1
Biomaterials for Biomedical Applications

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1.1
Introduction

Biomaterials play numerous critical roles in biomedical applications. Historically, biomaterials were obtained from natural sources, such as purified collagen, gelatin, silk, or cotton. Advances in polymer chemistry supplemented these natural polymers with first-generation medical polymers. Currently, polymers are used in a wide range of biomedical applications, including applications in which the polymer remains in intimate contact with cells and tissues for prolonged periods. Although many of these polymer materials have been tested for various applications, it is widely recognized that the current range of biomaterials available will not be adequate for the vast range of applications in drug delivery, artificial organs, and tissue engineering technologies. To select appropriate materials for biomedical applications, it will help to understand the influence of these materials on viability, growth, and function of attached or adjacent cells. The selection of biomaterials plays a key role in the design and development of biomedical products. While the classical selection criterion for a safe, stable implant dictated choosing a passive, inert material, it is now deduced that any such device is capable of eliciting a cellular response [1, 2]. Therefore, it is now widely accepted that a biomaterial must interact with tissue to repair, rather than simply be a static replacement. Furthermore, biomaterials used directly in tissue repair or replacement applications (e.g., artificial skin) must be more than biocompatible; they must elicit a desirable cellular response. Consequently, a major focus of biomaterials for tissue engineering applications centers on harnessing control over cellular interactions with biomaterials, often including components to manipulate cellular response within the supporting biomaterial as a key design component. Specific examples of such components include protein growth factors, anti-inflammatory drugs, gene delivery vectors, and other bioactive factors to elicit the desired cellular response [3, 4].

It is important for the developer of biomedical products to have several biomaterial options available, because each application calls for a unique environment for cell–cell interactions. Examples of some such applications are as follows:

a) Support for new tissue growth (wherein cell–cell communication and cell availability to nutrients, growth factors, and pharmaceutically active agents must be maximized);
b) Prevention of cellular activity (where tissue growth, such as in surgically induced adhesions, is undesirable);
c) Guided tissue response (enhancing a particular cellular response while inhibiting others);
d) Enhancement of cell attachment and subsequent cellular activation (e.g., fibroblast attachment, proliferation, and production of extracellular matrix (ECM) for dermis repair);
e) Inhibition of cellular attachment and/or activation (e.g., platelet attachment to a vascular graft); and
f) Prevention of a biological response (e.g., blocking antibodies against homograft or xenograft cells used in organ replacement therapies).

The processability of biomaterials is a key step for developing biomedical applications. Nine potential biomedical applications areas have been identified [5]:

1) Membranes in extracorporeal applications such as oxygenators;
2) Bioactive membranes, for example, controlled release delivery systems and artificial cells;
3) Disposable equipment, for example, blood bags and disposable syringes;
4) Sutures and adhesives including biodegradable and nonbiodegradable materials;
5) Cardiovascular devices such as vascular grafts;
6) Reconstructive and orthopedic implants;
7) Ophthalmic devices such as corneas and contact lenses;
8) Dental restorative materials including dentures;
9) Degradable plastic commodity products.

This chapter surveys the various biomaterials that have been used or are under consideration for use in biomedical applications.

1.2
**Polymers as Hydrogels in Cell Encapsulation and Soft Tissue Replacement**

Hydrogels are one of the most promising classes of biomaterials for biomedical applications because they have good biocompatibility and a large amount of equilibrium water content [6]. Wichterle [7] achieved the following four crucial criteria with the design.

a) Preventing component release.
b) Creating a stable chemical and biochemical structure.

c) Having a high permeability for nutrients and waste.
d) Assuming physical characteristics similar to those of natural living tissue.

Hydrogels have water content and mechanical properties that are similar to those of human tissue and find use in many biomedical applications. The first biomedical use for synthetic hydrogels, which was established in 1954, was as an orbital implant. Wichterle designed soft contact lenses from hydrogels in 1961. Since then, hydrogel use for biomedical applications has included wound dressings, drug delivery systems, hemodialysis systems, artificial skin, and tissue engineering [8–10]. The structural similarity of hydrogels to that of the human ECM creates promising applications as a scaffold material for cell-based tissue engineering [10]. Hern and Hubbell [11] first modified PEGA with the adhesive peptide arginyl–glycyl–aspartic acid (RGD) to enhance cell adhesion and promote tissue spreading. In separate experiments, PEG methacrylate has been modified with phosphoester and RGD to enhance bone engineering [12, 13]. In addition, hyaluronic acid has been copolymerized with PEGDA+RGD to support cell attachment and proliferation as well as to improve cartilage repair [14, 15]. Poly(γ-benzyl L-glutamate) (PBLG) is one of the synthetic polypeptides that has attracted attention for use in drug delivery matrices [16]. Hydrogels developed by combining polyisobutylene (PIB) and hydrophilic polymer segments were used for coating Gore-Tex vascular grafts and showed good biocompatibility [17]. These hydrogels were also used as membrane carriers for insulin-producing porcine platelet implants [18]. Shu *et al.* [19] synthesized thiolated HA and then conjugated it to PEG for the benefit of *in situ* injection and cell encapsulation and proliferation. PEG and HA may be further modified by physical cross-linking of bioactive factors, which is one of the methods used to create biomimetic hydrogels. Growth factors remain active after encapsulation to enhance the proliferation and differentiation of encapsulated cells or to improve local tissue regeneration [20, 21]. Growth factors that have been entrapped in hydrogels include bone morphogenetic protein-2 (BMP-2), fibroblast growth factor, vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), and transforming growth factor β (TGF-β), among others [21–25].

The examples in the following paragraph illustrate the effect of biomimetic hydrogels on three different tissues. Several groups have demonstrated *in vivo* secretion of cartilaginous matrix using chondrocytes encapsulated in hydrogels. The use of hydrogels to support chondrocyte growth and matrix production is well established. Current efforts focus on bringing hydrogels closer to clinical applications. Lee *et al.* [20] incorporated TGF-β1 into a chitosan scaffold in which chondrocytes were cultured. The chondrocytes cultured in scaffolds containing TGF-β1 exhibited significantly greater proliferation and GAG and type II collagen production than did chondrocytes cultured in control scaffolds lacking TGF-β1. Recently, thermoplastic biodegradable hydrogels have been designed for biomedical applications including drug delivery systems: polyisobutylene (PIB)-based materials as potential materials for soft tissue replacement, specifically for vascular grafts and breast implants [26] (Figure 1.1). Polyesters (PET),
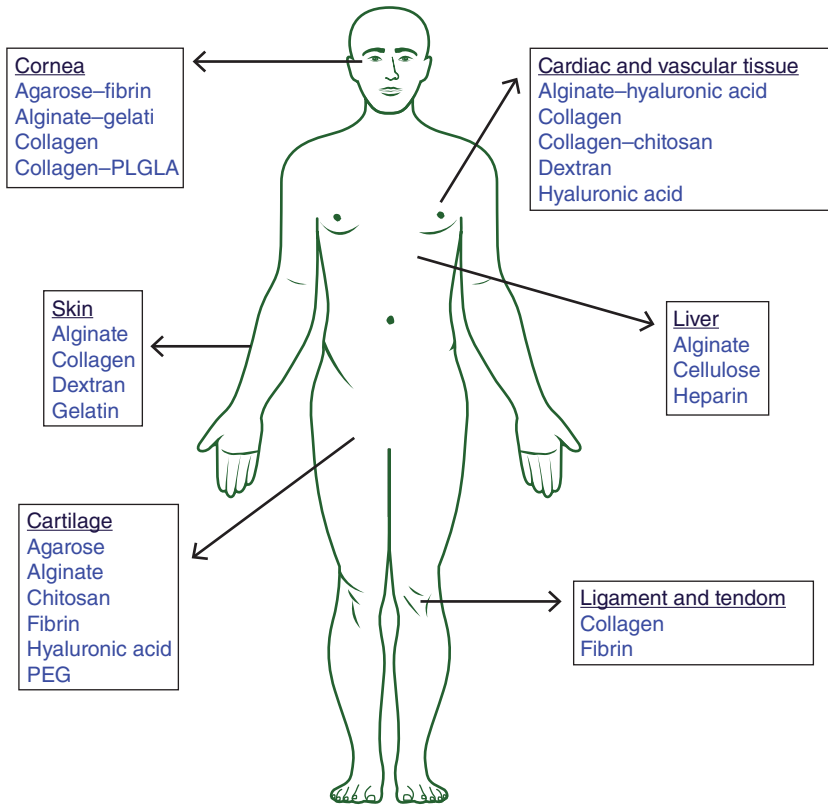
Figure 1.1 Polymer hydrogels used for tissue replacement.

fluoropolymers (PTFE), polypropylene (PP), polyurethanes (PU), and silicones have played a crucial role in the development of polymeric materials for soft tissue replacement [27]. This biomaterial represents a conceptually new soft biomaterial for potential biomedical application (Table 1.1).

1.3
Biomaterials for Drug Delivery Systems

A defining therapeutic feature of a biodegradable polymer used in modern drug delivery is facile degradation into oligomers or monomers with concomitant kinetically controlled drug release profiles. Polymeric delivery systems are mainly used to achieve either temporal or spatial control of drug delivery [28]. Essentially, polymeric vehicles enable drugs to be delivered over an extended period of time and to the local site of action. They are designed to enhance drug safety and efficacy, and to improve patient compliance. The use of polymers is designed to maintain therapeutic levels of the drug, reduce ide-effects, decrease the amount

Table 1.1 Natural and synthetic polymers commonly used in the synthesis of hydrogels [10].

Natural hydrogels	Synthetic polymers
Hyaluronic acid (HA)	Hydroxyethyl methacrylate (HEMA)
Chondroitin sulfate	Methoxyethyl methacrylate (MEMA)
Matrigel	*N*-Vinyl-2-pyrrolidone (NVP)
Alginate	*N*-Isopropyl Aam (NIPAAm)
Collagen	Acrylic Acid (AA)
Fibrin	Poly(ethylene glycol) acrylate (PEGA)
Chitosan	Poly(ethylene oxide) diacrylate (poly(ethylene glycol) diacrylate (PEGDA))
Silk	Poly(vinyl alcohol) (PVA)
Gelatin, Agarose, and Dextran	Poly(fumarates)

of drug molecule and the dosage frequency, and facilitate the delivery of drugs with short *in vivo* half-lives [29]. In polymer-based drug delivery, polyalkyl-cyanoacrylates (PACAs) have evolved diverse versatility as drug nanoparticle carriers for indomethacin [30], gangliosides [31], oligonucleotides [32], anti-epileptic medications including Ethosuximide [33], insulin [34], saquinavir [35], hemoglobin [36], and nucleoside analogs against human immunodeficiency virus (HIV) [37]. Translational research into poly(ethylene glycol) (PEG)–PACAs and actively targeted PACA systems [38, 39] have shown great promise for use *in vivo* such as the recently completed phase I and phase II studies of Doxorubicin Transdrug® for primary liver cancer.

Polyphosphazenes have been used for controlled release of naproxen [40–42], calcitonin [43], colchicines [44], (diamine) platinum [45], (dach) platinum (II) [46], insulin [47], other model proteins [48, 49], methylprednisolone [50, 51], methotrexate [52], tacrolimus [53], tempamine [54], and plasmid deoxyribonucleic acid [55]. Studies of blood biocompatibility *in vitro* with polyorganophosphazenes have shown no morphological changes or aggregation with platelets [56] and good biocompatibility after transplantation [57]. The first long-term biocompatibility *in vivo* study with polyphosphazene was reported in 2003 by Huang *et al.* [58] with a porcine coronary stent model, which showed no signs of either hyperplasia or proliferative response after 6 months. In the same family as polyphosphazenes, polyphosphoesters (PPEs) are inorganic polymers. To date, biocompatibility studies have been quite favorable, showing limited toxi-city [59]. Numerous studies by Leong's group have used PPEs for block copolymer design including poly(2-aminoethyl propylene phosphate) (PPE-EA) for gene delivery [60–63] and PPE microspheres for nerve growth factor delivery. *In vivo* studies with the Paclimer delivery system, 10% w/w paclitaxel encapsulated in biodegradable polyphosphoester microspheres, with a single intratumoral or intraperitonel injection showed 80% release of the drug after 90 days in a human lung cancer xenograft model. This sustained release showed significant inhibition

of nonsmall cell lung cancer nodules with three- to sixfold longer tumor doubling times compared with free paclitaxel and vehicle controls [64–66]. A recent translational canine study to evaluate dose escalation and neurotoxicity showed excellent results throughout the 120-day study with no evidence of systemic toxicity or gross morphological or physiological changes in the animals [67]. Polyesters represent perhaps the largest family of biodegradable polymers including aliphatic polyesters such as poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactide-co-glycolide) (PLGA), polydioxanone, polyglyconate, polycaprolactone, and polyesteramide [68]. Several biodegradable polyesters, many of which are PGA derivatives, have also been used in nonviral gene delivery primarily to alleviate cytotoxicity such as poly[α-(4-aminobutyl)-L-glycolic acid] (PAGA) [69, 70], poly(D,L-lactic acid-co-glycolic acid) (PLGA) [71–73], PEG–PLGA–PEG [74] and poly(4-hydroxyl-1-proline esters) [75, 76]. PCL block copolymers have been used to deliver doxorubicin [77], cyclosporine A [78, 79], geldanamycin [80], rapamycin [81], 97 amphotericin B [82, 83], dihydrotestosterone [84], indomethacin [85, 86], and paclitaxel [87]. Polyorthoesters (POEs) were developed and reported by Heller *et al.*, nearly 40 years ago for use as implanted biomaterials and as drug delivery vehicles [88] (Figure 1.2).

Biodegradable polymers have truly revolutionized controlled drug delivery design and biomaterial applications for implants and tissue engineering. A biodegradable derivative of poly(ethylene glycol)-co-poly(L-lysine) (PEG–PLL) with grafted histidine residues has been synthesized for local gene therapy with transgene expression levels fourfold higher than PLL alone [89, 90]. With the help of biodegradable stents, clinicians can site-specifically control drug release to treat coronary artery disease through delivery of traditional small molecules
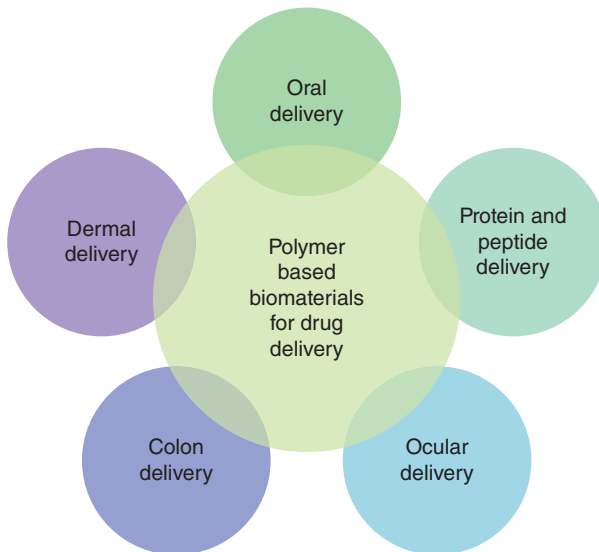

Figure 1.2 Biomaterials utilized for various drug delivery systems.

and, now, gene therapy [91, 92]. Biodegradable block copolymers and block copolypeptides have significantly endowed novel drug delivery systems with beneficial pharmacokinetic and biocompatible properties.

1.4
Biomaterials for Heart Valves and Arteries

Devices or natural tissues can be used to replace heart valves or arteries. These replacement materials are used when the natural heart valves or arteries fail to function properly, which can result in death or severe disability if left uncorrected. Such replacement materials help to restore the flow of blood that the body needs in order to function properly. Natural tissues are commonly used as replacement materials; alternatively, pyrolytic carbon mechanical valves are used to replace heart valves, while metal stents can be used to hold arteries open. However, there is interest in the development of polymers as replacement materials for heart valves and for use with stents. Heart valves are composed of connective tissue (collagen, elastin, and glycosaminoglycans [93], and open or close in response to pressure gradients and hemodynamics [94]. Flexible leaflet aortic replacement valves were developed in the 1960s [95]. There has been recent interest in developing polymeric valves from polyurethanes. Polyurethanes have good blood compatibility [96] and can be made into physiological shapes, forming valves that are flexible [97]. Synthetic poly(carbonate urethane) valves have been recently developed for both the aortic and the mitral positions [98]. *In vivo* results are promising, with tests being performed without anticoagulants in some cases, and show greater signs of durability than bioprostheses when tested in calves [99], or sheep [100].

   Materials such as braided polyester, polybutester (a butylene terephthalate and poly(tetramethylene ether glycol) copolymer), polypropylene, PTFE, or e-PTFE can be used for replacement of mitral valves related repairs. However, during chordal replacement, the synthetic suture acts as a neochord. PTFE has been found to have material properties that are closer in nature to natural chordae than other materials such as braided polyester [101]. An alternative to synthetic chordae is the use of natural tissues, such as glutaraldehyde-tanned pericardial strips [102]. However, PTFE has been found to produce better clinical results than glutaraldehyde-tanned pericardial strips for chordal replacement [103]. Developments of new chordal replacement materials may further improve mitral valve repair in the long term. Tissue engineered synthetic chordae made from cultured fibroblast and smooth muscle cells have been reported, with added type I collagen [104, 105]. However, replacement synthetic chordae with properties closer in nature to real chordae may well provide benefits for mitral valve replacement (Figure 1.3).

   Stents are usually composed of metal wires forming the outer boundaries of an open cylinder. The most widely used stents are made from stainless steel [106] and are relatively inert when in place. Stents have been very successful clinically and may well be used in over 50% of angioplasty procedures [107]. The placement of
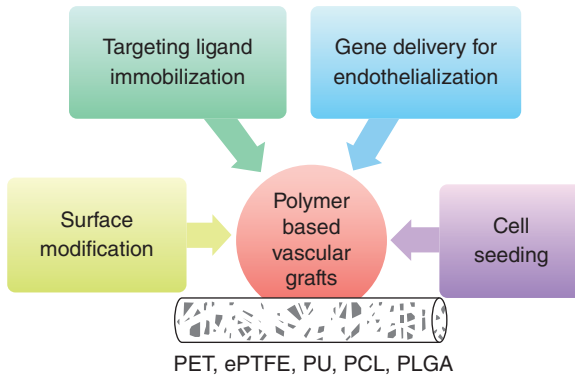
Figure 1.3 Polymers for artificial vascular grafts.

stents may damage the arterial endothelial layer [108], which may cause some of the problems associated with stents. Initially, stents were designed to be bioinert (by using materials such as stainless steel). However, coatings may be necessary to avoid restenosis. Polymer coatings, including natural polymers such as heparin (a polysaccharide), have been used on stents. Stents coated with resorbable polymers such as polycaprolactone and polyorthoester, and copolymers such as polyglycolic–polylactic acid, poly(hydroxybutyrate valerate), and poly(ethylene oxide)–poly(butylene terephthalate) have been compared *in vivo* as resorbable stent coatings [109]. Phosphorylcholine applied to the stents has the potential to prevent the stent from inducing the formation of a thrombus on its surface [110]. Currently, polymers within stents hold most promise as coatings used to control drug delivery or release from or near stents to reduce restenosis and thrombus formation.

Polymer fibers composed of polydioxanones (PDS) were first tested for use as monofilament biodegradable surgical sutures and the degradation profile was later found to be affected by gamma irradiation [111]. Katz *et al.* [112] reported biodegradable, poly(trimethylene carbonates) for monofilament surgical sutures currently marketed as Maxon. PLGA composed of LA–GA 10–90 has long-found utility as Vicryl (polyglactin 910), a biodegradable surgical suture licensed by Ethicon (Somerville, New Jersey) and, in 2002, Vicryl Plus became the first marketed suture designed to contain an antibacterial agent, Triclosan or 5-chloro-2-(2,4-dichlorophenoxy)phenol [113]. Lendlein and Langer reported a new thermoplastic elastomer based on PCL and poly(dioxanone), with both homopolymers having been used as suture materials [114]. Currently, much effort is being focused on using polyurethane (PU) in biomedical applications such as cardiac-assist pumps and blood bags, to chronic implants such as heart valves and vascular graft, hemodialysis bloodline sets, center venous catheters (CVCs), and intravenous (IV) bags [115, 116]. Lin *et al.*, demonstrated that water-soluble chitosan/heparin immobilized PU membranes effectively improved *in vitro* hemocompatibility and superior biocompatibility [117].

1.5
Biomaterials for Bone Repair

Bone is a metabolically active, highly vascularized tissue with a unique ability to regenerate without creating a scar [118]. Bone repair was proposed to be one of the first, major applications of tissue engineering [119]. The general concept of bone tissue engineering is based on the formation of a tissue engineering construct to encourage the regeneration of the damaged tissue [120]. The main physiological functions of the ECM include storage of the nutrients, growth factors, and cytokines as well as mechanical stabilization for anchorage-dependent cells [121]. In the context of bone tissue engineering, the scaffold should possess the following properties [122]:

a) biocompatibility,
b) bioresorbability/biodegradability,
c) open/interconnected porosity,
d) suitable topography and surface chemistry, and
e) appropriate mechanical properties.

To fulfill the above requirements, several different types of the materials have been proposed [123, 124]. Based on the origin, the scaffold materials may be divided into two main groups: (i) naturally derived materials such as collagen, glycosaminoglycans (GAGs), starch, chitosan, and alginates; and (ii) synthetic ones, including metals, ceramics, bioactive glasses, and polymers (listed in Table 1.2) [125–127]. In addition, the surface properties of the scaffold will influence cell adhesion and activity.

Table 1.2 Types of biomaterials used for preparation of scaffolds for bone tissue Engineering.

| Polymer	3D architecture
Naturally derived materials	
Collagen	Fibrous, sponge, hydrogel
Starch	Porous
Chitosan	Sponge, fibers
Alginates	Hydrogel, sponge
Hyaluronic acid (HA)	Hydrogel
Polyhydroxyalkanotes (PHA)	Porous, hydrogel
Synthetic polymers	
Polyurethanes (PU)	Porous
Poly(-hydroxy acids) (i.e., PLLA, PGLA)	Porous
Poly(ε-caprolactone) (PCL)	Sponge, fibers
Poly(propylene fumarates) (PPF)	Hydrogel
Titanium	Mesh
Calcium phosphate	Porous

The current generation of synthetic bone substitutes is helping to overcome the problems associated with availability and donor-site morbidity. Alternatives to autografts and allograft preparations have included calcium-phosphates, bioactive glass, polymers, and many other composite materials [128–130]. Over the years, many materials have been described for application in bone repair (Table 1.3).

Organic and inorganic synthetic polymers have been used in a wide variety of biomedical applications. Other biodegradable polymers currently being studied for potential tissue engineering applications include polycaprolactone, polyanhydrides, and polyphosphazenes [131–133]. PMMA has also been widely used in dentistry. Other polymers such as polytetrafluoroethylene (PTFE) have also been used for augmentation and guided bone regeneration [134, 135]. Ceramics have also been widely used in orthopedic and dental applications [136] (Figure 1.4).

HA is biocompatible, and stimulates osseo-conduction [137, 138]. By recruiting osteoprogenitor cells and causing them to differentiate into osteoblast-like bone-forming cells, it is resorbed and replaced by bone at a slow rate [139]. Bioactive glasses are another class of interesting material as they elicit a specific biological response at the interface of the material, which results in the formation of a bond between tissues and the material [140]. Calcium phosphate (CaP)-based biomaterials have found many applications for bone substitution and repair. These materials show excellent *in vivo* biocompatibility, cell proliferation, and resorption [141].

Table 1.3 Types of biomaterials (polymers, ceramics, and composite) used for preparation of scaffolds for bone tissue Engineering.

Polymers	Ceramics	Composite/natural
Polylactic acid	Bioglass	Poly(D,L-lactide-co-glycolide) - bioactive glass
Polyglycolic acid	Sintered hydroxyapatite	Extracellular matrix (ECM)
Polycaprolactone	Glass-ceramic A–W	Hyaluronan-linear glycosaminoglycan (GAG)
Polyanhydrides	Hydroxyapatite (HA)-calcium phosphate-based ceramic	Demineralized bone matrix (DBM)
Polyphosphazenes	Collagraft – commercial graft. HA tricalcium phosphate ceramic fibrillar collagen	
Polymethylmethacrylate (PMMA)	Bioactive glass	
Polytetrafluoroethylene (PTFE)	Sol–gel-derived bioactive glass	
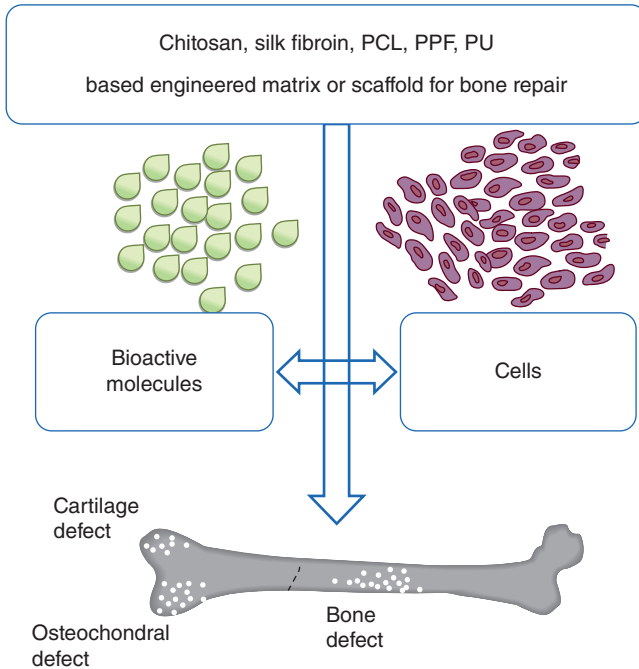
Figure 1.4 Polymer based matrix for bone repair.

1.6
Conclusion

In this chapter, a range of biomaterials from various polymers used for biomedical applications have been described. Biomaterials need to possess a number of key features to meet the stringent requirements of biomedical applications. The chosen biomaterial must provide a biocompatible and biodegradable matrix with interconnected pores to ensure that the body tolerates the conduit and also promotes nutrient and cellular diffusion. Furthermore, the material initially needs to provide mechanical stability and act as a template to guide three-dimensional tissue growth. There is great potential to produce replacement blood vessels and heart valves, which can be met with further advancements in tissue engineering. Developments in the area of cellular replacement tissues have led to replacement arteries and heart valves that can potentially allow host cell infiltration. Tissue engineering of an artery with an ECM made by cells in culture also led to a replacement artery with suitable properties for implantation. It is likely that there will be further advances with these technologies. Developments in polymeric material for use with stents in drug delivery systems, and to produce heart valves may allow further developments in replacement devices. While, at present, polymer stents have not proved to be successful, improvements in technology may allow their use in the future. The ultimate test for all new devices that

are used to repair or replace arteries or heart valves is how well they perform clinically, and how they compare with existing devices. The development of these valves into successful clinical implants will ultimately depend on their long-term function, which can only be determined clinically. Furthermore, their long-term durability will also determine their clinical value and lead to complete optimization of their production; very useful techniques will be available that may help produce prominent cardiovascular replacement materials. Furthermore, just as it is true that no one material will satisfy all the design parameters required in all applications within the tissue engineering field, it is also true that a wide range of materials can be tailored for discrete applications, through the use of the most appropriate processing methodologies and processing parameters selected.

Abbreviations

AA	acrylic acid
BMP-2	bone morphogenetic protein-2
CVCs	center venous catheters
DBM	demineralized bone matrix
GAG	glycosaminoglycan
HA	hyaluronic acid
HEMA	hydroxyethyl methacrylate
IGF-1	insulin-like growth factor 1
IV	intravenous
MEMA	methoxyethyl methacrylate
NIPAAm	*N*-isopropyl Aam
NVP	*N*-vinyl-2-pyrrolidone
PACAs	polyalkylcyanoacrylates
PAGA	poly[α-(4-aminobutyl)-L-glycolic acid]
PCL	Polycaprolactone
PDS	polydioxanones
PEG	poly(ethylene glycol)
PEGA	poly(ethylene glycol) acrylate
PEGDA	poly(ethylene oxide) diacrylate (poly(ethylene glycol) diacrylate
PEG−PLL	poly(ethylene glycol)-co-poly(L-lysine)
PET	polyesters
PIB	polyisobutylene
PIB	polyisobutylene
PLA	poly(lactic acid)
PLGA	poly(D,L-lactic acid-co-glycolic acid)
PLGA	poly(lactide-co-glycolide)
PMMA	polymethylmethacrylate
POEs	polyorthoesters
PP	Polypropylene
PPE-EA	Poly(2-aminoethyl propylene phosphate)

PPF	poly(propylene fumarates)
PTFE	polytetrafluoroethylene
PTFE	fluoropolymers
PU	polyurethane
PVA	poly(vinyl alcohol)
TGF-β	transforming growth factor β
VEGF	vascular endothelial growth factor
CaP	calcium phosphate
ECM	extracellular matrix
PBLG	poly(γ-benzyl ʟ-glutamate)
RGD	arginyl−glycyl−aspartic acid

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