Lecture Notes in Bioengineering

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Polymer Nanocomposites in Biomedical Engineering

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Preface

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

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

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

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

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

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

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

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

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

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

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

Contents

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

Rajan Choudhary, Mohit Saraswat and Senthil Kumar Venkatraman

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

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

1 Introduction

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

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

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

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

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

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

2 Polymers

2.1 Classification of Polymers

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

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

2.2 Natural Polymer and Their Composites for Biomedical Applications

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

2.2.1 Collagen

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

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

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

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

2.2.2 Silk

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

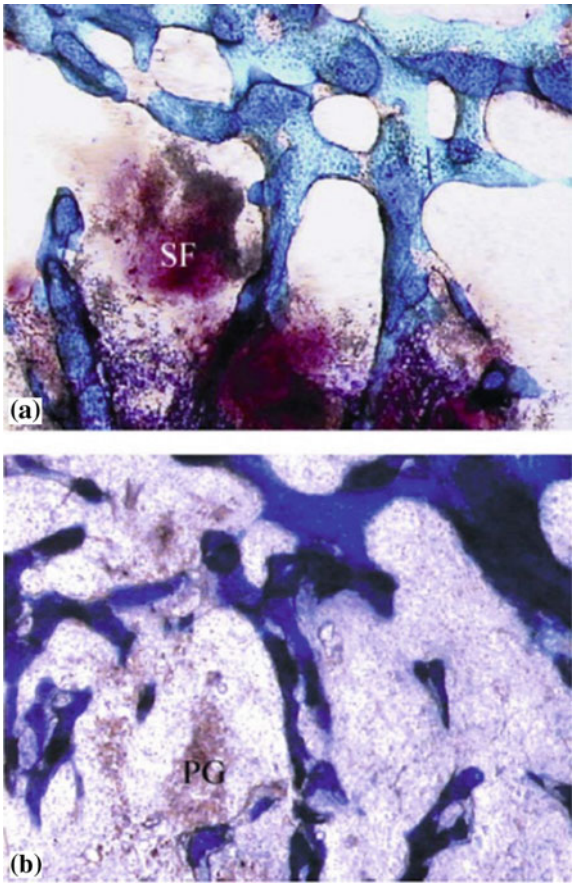

Fig. 1 Histological section of silk fibroin hydrogel treated defect (**a**) and synthetic polymeric gel-treated defect (**b**) after twelve weeks. Trabecular bone tissue having a microarchitecture similar to the normal healthy bone surrounding implant residues (PG) was noticed (Fini et al. 2005). Copyright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

2.2.3 Hyaluronic Acid (HA)

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

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

2.2.4 Chitosan (CS)

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

2.2.5 Cellulose

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

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

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

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

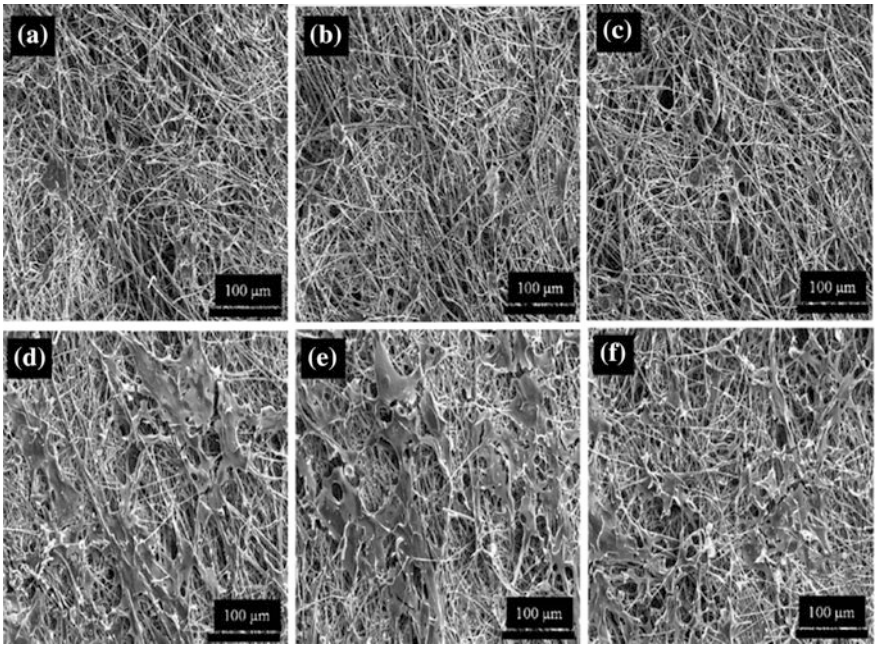

Fig. 2 FE-SEM images of the NIH3T3 fibroblastic cells on the surface of composites (pristine FP, CS-FP and Ag-CS-FP). **a–c** shows after 1 day and **d–f** shows after 3 days of incubation (Haider et al. 2018). Copyright 2018. Adopted with the permission from Elsevier

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

2.2.6 Alginate

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

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

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

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

2.3 Synthetic Polymers and Their Composites for Biomedical Applications

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

2.3.1 Polycaprolactone (PCL)

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

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

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

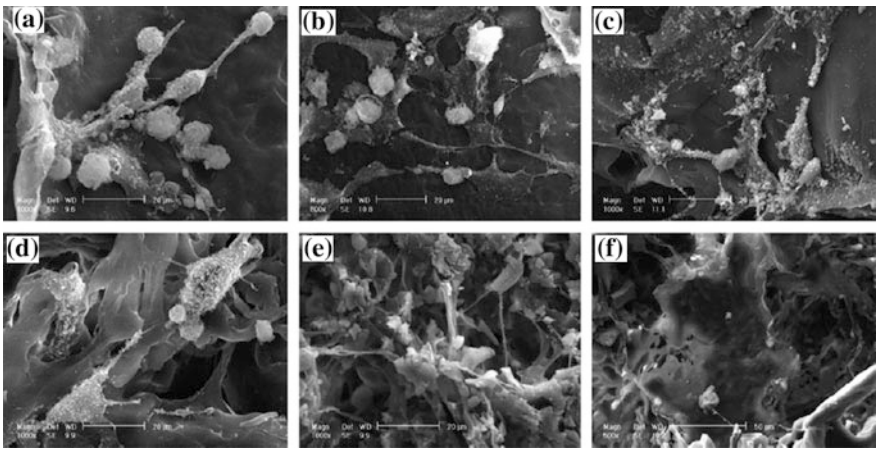

Fig. 3 Scanning electron microscopy images of the pure PCL (**a**) and nanocomposite scaffolds containing **b** 10 wt%, **c** 20 wt%, **d** 30 wt%, **e** 40 wt%, and **f** 50 wt% forsterite cultured with SaOS-2 cells for 2 days (Diba et al. 2012). Copyright 2012. Adopted with the permission from Elsevier

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

2.3.2 Poly(Methyl Methacrylate) (PMMA)

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

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

2.3.3 Poly(L-Lactic Acid) (PLLA)

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

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

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

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

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

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

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

2.3.5 Poly(Ethylene Glycol) (PEG)

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

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

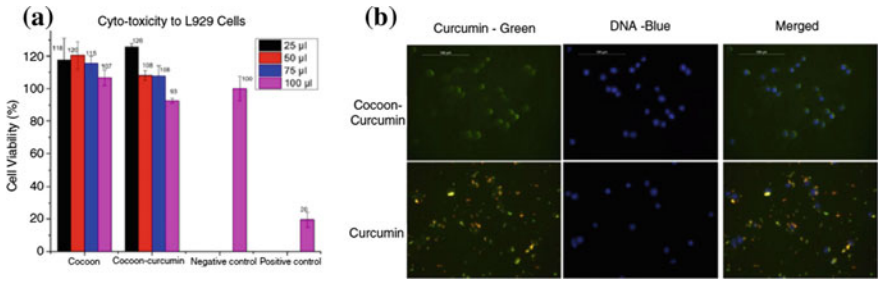

Fig. 4 Cytotoxicity of cocoon and curcumin samples at various concentration (**a**) and Uptake of cocoon–curcumin (**b**). Images revealed that the uptake of curcumin with cocoon and no uptake without cocoon (Hindumathi et al. 2018). Copyright 2018. Adopted with the permission from Elsevier

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

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

2.3.6 Polystyrene (PS)

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

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

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

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

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

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

2.3.7 Polyvinylidene Fluoride (PVDF)

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

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

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

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

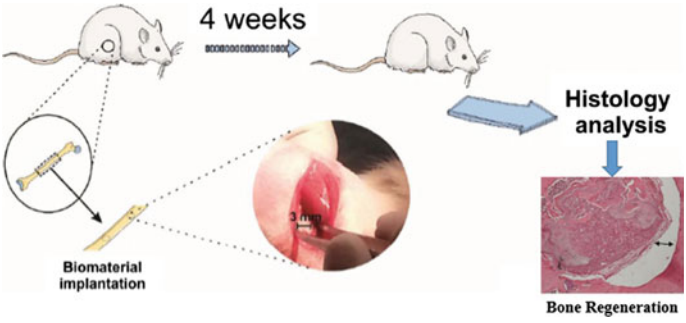

Fig. 5 Bone regeneration at the defected site in Wistar rats (Ribeiro et al. 2017). Copyright 2017. Adopted with the permission from Elsevier

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

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

2.4 *Gas Permeable Polymeric Membranes for Biomedical Applications*

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

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

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

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

2.5 Other Polymeric Composites for Biomedical Applications

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

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

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

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

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

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

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

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

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

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

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

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

2.6 Polymer Microarrays for Biomedical Applications

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

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