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Biodegradable polymers—an overview†

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The revelation of biodegradable polymers dates back to many years ago. From then, their emergence leads to the surge of many biomaterials applicable in various fields like controlled drug delivery, regenerative medicine, orthopedic and long-term implants which proved out to be momentous contributions of these materials. The immense effort and investigation kept on these materials are reflected by significant upsurge of the biodegradable polymer-based marketed products and ongoing clinical trials of these materials. The synthetic versatility and flexible features of these polymers to get custom designed in accordance with need make them attractive for various therapeutic strategies. Long-term biocompatibility and avoidance of surgery to remove implants are the main advantages of biodegradable materials over biostable polymers by which the former stand in for various indications over the latter. This review gives an overview on various biodegradable polymers with details on properties, mode of degradation and the potential biomedical applications associated with them. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: biodegradable polymers; biomedical applications; drug delivery

INTRODUCTION

Biodegradable polymers are generally divided into two groups, natural and synthetic based on their origin. Synthetic origin polymers offer advantages over natural polymers by being versatile with a wide spectrum of applications, having a capability to tailor mechanical properties and altering the rate of degradation according to the need. On the other hand, natural polymers seem to be attractive due to their excellent biocompatibility, but they have not been fully investigated due to their undesirable properties like antigenicity and batch-to-batch variation.[1–3]

The instability of the polymers leading to biodegradation has proven to be immensely important in many medical applications.[4] Biodegradable polymers offer tremendous potential in many exciting applications like drug delivery, tissue engineering, gene therapy, regenerative medicine, temporary implantable devices, coatings on implants, etc.[5–8] The basic criteria for selecting a polymer for use as a degradable biomaterial are to match the mechanical properties and the degradation rate to the needs of the application, non-toxic degradation products, biocompatibility, shelf life/stability, processability and cost.[1,9] The mechanical properties should match the application so that sufficient strength remains until the surrounding tissue has been healed.[10] There are many polymers available for different application (Fig. 1) where the choice of the polymer is dependent on the requirements that a particular biomaterial demands. With respect to drug delivery, it is the time of release that governs the type of polymer, size and shape of the device.[1,11] However, clinically approved polymers such as lactide and glycolide polymers are the polymer of choice for any application.

Polymers found a multitude of uses in the medical industry, beginning with biodegradable sutures first approved in the 1960s.[4] Polyesters which are the representative class of biodegradable synthetic polymers continue to remain attractive in many clinical applications due to their unique properties. Other classes of polymers which made a significant contribution to the field of biomaterials include polyurethanes, polyanhydrides, polyaminoacids, etc.[2,10,12,13] Some of the natural polymers which are found to be biocompatible are extensively investigated which lead to some breakthrough innovations like *Abraxane* (paclitaxel-loaded albumin particles) based on nab technology.[14,15] There are various successful products in clinical practice, and the number of such products is ever increasing and at a faster rate from the past few decades.[1,11] Attempts have been made to develop injectable polymer compositions for use in tissue engineering applications which offer many advantages like avoiding surgery, filling cavities with complex geometries, and providing good bonding to tissue.[9] The inability of a single biodegradable polymer to meet all the requirements for biomedical scaffolds leads to the development of biodegradable polymer matrix nanocomposites in the field of tissue engineering. These nanocomposites increase and modulate mechanical, electrical and degradation properties. Polymer matrix composites have the advantage of being very versatile, allowing fine tuning of their final properties.[16] Biodegradable copolymers exhibiting temperature-responsive sol–gel transition have recently drawn much attention with their promising application in the fields of drug delivery, cell implantation and tissue engineering.[17] This class of copolymers exhibit amphiphilic nature due to the presence of hydrophilic (PEG)/hydrophobic segments (PLA/PLGA/PCL). These injectable hydrogels can be implanted in the human body with minimal surgical invasion. Strategies based on gene delivery or gene-activating biomaterials have

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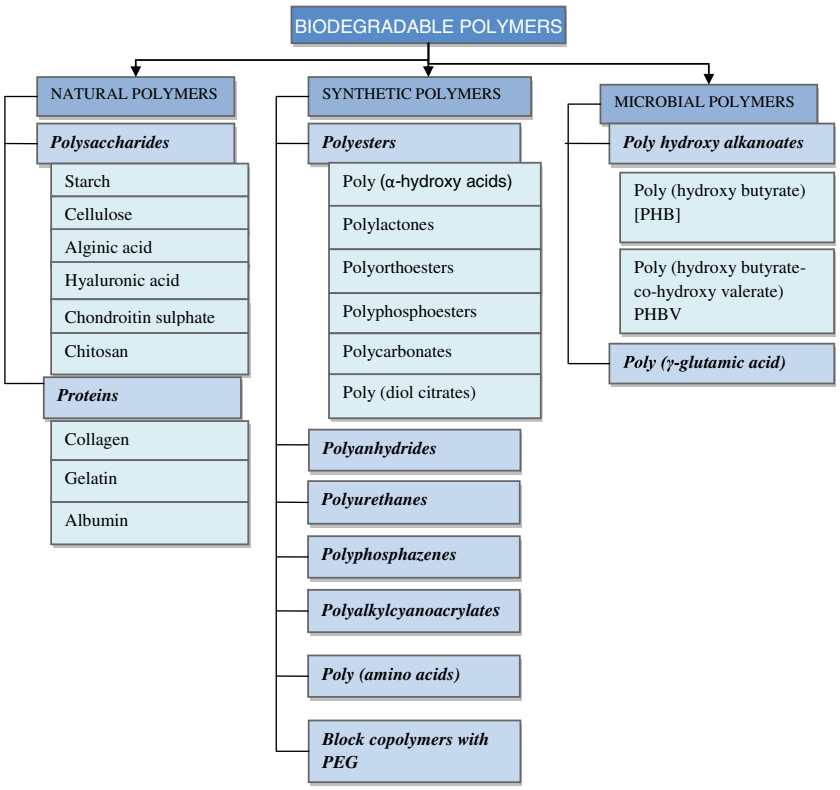

Figure 1. Classification of Biodegradable polymers.

a great potential in regenerative medicine, but the long-term safety of such therapies remains to be proven (Fig. 2 and Fig. 3).[18]

SYNTHETIC POLYMERS

Polyesters

Poly (α-hydroxy acids)

This class of polyesters is most extensively investigated for biomedical applications due to their excellent biocompatibility and tunable degradation properties. They laid the foundation for the development of the first synthetic suture material based on polyglycolide. The category of poly (α-hydroxy acids) includes poly (glycolic acid), poly (lactic acid) and a range of their copolymers (poly (lactic-co-glycolic acid). These polymers are synthesized by ring opening or condensation polymerization depending on the starting monomer units.[2,9,10] Poly (α-hydroxy acids) undergo degradation by non-enzymatic hydrolysis of ester linkages along the backbone into lactic acid and glycolic acid which are resorbed through natural metabolic pathways. The emergence of these polymers from initial resorbable sutures into most preferred materials for controlled drug delivery makes them the representative class of biodegradable polymers.[6,11] The first FDA approved biodegradable synthetic suture based on polyglycolide DEXON® was developed in 1970. Polyglycolide with high crystallinity shows low solubility in organic solvents and good mechanical properties due to which it is indicated for orthopedic applications (Biofix®). Despite many advantages, its application is limited due to higher rate of degradation,

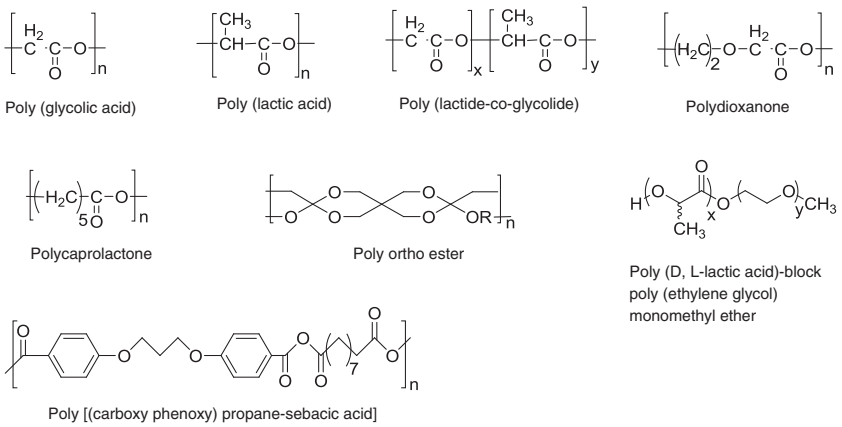

Figure 2. Chemical structures of common biodegradable synthetic polyesters and anhydrides.

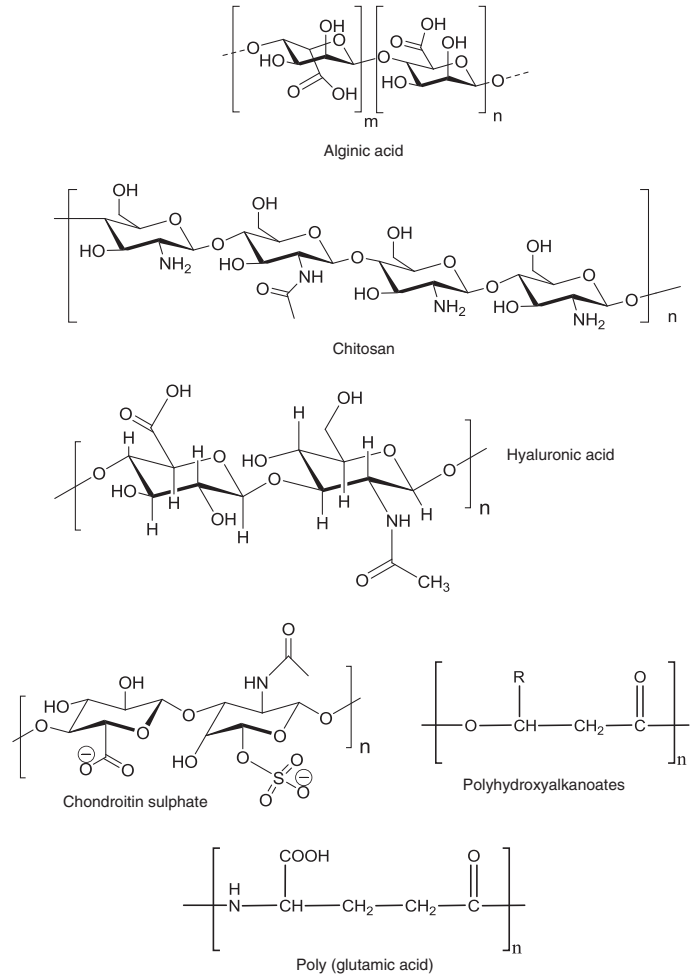

Figure 3. Chemical structures of biodegradable natural polymers.

lowsolubility and accumulation of acidic degradation products.[1,19,20] Polylactides unlike polyglycolide are present in many forms due to the optical isomerism of lactic acid. Polymerization of isomers of lactide (L-lactide and D-lactide) results in crystalline polymers with about 40% crystallinity, whereas polymerization of racemic mixture (DL-lactic acid) results in amorphous polymers with lower mechanical strength. Poly (L-lactic acid) and poly (DL-lactic acid) are more preferred for biomedical applications in which the former is used for bone fixation devices (Bio Interference Screw®, BioScrew®, Bio-Anchor®) and the latter is suitable candidate as a drug delivery vehicle.[5] The rate of degradation depends on the molecular weight of polymer, crystallinity and porosity of the matrix. Being more hydrophobic compared to polyglycolide, it shows a slower rate of degradation.[12,13,21] Copolymers of polylactides and polyglycolides [poly (lactide-co-glycolide)] were developed to overcome the demerits of individual polymers and for better property modulation. The properties of these copolymers like crystallinity and rate of degradation are decided by the proportion of each of the polymers. Synthetic versatility obtained by different LA/GA ratios makes it suitable for different applications (PuraSorb®PLG: 80 L/20G; Vicryl®: 90G/10L; Vicryl Mesh®; Dermagraft®). PLGA is being extensively investigated for their potential in tissue regeneration, drug and protein delivery which is proven successful by CYTOPLAST Resorb® and LUPRON DEPOT®. As bulk degrading polymers like poly (α-hydroxy acids) cannot follow zero-order kinetics, surface eroding polymers were developed to overcome this disadvantage.[1,9,11,20]

Polylactones

Polycaprolactone (PCL) is a semicrystalline polymer with solubility in common solvents making it easily processable. Hydrolytically labile ester linkages are responsible for its degradation although slow (2–3 years). Copolymer blends and mixtures of polycaprolactone with other polymers, low molecular weight polyols and macromers alter the rate of degradation and other properties which broaden their potential in a range of applications.[10,22–24] For instance, copolymer of PCL with polyglycolide or polylactide results in rapid degradation and less stiffer fibers (MONACRYL®). The property of slow degradation leads to investigation of PCL as a vehicle for long-term delivery of drugs/vaccines (Capronor®) and cell-based therapies. Capronor® is a long-term contraceptive device loaded with levonorgestrel.[1,2]

Poly (p-dioxanone) [PDS], another polylactone, was used in the development of first commercial monofilament suture in 1980s. It is a semicrystalline polymer with a very low *Tg* of −10°C to 0°C.[25–27] The slow to moderately degrading PDS breaks down by non-specific scission of ester backbone in to glycoxylate which is further converted into glycine. Bone fixation screws based on PDS are available as Orthosorb Absorbable Pins®.[1,6]

Polyorthoesters

Polyorthoesters (POE), surface eroding polymers which overcome the disadvantages of bulk eroding biodegradable polymers, were first developed by ALZA Corporation (Alzamer®).The hydrophobic nature of these polymers combined with hydrolytically labile bonds on the surface makes them excellent materials for drug delivery of hydrolytically sensitive agents. Moreover they offer zero-order release profile combined with enhanced stability of the drug which is very difficult to attain with conventional polyesters.[1,2,11] These are relatively easily synthesized by reacting a diol and a diketene. The rates of degradation can be altered by using diols with different degrees of flexibility and by addition of acidic and basic excipients. Polyols based on lactides can be copolymerized to increase degradation rates ranging from 15 to hundreds of days. Apart from tailoring the polymer to suit the degradation profile, pH sensitivity of them also makes them attractive for many drug delivery systems. So far, four different classes of poly (ortho esters) have been developed with different properties among which POE IV has been considered as a potential candidate for biomedical applications because of its excellent scalability and well controlled release profile offered by it. γ-Hydroxybutyric acid, the degradation product of POE I, showed the autocatalytic effect for which POE II was developed to overcome it. Scalability issues and poor consistency of POE III have led to the development of POE IV which is in turn a modified version of POE II. Lactic and glycolic segments were incorporated into POE IV to achieve the required degradation rates.[28–32]

Polyphosphoesters

Polyphosphoesters (PPE) were developed in the 1970s by Penczek and his colleagues. They belong to a class of inorganic polymers containing phosphorous atom in their backbone. These polymers are synthesized by various routes like ring opening, poly condensation and poly addition reactions. Hydrolytic or enzymatic cleavage of phosphoester bonds in the backbone produces phosphate, alcohol and diols as breakdown products. Novel polymer prodrugs are developed using the pentavalency of phosphorous atom which helps in linkage of drugs or proteins to the polymer. Aminoethyl, aminohexyl and methyl-amino ethyl PPEs are being investigated for gene delivery.[25,33–36] Synthetic versatility of this polymer has led to the development of a copolymer poly (lactide-co-ethyl phosphate) for the delivery of chemotherapeutic agents (PACLIMER®). This polymer further finds its application as nerve conduits and as scaffolds for tissue engineering.[2,6]

Polycarbonates

Polyimino carbonates, tyrosine-based carbonates, cholesterol end-capped polycarbonates and ethyl ester pendant group containing polycarbonates are important materials of this class explored in biomedical applications. The low mechanical strength of this class of polymers turned out to be advantageous in soft tissue generation like poly trimethylene carbonate, as an implant material for soft tissue regeneration. The same property is not suitable for orthopedic applications and other fields where mechanical strength is required. Hence, the copolymers of polycarbonates were developed with glycolides and other cyclic lactones for application as suture materials and bone fixation devices (Maxon®, Acufex®, BioSyn®). More specifically, cholesterol end-capped polycarbonates are investigated in tissue engineering and tyrosine-based carbonates in orthopedic applications, and ethyl ester group containing polycarbonates are explored for bone fixation devices. Degradation of polycarbonates occurs by hydrolysis of the carbonate group, and the rate can be altered by variation in the pendant groups of the side chain.[6,9,10,33,37–39] Also, degradation of polycarbonates into two alcohols and carbon dioxide which alleviates the acid bursting effect of polyesters is worth mentioning.

Poly (diol citrates)

They belong to a group of elastomeric polyesters obtained by polycondensation reaction between citric acid and various diols. The variation in diols alters mechanical and degradation properties. Poly (1, 8-octanediol-co-citrate) (POC), one of the first poly (diol citrates), has been investigated for ligament reconstruction and vascular engineering due to its excellent mechanical properties and hemocompatibility. Other effects like decreased platelet adhesion and clotting exhibited by POC were shown to be better relative to the effects shown by PLGA or PTFE with regard to vascular engineering.[6,33,40,41]

Polyanhydrides

The low hydrolytic stability of these polymers coupled with hydrophobic nature makes them ideal candidates for short-term (weeks) controlled drug delivery applications. These types of surface eroding polymers allow the release of drug at a known rate at any time during erosion. Diacids are the most commonly used monomers for the synthesis of polyanhydrides by condensation activated by acetic anhydride. Apart from the basic types of aromatic, aliphatic, fatty acid polyanhydrides, there are other types of polymers belonging to this class with ester, ether and urethane linkages obtained from immense variety of diacid monomers available. Polyanhydrides degrade by hydrolysis of highly hydrolytically labile anhydride linkage. The rate of degradation can be custom designed according to application by means of minor changes in the polymer backbone. Aliphatic variety of polymers is soluble in organic solvents and degrades at a faster rate, whereas aromatic polyanhydrides are insoluble in organic solvents and degrade slowly. However, both are crystalline in nature.[4,9,42,43] The basic types are investigated for drug delivery, whereas modified versions are useful in orthopedic applications and tissue engineering. The most extensively investigated polyanhydride is poly [(carboxy phenoxy) propane-sebacic acid] (PCPP-SA). Gliadel® is based on PCPP-SA which is used as a delivery matrix for controlled delivery of the chemotherapeutic *carmustine* to treat brain cancer. Septacin®, a copolymer based on 1:1 sebacic acid and erucic acid dimer, is used for the delivery of gentamicine in the treatment of osteomyelitis. Poly (anhydrides-co-imides) have been developed in order to combine the mechanical properties of polyimides with surface eroding properties of poly anhydrides, and they are being explored as scaffolds for tissue engineering.[1,2,6,44,45]

Polyurethanes

These polymers belong to a class of thermoplastic synthetic polymers which are widely investigated for the development of long-term implants. Excellent biocompatibility, biological performances, mechanical properties and synthetic versatility lead to the development of biodegradable polyurethanes. Initially, biostable polyurethanes were used in various biomedical applications. Conventional polyurethanes (PUs) are synthesized by using three monomers like a diisocyanate, a diol or diamine chain extender and a long-chain diol. However, an equimolar

polymers in advanced technologies

portion of a diisocyanate and a diol yields biodegradable polyurethanes whose composition in turn plays a pivotal role in the rate of degradation. It is the degradation product (diamine obtained after hydrolysis of PU) that decides selection of starting diisocyanate. Accordingly, aliphatic diisocyanates yield less toxic corresponding diamine rather than aromatic diisocyanates.[1,6,9] For instance, ethyl lysine diisocyanate, methyl lysine diisocyanate, hexamethylene diisocyanate and 1, 4-butanediisocyanate are among the most preferred in formulating biodegradable polyurethanes whereas diphenyl diisocyanate and toluene diisocyanate are least the preferred due to high toxicity of the respective degradation products. Generally PUs comprises of hard segments composed of diisocyanate and chain extender, whereas soft segments are made up of diol. Polyols based on polyesters are mostly preferred because of their sensitivity to hydrolysis and their susceptibility to enzyme hydrolysis. PUs are being explored as cardiac pacemakers and vascular implants because of their tissue compatibility. An investigation in this field leads to development of more biocompatible and stable siloxane bases PUs which served as synthetic heart valves (Elast-Eon™). Adaptable chemistry and mechanical properties of PU are responsible for its application in various fields such as regeneration of neurons, vasculature, smooth muscle, cartilage and bone.[46–49]

Polyphosphazenes

They belong to a group of inorganic polymers with a backbone containing phosphorous and nitrogen atoms and two side groups attached to phosphorous atom on either side. Poly (dichlorophosphazene) was the first successfully synthesized polyphosphazene which has been used as intermediate for synthesis of different polyphosphazenes by using substitution reaction. The high reactivity of P–Cl linkage in poly (dichlorophosphazene) was used to replace the Cl group by alkoxide, aryloxide and other groups. Substitution by groups like amines, amino acid esters, glucosyl, glyceryl, lactate or imidazolyl units on phosphorous makes them biodegradable.[50,51] Glycolic or lactic acid substituted polymers show excellent hydrolytic degradability compared to monomers PLA/PGA. The rate of degradation can be finely tuned by appropriate substitution with a specific group and required proportion of the pendant groups. Apart from substituted side group, the pH and temperature of the surrounding environment also govern the rate of degradation. The degradation of these polymers yields a product composed of a side chain group along with phosphate and ammonia. These polymers are being investigated in drug delivery and skeletal tissue regeneration. Ionic polyphosphazenes obtained by substitution of glucosyl, glyceryl and methyl amino side groups are investigated as vaccine deliver systems. Pentavalency of phosphorous atom helps in the development of prodrugs and targeted delivery systems. Monolithic drug delivery matrices based on biodegradable polyphosphazenes are currently in development stage.[52,53]

Poly alkyl cyano acrylates

They belong to a unique class of biodegradable polymers which degrade by cleavage of C—C bond due to the activation by electron withdrawing groups. Knoevenagel condensation reaction is used in the synthesis of poly alkyl cyano acrylates (PACAs). The alkyl chain length is the deciding factor for the various properties of these polymers. Lower alkyl chain length polymers degrade in few hours and vice versa. Predominant mechanism is the hydrolysis of ester bond of the alkyl side chain of the polymer. Alkyl alcohol and poly (cyano acrylic acid) are water-soluble degradation products of ester hydrolysis. PACAs are one of the most perspective synthetic materials for the preparation of colloidal drug carriers, being biocompatible, biodegradable and low toxic. They have been investigated as tissue adhesives, embolization agents and hemostatic sealants (Dermabond®-used for wound closure is based on 2-octyl cyanoacrylate, TRUFILL® n-butyl cyano acrylate liquid embolic system is an artificial embolization device). They also find application in drug delivery using nanoparticle technology.[54,55] By grafting of PEG onto the nanoparticles, the surface of PACA-based nanosphere can be modified which leads to the formation of long circulating colloidal devices. Presently, higher chain length cyanoacrylates are being under investigation. Another active area of research is the treatment of gastric varices for which cyanoacrylates are the first choice. LIVATAG® (doxorubicin transdrug) based on PACA which demonstrates significant survival increase in advanced hepatocellular carcinoma patients is still in phase-II clinical trials. Several PACA-based nanoparticles are currently undergoing late stage clinical trials for cancer therapy.[56,57]

Poly (amino acids)

This class of polymers has been widely investigated for various biomedical applications owing to their structural similarity to natural proteins. However, due to immunogenicity and poor mechanical performances of these polymers, emergence of pseudo poly (amino acids) took place. Amino acid-derived polymers were obtained by grafting amino acids on synthetic polymers, copolymerization of amino acids with other monomers, derivation of block copolymers with amino acid sequences and PEG, and by development of pseudo poly (amino acids). The pseudo poly (amino acids) consists of amino acids linked by non-amide bonds like esters, imino-carbonates and carbonates.[6,10,58,59] Again, poly (amino acids) can be poly (acidic amino acids) [poly (l-glutamic acid), poly (aspartic acid)], poly (basic amino acid) [polylysine, polyarginine, poly l-histidine] and poly (neutral amino acids). Tyrosine-based poly (amino acids) are one among the most explored in this class. Tyrosine-based polycarbonates, polyarylates and polyesters are derived with differing physical and mechanical properties. Polycarbonates show exceptional strength and high degree of tissue compatibility, and polyarylates show flexibility and elastomeric behavior whereas copolymers with PEG exhibit water solubility and self-assembly properties. These polymers undergo degradation by hydrolysis of non-amide bonds, and the amino acid used in polymerization will be the product of degradation. Poly (DTH carbonates) has been extensively investigated for orthopedic applications due to its high mechanical strength and stiffness. Poly (l-glutamic acid) has been investigated as an attractive biodegradable biological adhesive and hemostat, whereas poly aspartic acid has been extensively investigated as a plasma expander. Peptide-amphiphile hydrogels are explored in the field of dental tissue engineering.[60,61]

Block co-polymers of polyesters/polyamides with PEG

These block copolymers were developed for injectable drug delivery applications. Triblock copolymers with blocks of different properties were developed, and the biodegradability depends on this composition. For instance, triblock copolymer (A-B-A) with poly (ethylene oxide) as A-component and poly (propylene

oxide) as B-component has been developed. This can be made biodegradable by substitution of B-component with hydrophilic PLA/PGA. These triblock copolymers exhibit thermo responsive behavior where they get converted into hydrogels after injection with response to the temperature of the surrounding environment.[6,62–64]

NATURAL POLYMERS

Polysaccharides

Cellulose

Cellulose is a polysaccharide consisting of a linear chain of D-glucose units. Cellulose is derived from D-glucose units, which condense through β (1 → 4)-glycosidic bonds. It is an important structural component of the primary cell wall of green plants, many forms of algae and the oomycetes. Cellulose consists of crystalline and amorphous regions. By treating it with strong acid, the amorphous regions can be broken up, thereby producing nanocrystalline cellulose, a novel material with many desirable properties which can be used as the filler phase in bio-based polymer matrices to produce nanocomposites with superior thermal and mechanical properties. Although it is a hydrophilic linear polymer, it is insoluble in water and organic solvents due to the presence of strong hydrogen bonds between polymer chains. Due to the high reactivity of hydroxyl groups, many derivatives of cellulose like methyl cellulose, hydroxypropylcellulose, hydroxypropyl methyl cellulose and carboxy methyl cellulose were developed. This polymer is enzymatically biodegradable by glycoside hydrolases into D-glucose units. It has been investigated as a wound dressing (AQUACEL®), hydrogel base and matrix for drug delivery.[2,65]

Starch

Starch or amylum is a carbohydrate consisting of a large number of glucose units joined by glycosidic bonds. This polysaccharide is produced by most green plants as an energy store. Starch is composed of linear and unbranched amylose and branched amylopectin units. Amylose with α (1 → 4) and amylopectin with α (1 → 6) linkages gets hydrolyzed by amylases and glucosidases, respectively. Thus, starch undergoes enzymatic degradation by amylases and glucosidases into corresponding sugar units. Due to its biocompatibility and biodegradability, the blends with this polymer were being investigated as drug delivery matrix (Contramid®), bioadhesive drug delivery systems and scaffolds for tissue engineering. Ease of processability of starch allows it to be applicable in various other applications as a film former, a fiber and as a porous matrix.[66,67]

Alginic acid

Alginic acid, also called algin or alginate, is an anionic polysaccharide distributed widely in the cell walls of brown algae. It is capable of absorbing 200–300 times its own weight in water and forms a viscous gum. It is composed of D-mannuronic acid and L-guluronic acid. Commercially, it is available as sodium alginate in which sodium can be replaced by calcium in the presence of divalent cations. Because of its anionic nature, it has been investigated for the controlled delivery of cationic drugs, and the release from alginate matrices depends on ionic interaction between drug and alginate gel. Alginate gels are widely applicable for enzyme immobilization and encapsulation of cells like chondrocytes due to their low cell interaction and better compatibility. Polyelectrolyte complexes of alginate with other cationic polymers such as chitosan were also developed. Several calcium alginate-based wound dressings were marketed due to their excellent water absorbing capacity and hemostatic potential (AlgiDERM, Algisite, Hyperion, and Kaltostat).[2,68,69]

Chitosan

It is a naturally occurring cationic polysaccharide derived by partial N-deacetylation of chitin from shrimp and crustacean shells. Chitin consists mostly of N-acetyl-D-glucosamine-unit. During the preparations of chitosan, most units are deacetylated to D-glucosamine units. Chitosan is a linear polymer of β-D glucopyranose units characterized by degree of deacetylation. It is structurally similar to cellulose, but it has acetamide groups at C-2 position. The amino and hydroxyl groups of chitosan that are chemically modifiable make it a highly versatile molecule for various applications. Chemical modifications due to the presence of amino group at C-2 and primary and secondary hydroxyl groups at C-6 and C-3 improve the mechanical properties and impart new biological activities in chitosan. The cationic property of chitosan imparts key bioactive properties like biodegradability, biocompatibility and microbicidal and mucoadhesive nature. Chitosan which is structurally similar to glycosaminoglycans (GAG) plays a key role in modulating chondrocyte morphology, differentiation and function and finding its application in cartilage engineering. It also exhibits biosensor and antihyperlipidemic actions. The metabolism of chitosan by lysozyme makes it biodegradable. It also finds its application as a vehicle for drug, vaccine and gene delivery (PROTOSAN®), as a hydrogel for delivering anti cancer agents and as a regenerative medicine.[70–74]

Hyaluronic acid

Hyaluronic acid, one of the major elements in the extracellular matrix of vertebrate tissues, is also found in almost all body fluids and tissues, such as the synovial fluid, the vitreous humor of the cieye and hyaline cartilage. HA is an unbranched non-sulfated glycosaminoglycans composed of repeating disaccharides β-1,4-D-glucuronic acid and β-1,3-N-acetyl-D-glucosamide. Three types of enzymes like hyaluronidase (hyase), β-d-glucuronidase and β-N-acetyl-hexosaminidase catalyze the enzymatic degradation of HA. The degradation products of hyaluronan, oligosaccharides and very low molecular weight hyaluronan exhibit pro-angiogenic properties. It has been investigated for dermal filling (Restylane-L Injectable Gel®, Hylaform®) antiadhesive and chondroprotective effects, applied in various ophthalmic (viscosity enhancer in eye drops), orthopedic (lubricant and shock absorber) and cardiovascular (increasing compatibility of vascular grafts and stents) applications.[75–77]

Chondroitin sulphate

Chondroitin sulphate found extensively in the extracellular matrix of particular cartilage is obtained by extraction from tissues of several animals (bovine, porcine, avian, cartilagenous fishes, etc). Chondroitin sulphate, a GAG of the same class as glucosamine, is composed of alternate sequences of differently sulfated residues of D-glucuronic acid and N-acetyl-D-galactosamine linked by β bonds. It is non-immunogenic and biodegradable to non-toxic oligosaccharides. These characteristics together with their defined physical and chemical characteristics make it a very interesting material for tissue engineering. Chondroitin sulfate with negative

charge interacting with positively charged molecules such as polymers or growth factors is anticipated being a key issue to facilitate the design of delivery systems. Chondroitin sulfate–chitosan sponges are being investigated as delivery systems for platelet-derived growth factor-BB, for bone regeneration (Integra®) and chondroprotective effects. Viscoat® based on CS was marketed which acts as a surgical aid in cataract extraction.[78,79]

Proteins

Collagen

It can be obtained from multiple sources including porcine, bovine, equine or human and offers many biomedical applications. Collagen is synthesized by fibroblasts, which usually originate from pluripotential adventitial cells or reticulum cells. The categories of collagen include the classical fibrillar and network-forming collagens, the fibril-associated collagens with interrupted triple helices, membrane-associated collagens with interrupted triple helices and multiple triple-helix domains and interruptions. The sequence and amino acid composition of collagen help in choosing a particular collagen for specific application.[80–84] At neutral pH, only specific collagenases, i.e. zinc containing metalloproteinases, cleave the native helix at a position, about three quarters of the way from the N-terminus. Fibrils as aggregates of collagen molecules are degraded starting from the exterior. It has been investigated as a dermal filler (Artefill®, Cosmoderm™) vehicle for protein delivery and in ophthalmic applications.[85,86]

Gelatin

It is the product obtained from the acid, alkaline or enzymatic hydrolysis of collagen, the chief protein component of the skin, bones and connective tissue of animals, including fish and poultry. Gelatin derived from an acid-treated precursor is known as Type A, and gelatin derived from an alkali-treated process is known as Type B. It consists of a distribution of polypeptide fragments of different sizes. Gel strength is expressed in (gram) bloom. Commercial gelatins may vary from low bloom (<150) medium bloom (150–220) to high bloom (>220) types. The possible degree of degradation will depend on several parameters such as pH, temperature, time and concentration.[87,88] Gelatin possesses hemostatic application which produces hemostasis by accelerating the clotting process of blood (Gelfoam®, Surgifoam®, Floseal matrix®).

Albumin

The albumins are a family of globular proteins, the most common of which is serum albumin. Albumins are commonly found in blood plasma and are unique from other blood proteins in that they are not glycosylated. Substances containing albumins, such as egg white, are called albuminoids. They also serve as carriers for molecules of low water solubility which includes lipid soluble hormones, bile salts, unconjugated bilirubin, free fatty acids (apoprotein), calcium, ions (transferrin) and some drugs.[15,89] Albumin being non-toxic, non-immunogenic and with other favorable properties like greater stability and ease of preparation makes it an excellent candidate for nanoparticulate delivery systems (nab-technology). The different uses of albumin as a drug carrier that have emerged so far are fascinating and range from extending the half-life of therapeutically active proteins and peptides (e.g. Albuferon, Levemir) and drug targeting (e.g. MTX-HSA, Abraxane). Recently, FDA approved a surgical tissue adhesive based on bovine albumin and glutaraldehyde.[14,90,91]

POLYMERS OF MICROBIAL ORIGIN

Poly hydroxy alkanoates

These belong to a class of intracellular biopolymers synthesized by many bacteria and act as carbon and energy storage granules. They are composed of β-hydroxy fatty acids where the R group changes from methyl to tridecyl. The main biopolymer of the PHA family is the poly hydroxybutyrate (PHB), and many copolymers were synthesized based on PHB namely poly (hydroxybutyrate-co-hydroxyvalerate, poly hydroxybutyrate-co-hydroxyhexanoate) and poly (hydroxybutyrate-co-hydroxyoctanoate.[92] PHB is highly crystalline polyester (above 50%) with a high melting point of 173–180°C, compared to the other biodegradable polyesters, and with *T*g around 5°C. PHAs are generally classified into short-chain-length (four or five carbons) PHA and medium-chain-length (six or more carbons) PHA. Biocompatibility and biodegradability by simple hydrolysis of ester bonds in aerobic conditions and piezoelectric properties make them suitable for drug delivery, tissue engineering and orthopedic applications.[2,93]

Poly (γ-glutamic acid)

It is a water-soluble, anionic, biodegradable homo-polyamide produced by microbial fermentation. This is actually a copolymer composed of D- and L-glutamic acid in various proportions. Apart from α-amide linkages between α-amino and γ-carboxylic acid groups, they exhibit other types of amide linkages that involve β- and γ-carboxylic groups as well as ε-amino groups. It has been investigated so far as a drug delivery vehicle (delivery of taxol using covalent immobilization technique), scaffolds for tissue engineering application and as a thermosensitive polymer. A surgical adhesive and haemostatic agent based on gelatin and poly (glutamic acid) has been developed.[2,58,94]

CONCLUSIONS

Biodegradable polymers with indispensable properties of biodegradability and biocompatibility have been proved to be versatile materials with enormous potential in biomedical field. The trend of biomaterials in the market is reflecting the immense effort that has been kept in the development of these polymers. The applications in various fields starting from surgical sutures and wound dressing to tissue regeneration, enzyme immobilization, controlled drug delivery and gene delivery prove the significance of these amazing materials. The emergence of the biomaterials based on biodegradable polymers by overcoming disadvantages associated with them leads to development of novel strategies for various therapies. Breakthrough innovations like Nab technology and constantly growing research work in this field are representative of significant contributions made by these polymers. Extensive effort has been kept in order to mold these polymers according to the suitability in a particular application. Furthermore, they open up very interesting perspectives for investigation of new properties in them suitable for new indications.

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