with a very high molecular mass, i.e., M_w around 250,000 can also be spun which is not the case in melt spinning because the limiting viscosity at zero shear η_0 and the spinning pressure increases in proportion to $M_w^{3.4}$. In the solution spinning, the effect of molecular mass on viscosity can be compensated by appropriate dilution [16]. However, the concentration used should not be low since this will affect less polymer throughput and increase the cost of solvent recovery. This is classified into as (a) dry spinning technique and (b) wet spinning technique.

Dry spinning technique:

In the *dry spinning* process, the polymer solution is spun in the presence of hot gas where the temperature is higher than the normal boiling point of the solvent. The

evaporation of the solvent by the drying gas along the spinning path is determined mainly by its rate of diffusion through the strand, which decreases with the solidification rate. Solidification occurs because of the decrease in solvent concentration and the associated increase in viscosity. In this process, the strand bears a residual solvent content of 5–25 wt%. This is desirable because it plasticizes, thereby facilitating the subsequent drawing of the filament. The residual solvent is removed later in the process. The spin–draw ratio is based on the extrusion rate of the spinning solution [17]. The schematic of the dry spinning process is shown in Fig. 2. Gogolewski and Pennings 1985 fabricated nylon-6 filaments from nylon-6 solution using solvent mixture of formic acid and chloroform followed by hot drawing in the temperature range 200–240 °C and the strength of fiber was reported to be 1 GPa [18]. PLLA fiber of high strength was drawn by dry spinning followed by hot drawing by Leenslag and Pennings [19] with 2.1 GPa tenacity and 16 GPa modulus.

Wet spinning technique:

In the *wet spinning* process, the polymer is dissolved in a nonvolatile solvent which necessitates a subsequent reverse reaction. In this process, the polymer solution is spun into a liquid coagulating bath. The heat exchange within the spinning medium is not responsible for solidification of the strand. Instead, solidification results due to coagulation caused by phase separation which is induced by a component of the spin bath which is incompatible with the polymer which is a non-solvent [20]. Um et al. [21], utilized wet spinning technique to fabricate silk fibroin filaments using formic acid solvent and methanol coagulation bath. With decrease in the drawing ratio, the fracture stress decreased and the elongation increased for the fibers [21].

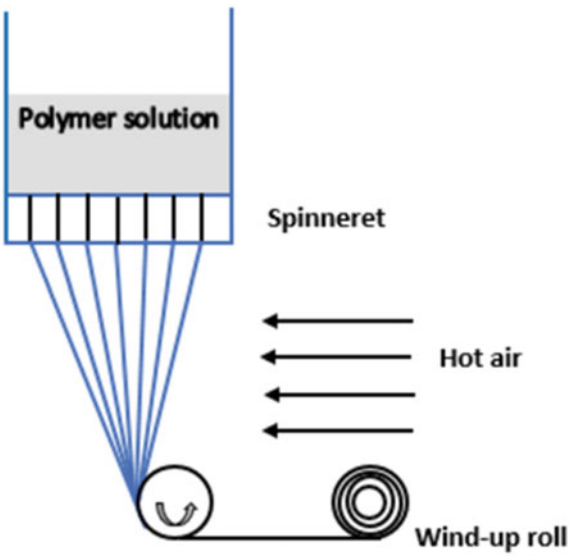

Fig. 2 Schematic of dry spinning

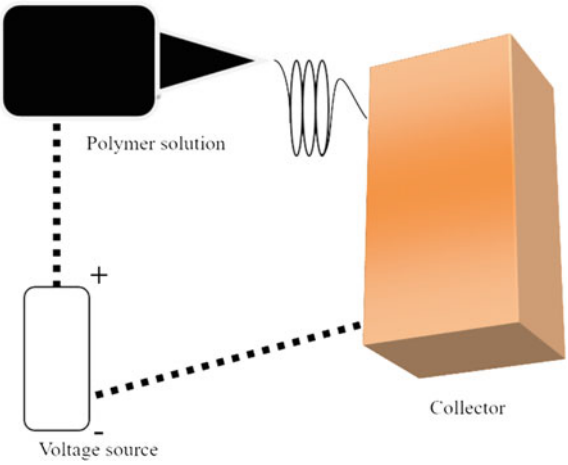

Fig. 3 Schematic of electrospinning

In the *electrospinning* process, the polymer solution or melt is drawn to continuous fiber with diameter ranging from few microns to nanometers which is shown in Fig. 3. It is processed under the influence of an electric field. Voltage difference, solution viscosity, nozzle type, etc., influence the fiber property [20]. Hu et al., 2014, fabricated different polymer-based electro-spun fibers for drug delivery application with variety of surface properties [22]. Matthews et al., 2001, fabricated collagen nanofiber by electrospinning technique. Acid soluble collagen was used and voltage difference was 15–30 kV. The fibers were applied for tissue engineering application [23].

4 Biodegradable Suture

Biodegradable Polymers

The biodegradable polymers have been sparked by the recent advances in the fields of biomedical, packaging, textiles, etc. Biodegradable polymers break down into stable end products under physiological conditions. When a neat polymer, blended product or composite is obtained completely from renewable resources, it may be considered a green polymeric material [24]. Biodegradable polymers can be either natural or synthetic. Natural polymers such as protein, polysaccharide, and nucleic acid are degraded in the biological systems by oxidation and hydrolysis [25]. For the synthetic polymers, enzymatic degradation is witnessed, wherein the microbes utilize the carbon backbone as a carbon source when is required. This technique offers a solution to biodegradable waste management. However, the emerging research and interest have focused the attention of biodegradable polymers for biomedical applications owing to their biocompatibility (in some cases) [26]. In the terms of biocompatibility, biopolymers offer an alternative to traditional biodegradable materials and non-biodegradable polymers. The polymeric biomaterials can be broadly classified

as enzymatically degradable and hydrolytically degradable polymers. Bioabsorbable polymers can be blended to improve their overall functional properties. These are processed to fabricate different objects such as fibers, films, screws, plates, sutures which are cost-effective too. The fundamental aspects of biodegradability are

- The effect of polymer structure on biodegradation.
- The effective relationship between degradation and absorption.

The polymer structure on biodegradation is important to understand the correct approach for the production of composites, the properties of the biopolymers and how well they recombine with the natural polymers such as polypeptides, polysaccharides, polynucleotides, fibers, etc. Biodegradable polymers, mostly used for biomedical applications in tissue engineering, should have parallel rate of absorption and curing. It depends on the location of the tissue or organ in the human body. These should maintain the desired strength, modulus and function until the tissues are completely cured by minimizing unwanted side effects. The synthetic polymers, on the other hand, remain in the host after their practical functions are lost. Although, for most of the biodegradable polymers, the complete decomposition rate is much slower than the curing rate of bio-tissues, the products are likely to reside in the cured tissues even after the therapy. The rate depends on many factors which includes the chemical composition of the main chain and side groups, the state of aggregation, extent of crystallinity, hydrophilic–hydrophobic balance, surface area, and morphological behavior of the polymer material. It is also strongly affected by the primary and higher order structure, solid-state structures of the polymer. The polymer surface area also becomes the main factor for biodegradability. A polymer having both hydrophobic and hydrophilic characteristic serves better for biodegradation by hydrolysis reactions [1]. Sir John Charnley successfully made the first clinical application of biomaterial which dates back 50 years ago, poly(methyl methacrylate) (PMMA), an acrylic cement which was used to attach a femoral head prosthesis [27].

4.1 Biodegradable Polymer-Based Suture (BPBS)

Generally, the sutures are made from natural and synthetic origins. The synthetic polymers possess acceptable mechanical strength and their rate of degradation along with the shape can be easily modified. Their hydrophobic surfaces and cell recognition signals can be easily tuned. The polymers which are derived from natural resources are likely to possess the advantage of cell support and cell proliferation. These kind of natural polymers bear poor mechanical properties and are costly when the supply is limited [28]. The natural sutures are usually made of catgut or reconstituted collagen, cotton, silk. The two naturally absorbable sutures (types) available in the market are catgut and regenerated collagen. Catgut is available as plain catgut (untreated) and chromic gut (tanned by chromium trioxide).Since 1930s, catgut has been used as the staple absorbable suture material, whereas silk and cotton are used

as non-absorbable materials. These sutures are noted for their toughness and tenacity. The basic constituent of catgut is collagen and is the major structural protein found in all multicellular organisms. These sutures are coated with glycerin to eliminate the requirement of alcohol packing. During the early 1970s, absorbable synthetic polymer PGA was developed and its copolymer is commercially available as a suture material. The absorbable sutures are established to behave favorably both in vitro and in vivo [29]. Owing to their controlled manufacturing processes and reproducible properties, these kinds of biomaterials have received a great deal of interest in the biomedical field [30]. The advantage of synthetic absorbable sutures is their reproducibility and degradability within a biological environment which enables them to minimize undesirable reactions in the tissues after the sutures discontinued their function. These synthetic-based sutures have replaced the natural ones for the wound-closure management. A braided suture marketed as Vicryl® is a copolymer of (glycolic acid/lactic acid), GA/LA mol/mol composition. Further, a homopolymer of GA is a braided suture commercially available with the trade name Dexon®. The most susceptible monofilament suture till date is Maxon®, which is a segmented block copolymer of glycolide and ε-CL. Another commercial suture named as Panacryl® is a copolymer with a high LA/GA ratio [31]. The copolymers of linear aliphatic polyesters like PLA, PGA which are also biodegradable in nature are frequently used in tissue engineering [32] and as in vivo degradable surgical sutures which achieved (US Food and Drug Administration) FDA recognition for medical use. The other linear polyesters which are also used in tissue engineering applications are polyhydroxylbutyrate (PHB), PCL. PCL though possessing a slower degradation rate which is not desirable for most of the biomedical applications but, it finds its usefulness in long-term implants, controlled drug delivery applications. It has also appeared as a perfect candidate for fabricating suture and scaffold materials [3]. Some absorbable natural- and synthetic-based sutures are highlighted in Table 1.

Furthermore, some of the non-absorbable polymer sutures marketed are

- Polyamide (Ethicon)
- Tantalum (B. Braun)
- Polyethylene/Polypropylene (Ethicon)
- Poly-but-ester.

4.2 Biodegradable Composite-Based Sutures (BCBS)

Biodegradable polymers have several shortcomings like low thermal stability, mechanical strength, brittleness which are detrimental for the applicability of the polymer. For the biomedical applications, the biocompatibility, strength sustainability under buffer solution, mineralization, mechanical strength and processability of the polymers are essential to be modified by using suitable reinforcement. Different reinforcements like hydroxyapatite, silicates, carbon nanotubes are incorporated into the biodegradable polymers in order to fabricate bionanocomposites for biomedical

Table 1 Commercially available sutures from natural and synthetic polymers

Natural polymers			
Sr. No.	Name of polymer	Trade name	Year of manufacture
1.	Bovine origin	Catgut plain	Sixteenth century
2.	Collagen/intestines of sheep	Surgical catgut	1880 (Ethicon)
3.	Collagen	Chromic gut	1950–1960 (Ethicon)
Synthetic polymers			
1.	Polyvinyl alcohol	HS-PVA braids	1931
2.	PGA	Dexon®	1970
3.	PGA	Medifit®	1974
4.	PGA/PLLA(glycolide-L-lactide)	Polyglactin 910 (Vicryl®)	1974
5.	Poly(glycolide-L-lactide)	Polysorb®	1981
6.	Polydioxanone (PDS)	PDS II®	1981
7.	Poly(glycolide-ε-caprolactone)	Polyglecapron 25, (Monocryl®)	1992

applications like tissue engineering, orthopaedic implants, suture. Some of the nano-based material used for fabrication of composite materials maybe given as follows [33]:

Hydroxyapatite (HAP): Hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$), which is both osteoconductive and biocompatible, is used mainly for bone tissue applications as it is a major mineral component of the bones consisting of 69 wt% of the hard tissues [34]. It is both naturally available in bones and teeth and can be synthesized to promote bone growth, tissue repair with a Ca/P range of 1.50–1.67. In case of PLA/hydroxyapatite composites, where hydroxyapatite serves as the filler, the alkaline part of it neutralizes the acidic neutralization of the PLA matrix to make it bio-functional. The recent research proved that nano-sized HAP (n-HAP) due to its huge surface area showed prominent increase in protein adsorption and osteoblast adhesion than the micro-sized ceramic HAP [35]. In the year 1992, Verheyen et al. investigated the mechanical behavior of the L-lactide/HAP biocomposite for applications in orthopaedics surgery. Gupta et al. in the year 2017 fabricated high molecular weight stereocomplex PLA (sPLA)/n-HAP bionanocomposites for orthopaedic implants [36].

Carbon nanotubes (CNT): These can be of single sheet (single-walled carbon nanotubes) (SWCNTs) and multi-walled sheets (multi-walled carbon nanotubes) (MWCNTs). Because of their regular structure and excellent electrical and mechanical properties, it can find application in sensors, biomedical and electronic devices [37]. It serves as a structural reinforcing agent for biomedical applications. Incorporation of SWCNTs enhances the bioactivity of the composite material. Cheng et al. prepared CNT/PLGA composite by solvent-casting/particle-leaching method for scaffold fabrication [38]. Also, Pan et al. prepared PCL/MWCNT composite by solvent-casting method and found the increase of cell adhesion [39].

Chitosan: Chitosan is a linear polymer which is obtained from the parent origin chitin and is widely available in nature such as in certain fungi and crustaceans. It is biocompatible, biodegradable and also possesses inherent antimicrobial property which makes it a good candidate for biomedical applications. Chitosan promotes wound healing and protects the cell from infection. It enhances vascularisation and also endothelial cell proliferation. Besides, the repairing nature of the chitosan, it can also be used a gels for therapeutic delivery to the local wound. Kashiwazaki et al. in the year 2009 prepared HAP/chitosan composite by co-precipitation method. These were used for fabrication of scaffolds in the rat model [40].

Cellulose: Cellulose is a naturally occurring filler which is most abundant in nature. It has hydroxyl functional groups on its surface which helps in even mixing for the preparation of the composite. It can be easily modified and helps in enhancing the properties of the material. Jiang et al. have used cellulose nanocrystals which directly acted as a nucleating agent in the PLLA/PDLA blend matrix that improved crystallizability of the material [41].

Silk: It is a fibrous protein which is known for its biocompatibility, ease of functionalization, flexible morphology and better mechanical properties. It is viable candidate for various tissue engineering, wound healing applications. It shows promising in vivo response. Patwa et al. in the year 2018 prepared magnetic silk/PLA composite by electrospinning method and studied the cytocompatibility which is effective for cancer therapy [42].

Silver nanoparticles: It is known for its disinfectant and antimicrobial property. It is capable of releasing silver ions and serves as an antibacterial agent. It has a high surface area which enhances its inhibitory property. Simone et al. prepared novel silver treated suture and studied its antibacterial effect for the prevention of surgical infections [43].

4.3 Advantages of BCBS Over BPBS

- The incorporation of fillers like CNT, hydroxyapatite can improve the mechanical strength of BCBS compared to the polymer.
- Collagen, peptides, etc., can improve bioresorbability of BCBS over BPBS.
- Different magnetic materials and electrically conducting filler loaded BCBS can be tuned for particular applications using external stimulus.
- Different composite-based sutures can be utilized for drug carrier system more effectively as compared to the polymer system.
- The degradation behavior, especially the mechanical strength retention under in vivo and in vitro condition, is improved for the composite.
- The surface property of BPBS can be tuned by using suitable modification and thus biocompatibility and cell adhesion are controlled.
- In some cases, incorporation of fillers into polymeric system can improve the bone growth as compared to the pure polymer.

5 Stimuli-Responsive Polymers

A Brief Introduction

Polymers that respond to external stimulus exhibit dramatic changes in their properties in the presence of different environment such as pH, solvents, salts, light, electrical, and electromagnetic radiation. These changes may include conformation, surface, hydrophilic, and hydrophobic behavior and solubility. These kinds of polymers behave intelligently in varied applications such as in biomedical, micromechanical, biosensors, commodity, and packaging applications. The emerging interests in the stimuli-responsive polymers have endured since decades and an ample amount of work have been carried out to develop macromolecules to be crafted into smart materials. In the living cells, the macromolecules regulate their functions which respond to changes in environment locally and these biopolymers control all the major natural processes. The initial motive using such material was to develop biomaterials only for smart therapeutic delivery methods. Recently, many synthetic polymers have been explored that are responsive to various stimuli and can be considered as biomimetic leading to the development of smart applications in tissue engineering and wound healing applications. The responsive behavior to an external stimulus is a nonlinear behavior [44]. There are different aspects of stimuli such as to attune the response by integrating different responsive elements for the case of biodegradable macromolecules. Applications of these smart polymers in the targeted-delivery of therapeutics, tissue engineering, bio-separations and sensors have been studied diversely, and innumerable publications are evident in this area. Additionally, to achieve the macromolecular assemblies (combining two or more chemical, physical, biological stimuli-responsive materials) with stimuli-responsive characteristics, different controlled polymerization techniques have been reported such as reversible addition–fragmentation chain transfer polymerization (RAFT), atom transfer radical polymerization (ATRP), nitroxide-mediated radical polymerization (NMRP) and ring-opening metathesis polymerization (ROMP).

In the present days, researchers are exploring different stimulus like magnetic field, electric field, ultraviolet, pH, ultrasonication and chemical environment to enhance the development of suture-based stimuli-responsive materials. A schematic representation of the external stimulus affecting the properties of the polymers is shown in Fig. 4. The fabrication of such multi-stimuli-responsive polymers is synthetically challenging but is of active interest for their application in various biomedical fields [45]. The development of these kinds of materials to tune the properties of the end product can be helpful to fabricate custom-designed materials. The knowledge of structure–property relationship is necessary for further development and designing of new functional materials. Some of the stimuli components are highlighted below.

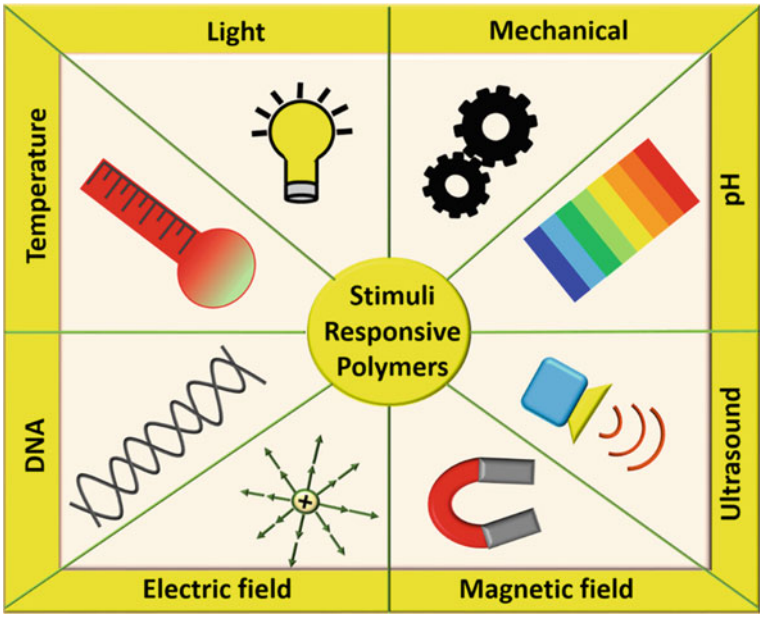

Fig. 4 Different external stimuli that affect the properties of the polymers

5.1 Magnetic Field Responsive Polymers

These kinds of polymer materials respond to the changes in the magnetic fields. These provide exciting applications in biomedical applications such as in controlled drug delivery. Based on the polymer matrix, magneto-active polymers can be divided into magneto-active elastomers and magneto-active gels. Magnetic field responsive materials can form different materials such as magnetic cellulose, magnetic hydroxyapatite, magnetic carbon fibers. Different types of direct and alternating fields are used based on the application of magnetic-based stimuli-responsive materials in cell adhesion, antimicrobial activity and drug delivery applications. De Santis et al. designed 3D PCL-magnetic HAP-based scaffolds that showed enhancement in cell growth and histocompatibility in both in vitro and in vivo studies [46]. The incorporation of magnetic material increased the cell population by 2.2 fold higher than normal PCL-based scaffold. Patwa et al. 2018 successfully synthesized Fe-doped crystalline silk nano-disks (CSNs) by co-precipitation method. The polylactide/CSNs scaffolds were prepared using electrospinning method. Under static magnetic field, this scaffold showed remarkable increase in cell growth of BHK-21 by 27% for aligned PLA composite and 40% for nonaligned PLA composite. In the presence of alternative field, magnetic materials generate heat which is called as 'hyperthermia' in order to control targeted release of drug and regulate antimicrobial activity. To obtain the desired temperature for hyperthermia effect which is 42 °C, the magnetic field frequency and strength were kept at 293 kHz and 12.57 kA/m respectively. The

drug-loaded composite scaffold showed 63% reduction in cell viability. In the post-hyperthermia effect, the cancer cells failed to resist higher temperature, resulting in reduced cell counts irrespective of the presence or absence of drug. Using magnetized CSNs disk in reinforced PLA-based scaffold, it showed cytocompatibility under magnetic effect which are capable of destroying cancer cells depicting hyperthermia [42]. In the similar fashion, Chertok et al. in the year 2008 used iron oxide nanoparticles for targeted drug delivery toward brain tumor under magnetic field [47]. Similarly, Fuchigami et al. in the year 2012 used porous iron/platinum capsules for targeted drug delivery for cancer therapy under the guidance of magnetic field [48].

5.2 Electric Field Responsive Polymers

These polymers that respond to the electric field and undergo change in their properties are termed as electric field responsive polymers. Such materials convert electrical energy into mechanical energy which are applicable in biomechanics, actuators, chemical separations and controlled drug delivery. The electric field can act as a stimulus for different biomedical applications like nerve regeneration, drug delivery. In the presence of electric field, there is a variant in cell growth from cathode to anode which can help in nerve regeneration where conductive composites and blends are utilized as nerve conduit. Jeong et al. in the year 2008 fabricated the blends of polyaniline (PANI)/poly(L-lactide-co-ε-caprolactone) PLCL doped with camphorsulfonic acid using electrospinning process. They found the conductivity value around 0.0138 S cm^{-1} for 30:70 v/v of the blend. There was a significant enhancement in the cell adhesion in the blends (PACL) than that in the neat PLCL fibers. These were considered as potential candidates for studying the effect of electric field to improve desirable cell activity for tissue engineering applications. These blends were also used for modeling of the system to study the effect of electric field on the mitochondrial activity of the NIH-3T3 cells. In case of higher loading, i.e., at 20 mA, the cell culture showed enhancement in the activity on the blends [49]. Wei et al. in the year 2007 fabricated electroactive polymer using aniline and oligopeptide. They used PC12 neuronal-like cell lines to check the neurotrophic cell growth and found significant cell adhesion and proliferation [50]. Huang et al. in the year 2008 synthesized multiblock copolymer using PLA and aniline pentamer by group-shielding approach and fabricated scaffold pertaining better mechanical strength, excellent electroactivity, and biodegradability. The copolymer showed improved cell adhesion and proliferation in the in vitro studies. Under the effect of electric field, the copolymer also showed enhancement in cell differentiation of rat neuronal pheochromocytoma PC12 cells. This copolymer possessed the properties in vivo as nerve regeneration scaffold materials in tissue engineering applications [51]. Similarly, Hu et al. in the year 2008 fabricated electrically active cell using chitosan and aniline pentamer [52]. In the similar way, Rivers et al. synthesized biodegradable,

conducting blend using pyrrole and thiophene via degradable polyester for tissue engineering application [53].

5.3 Temperature and pH Responsive Polymers

The thermal nature of the environment also acts as stimulus for some applications where polymer and composites are thermosensitive. The change in temperature alters the solubility of the components. It is specially observed for the colloid systems [54]. Peng et al. synthesized PEG-based random copolymer having thermosensitivity. Change in sol–gel behavior was reported at 25–39 °C from %T value because of lower critical solubility temperature change. Thermo-responsive gels and hydrogels incorporated with drug can be controlled by varying temperature. In some of the cases, activity of enzyme can be controlled by altering temperature. Shape memory polymers are also utilized as stimuli-responsive materials for fabrication of biomedical devices. Property of this kind of polymers also can be controlled by varying temperature [55].

Biodegradable polymer-based gel characteristics are based on the nature of the polymer, cross-linker as well as physical condition like pH and temperature. Marsano et al. showed that network formation between chitosan and polyvinylpyrrolidone is dependent on different pH condition. It swells around pH = 4, whereas shrinks at pH = 9 [56]. Dai et al. well described how pH can be used as stimulus for drug delivery in different gel, micelle and copolymer systems [57]. Yan et al. noticed that pH can alter surface wettability between oil to water for surface treated fabrics. Fabric showed super hydrophobicity at pH = 7, however, noticed to have hydrophilic nature at pH = 12 [58]. Efficiency of chitosan-based drug carrier under pH change also investigated by Hua et al. Chitosan-based conjugate graft copolymer was prepared in two steps. First chitosan–lilial conjugate was synthesized using DMF solvent and then graft polymerization was conducted with carboxyl terminated PNIPAM. It was observed that lilial was not released from chitosan core at neutral pH up to 72 h, whereas 70% of lilial was released after 30 h at 4.5 pH [59]. Zhang et al. 2007 investigated release behavior of anticancer drug Paclitaxel which is water insoluble in nature using P (N-isopropylacrylamide-co-acrylic acid) block and a biocompatible hydrophobic polycaprolactone (PCL) block polymer. Faster drug release was reported at higher temperature and lower pH [60].

5.4 Chemical Environment, Photo Effect, Sonication and Other Stimulus

Chemical environment of living system is different and based on the components as well as pH. This also can act as stimulus for targeted applications such as glucose-rich

condition can be treated using glucose oxidase-based conjugate systems. Glucose oxidase and polyacrylic acid-based hydrogels are found to be active and glucose responsive [61].

The activity of some of the polymers can be controlled by the enzymatic action. The blood clotting and hydrolysis of peptide have been investigated by different groups under different enzymatic conditions. Effect of protease enzyme on *E. coli* cells was investigated by Ulijin et al. by entrapping in a protein–gelatin mixture hydrogel. It was observed that transglutaminase enzymes are only active in the calcium ion's environment, and exposure to Ca^{2+} can also enhance enzymatic crosslinking [62]. Similarly, other chemical environments like antigen, thiol can act as stimulus for different targeted applications.

The photoresponsive polymers can vary their property when subjected to irradiation of light. This can control the efficiency of some of the biomedical applications like tissue engineering, protein bioactivity and drug delivery. Also, UV and near-infrared irradiations have been utilized to different drug delivery investigations by different groups.

Ultrasound also utilized as stimulus by different groups for controlled drug release studies. It gives local shock which can disrupt the shell of drug-loaded system and based on the amplitude, controlled release can be done.

Stimulus and Suture Application

Incorporation of stimuli-responsive ingredients in the form of biodegradable polymer or reinforcement for targeted environment application, suture is a lucrative area of research. Drug-coated suture can be applicable for both external healing and internal wound healing. Drug-loaded gels which are responsive to external stimulus can be utilized in order to control the release depending on the nature and location of wound. In the above-mentioned section, magnetic guidance of cell adhesion, hyperthermia controlled antibacterial, and drug delivery were discussed. The similar can be utilized for suture application which will serve both holding of stitches and control recovery based on application. Electro-spun fibers having conductive nature are utilized for nerve regeneration. These sutures also can serve the purpose for eye injury or any internal organ malfunction case. Orthopaedic application of suture has huge range of utilization of stimulus responsive suture. Bone growth, cell proliferation, biocompatibility, bioresorbability all can be controlled using suitable polymer-reinforcement composition under stimulus like pH, enzyme. Thus, control of behavior of biomedical application of suture has a huge importance for simplification and more effective medical treatment. Researchers across the world are investigating in various routes to fabricate smart suture or stimuli-responsive suture which are capable of addressing various wound healing issues based on the application and need.

6 Resorbable Sutures: In Vitro and In Vivo Studies

In vitro studies involve the examination of biological entities outside the living body, whereas the in vivo studies involve the examination of the entities within the living organisms and cells. Cell adhesion, cytotoxicity, bone regeneration, load bearing capacity under simulated body fluid, etc., are need to be studied for both in vitro and in vivo technique prior to implementation of any biomedical devices. The properties of suture also require in vivo and in vitro activity along with mechanical, surface property, etc. In the year 1992, Verheyen et al. fabricated PLLA/hydroxyapatite (HA) composites using in situ polycondensation of L-lactic acid in the presence of HA. The monomer to catalyst ratio was varied during the polycondensation. Tensile strength was 136.5 MPa in 600 M/I ratio and 30 wt% of HA. In vitro studies showed degradation in molecular weight with time in phosphate-buffered solution (PBS). In case of both in vitro and in vivo studies, all materials were found to retain their initial weight after six months [36].

Similarly, Kim et al. in the year 2006, fabricated poly(lactide-co-glycolide)/hydroxyapatite composite scaffold using gas foaming and particulate leaching (GF/PL) method. Commercial HAP was used for this particular work. PLGA/HAP/NaCl was mixed in a ratio of 1:1:9 loaded into a disk mold and compressed and exposed to high pressure CO_2 gas. NaCl was leached out using distilled water. In vivo analysis showed that HAP enhanced the cell growth and the GF/PL scaffold exhibited enhanced bone regeneration when compared to the SC/PL scaffold [63].

Okada et al. in the year 1990 reported in vivo and in vitro studies of the commercial suture. Collagen and pepsin were added to PBS solution for in vitro analysis. The results indicated the hydrolysis from surface of suture, wherein the fiber diameter decreased upon hydrolysis. The degradation of suture was found to accelerate in the presence of enzyme. In case of in vitro analysis, no cellular infiltration was noticed [64].

In the year 2007, Im et al. prepared poly(p-dioxanone) (PDO) and its copolymer by conjugate spinning method. The method used was conventional bulk ROP. The suture retained about 70 and 55% of its original linear tensile strength after two and four weeks of incubation. Strength retention percentage decreased with time in the in vivo degradation test. It was completely absorbed after 180–210 days of implantation, which was slightly faster than some of the commercially available PDO sutures [65].

Makela et al. [66] reported the in vitro study of the strong bio-absorbable self-reinforced/PLLA sutures (SR/PLLA) to investigate the mechanical properties in comparison with polyglyconate (Maxon®) and polydioxanone (PDS) sutures. PLLA was melt spun with die exit diameter of 1.5 mm and hot drawn with an oven temperature of 120 and 140 °C and drawing ratio of 7. The filament diameter was 0.3–0.7 mm which was found to increase with the density. The crystallinity of the suture was found to be 64–71%. The highest elongation found was ~62% for 0.3 and 0.5 mm sutures. The thicker sutures were found to fail at their knots [66].

Lee et al. prepared poly(lactic-co-glycolic acid) (PLGA) particles by loading dexamethasone (DEX, a model drug) using water–oil emulsion technique. They modified the surface of the DEX/PLGA particles using plasma treatment followed by dispersing in polyethyleneimine (PEI) to enhance its hydrophilicity. They used the absorbable braided suture (composition: 10% lactide, 90% glycolide) for immobilizing the PEI/DEX/PLGA particles onto the surface of the sutures to develop functional suture absorbable sutures [67]. The in vitro studies showed that the particles remained on the surface of the suture along with the sustained release of DEX during 4 weeks. They developed technique did not alter the mechanical properties of the suture. Thus, an indigenous strategy was developed to fabricate drug-eluting sutures which may be potential candidates for wound healing at the surgical sites along with anti-inflammatory response.

Being aware of the hydrolysis of the absorbable sutures resulting from the chain scission in the amorphous regions and hypothesizing that the rate of hydrolysis of suture would be directly dependent on the temperature, Cannizzo et al. evaluated the absorbable sutures, i.e., Monocryl and Maxon® used in fish surgery [68]. They maintained the sutures in the filtered water over a period of 8 weeks at 4, 25 and 37 °C temperature. In case of Monocryl, the tensile strength decreased after 2 weeks at 25 °C which was not the case at 4 °C. There was no decrease in tensile strength in case of Maxon® at 4 and 25 °C. Further, the Monocryl suture was found to disintegrate after 4 weeks at 37 °C and the tensile strength of Maxon® was decreased over a period of 6 weeks. It was concluded that the tensile strength of absorbable sutures was found to reduce slowly at ambient temperature as compared to that of the body temperature. Thus, such sutures when used for the fish surgery would be retained for a longer duration as the fishes usually reside in the water below 25 °C.

7 Future Perspectives

The utilization of novel resorbable copolymers and composite systems has a noteworthy development in various biomedical fields; however, the study of such materials needs to be extensively carried out for the development of sutures for targeted surgical sites. Different stimuli like magnetic, electric field, pH are found to govern the properties of biomaterials for drug delivery, cell adhesion, nerve regeneration applications which can be implemented by fabricating stimuli-responsive sutures. The drug-loaded gels and hydrogels can be used as a novel coating for synthetic- and natural-based sutures for wound healing, antimicrobial activity and drug delivery. Thus, the fabrication of stimuli-responsive polymers and composites can address both the mechanical support for wound healing as well can effectively serve for the recovery of wound under controlled conditions. The use of novel biodegradable polymer, protein, peptide in combination with different nanomaterial under various stimuli may also be explored and novel formulations may be developed for the targeted wound healing supported by essential in vitro and in vivo studies.

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