

Applications of synthetic polymers in clinical medicine

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Abstract

Multiple biological, synthetic and hybrid polymers are used for multiple medical applications. A wide range of different polymers is available, and they have further the advantage to be tunable in physical, chemical and biological properties in a wide range to match the requirements of specific applications. This review gives a brief overview about the introduction and developments of polymers in medicine in general, addressing first stable polymers, then polymers with degradability as a first biological function, followed by various other functional and responsive polymers. It is shown up that biomedical polymers comprise not only bulk materials, but also coatings and pharmaceutical nano-carriers for drugs. There is subsequently an overview of the most frequently used polymer classes. The main body of the review then is structured according to the medical applications, where key requirements of the applications and the currently used polymer solutions are indicated.

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1. Introduction

The basic principle of polymers, that is multiple assemblies of simple structural units for the formation of a 3-dimensional construct, has wide distribution in all biological systems. This ranges from intracellular filaments and cytoskeleton via structural proteins of the soft extracellular matrix and matrices with mechanical function in ligaments or cartilage to keratin of skin and hairs at the human surface interface with the environment and insects can produce silk polymers even for external constructions. Such natural polymers like horn, hair, or cellulose have been utilized by human since beginning of manhood, and they have found application in medicine, e.g. as suture material also for long time [1].

Man-made synthetic polymers are almost as manifold as the natural ones, although the most progress in development only started about in the Second World War. Newly developed polymers rapidly entered medical application, such as the polyesters and polyamides as synthetic suture materials.

Synthetic polymers gained high attraction for technical as well as for medical application for various reasons. A wide range of physical and chemical properties can be achieved based on the monomer units, polymerization reaction and formation of co-polymers consisting of different components at adjustable concentrations [2]. Technologies for synthesis and formation also of complex shaped devices are mostly established. These types of polymers mainly fulfill structural and mechanical properties. Mechanical self-reinforcement is achieved by integration of oriented fibers of the same material into the matrix [3,4]. There are also highly advanced mechanical properties, such as shape memory polymers, which can be

freely deformed and return to their original shape upon a special stimulus, which can be pH, temperature, magnetic field or light. They found application in biomedicine in drug delivery devices, vascular stents, sutures, clot removal devices, for aneurysm or ductus arteriosus occlusion, and orthodontic therapy as reviewed elsewhere [5,6].

Besides the mechanical properties also specific functional characteristics of polymers are used. Semipermeable membranes of biopolymers (cellulose) or polymers are used for hemodialysis or as drug delivery systems. Swelling or collapsing of pores of the membrane in response to pH, temperature or other stimuli leads to membranes for responsive drug release [7].

Due to their carbon based chemistry, polymers are closer to biological tissue than inorganic materials. This can be used for targeted interaction between the material and the body, but may also cause problems due to an interference of rest-monomers, degradation-products or additives with biochemical pathways. Reactive groups in the Polymers usually also offer the possibility for biofunctionalization of the surface, either because they provide reactive groups by themselves, or e.g. plasma technologies can be used to create such groups for covalent anchorage of molecules on the surface. The surface modification techniques allow independent optimization of the mechanical properties of the bulk and biocompatibility properties of the surface.

Functional types of polymers evolved for biomedical applications. Biodegradable polymers ideally stay in the body only as long as they serve their function and then they disappear without the need of a second surgical intervention [8–10]. Orthopedic fixation and ligament augmentation were the primary motivation for biodegradable polymers [11]. Since

the 1990ies, vascular stents developed as the main target application [12–16]. These degradable polymers have been further used for the delivery of drugs along with the degradation from microcarriers or macroscopic applications [17,18].

Synthetic, hydrolytically degrading polymers are preferred for many applications as implant or drug release system, because their degradation is relatively invariant from patient to patient and for different implantation sites [8,19]. In contrast to this,

enzymatic degradation is the typical degradation mode of biopolymers. This degradation mode is explored for scaffolds in tissue engineering and as substitute for extracellular matrix, where it is desired that they disappear with the physiological enzymatic turnover of the extracellular matrix [20,21]. Concerns of immunologic reactions against polymers of biological origin and limited batch-to-batch reproducibility caused a shift to biohybrid polymers, where synthetic polymers are engrafted

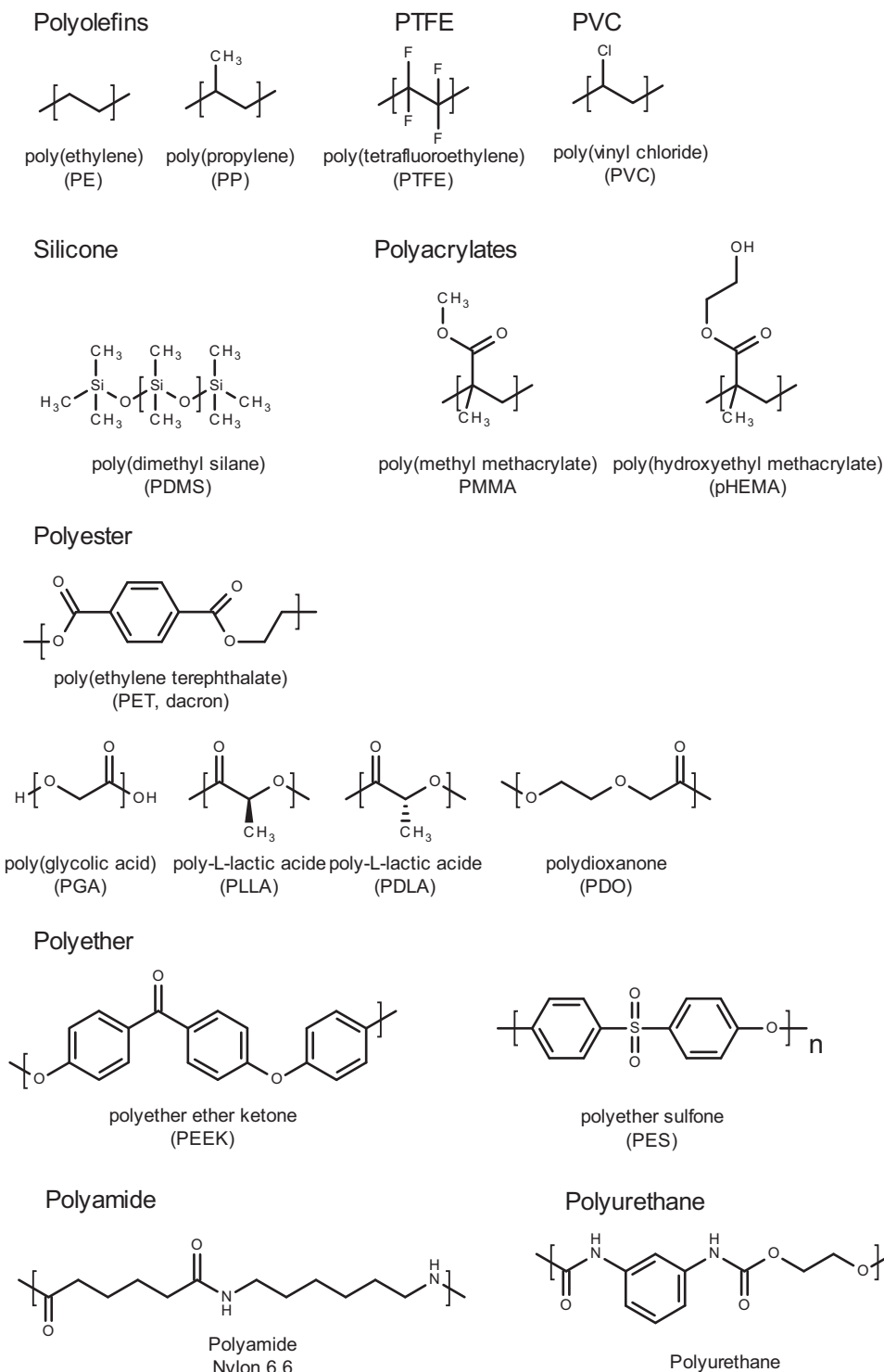


Fig. 1. Structure of common polymers in biomedicine. Variations are due to various chain lengths, crystallinity, side groups and co-polymers.

with biological functions like enzymatic degradation, conjugation with cell adhesion molecules, and growth factors which all should support homing, differentiation and proliferation of the tissue specific cells [21–23]. Also the stiffness of the scaffold polymers is adjusted to match the target tissue to support the appropriate cell differentiation [24].

Polymers which degrade or respond otherwise to environmental conditions gained special attention as functional materials. Responsiveness to physical stimuli like mechanical stress [25,26], electricity [27], temperature changes [28,29], or light irradiation [30,31], and combinations thereof [32,33] can be used to trigger a drug release by external stimuli. But polymers also can react on internal chemical and biochemical triggers like pH [34], drugs, metabolites, antigens or enzyme concentrations [35–40] and so autonomously respond to a physiological status. Suitable settings even allow feedback controlled homeostasis of blood glucose [35], urate concentration [38] or coagulation [39,41].

In these advanced applications, the polymers are typically not present as bulk materials. They are formed as coatings on biomedical devices, or as micro- and nanospheres for targeted drug delivery. Coatings may be non-structured homogeneous coatings, crosslinked coatings, polymer brushes or layer-by-layer deposited films. The spherical particles can include solid colloids, dendrimers, micelles, nanogels, capsules or core-shell particles, as reviewed elsewhere [42–45].

Despite the current wide spectrum of polymers available in biomedicine, it is frequently difficult to fulfill all requirements of a device at the same time in a cost efficient way. In addition, there are inherent problems with some types of polymer: Polymerization usually is a statistical process, and control of the molecular weight distribution differs for different reaction chemistries. While the polymers as such are mainly non-toxic, there are frequent concerns about remaining rest-monomers from incomplete polymerization and other leachable components, such as degradation products, auxiliary products and plasticizers. They require intensive testing of polymers before transfer to clinical application [46]. Another frequent issue of polymers is the restriction in modes for sterilization, as the polymer or conjugated bioactive molecules may not withstand the high temperature of steam sterilization, the crosslinking potential of ethylene oxide sterilization or energetic irradiation.

2. Inherent properties of synthetic polymers used in biomedical field

Fig. 1 sketches the basic structures of the main polymer types used in medicine, and Table 1 contains the polymer abbreviations used in the text.

2.1. Polyolefins

The polyolefins polyethylene (PE) and polypropylene (PP) are very inert and hydrophobic materials, which do not degrade in vivo. PE is produced at different molecular weights and different crystallinity. Low density PE (LDPE) with molecular weight 50,000–200,000 and 40–50% crystallinity is most soft with elastic modulus 100–500 MPa and has application mainly in

packaging. High density PE (HDPE) can have similar molecular weight but crystallinity of 60–80% and E-modulus of 400–1500 MPa; it is used to form stable devices as containers or also for implantation. Ultrahigh molecular weight PE (UHMWPE) has molecular weight above 2,000,000, 50–60% crystallinity and elastic modulus of 1000–2000 MPa. Its main applications are sliding surfaces of artificial joints. PE can undergo oxidation, especially gamma sterilization, which increases hydrophilicity, recrystallization and makes the polymer more brittle.

PP shows similar biological inertness as PE. Its main application is for suture materials and meshes.

2.2. Poly(tetrafluoroethylene) (PTFE)

PTFE (Teflon[®]) has an ethylene backbone with four covalently bound fluorine molecules. Its expanded, porous form with interconnecting fibrils is called ePTFE (Gore-Tex[®]). It is a highly hydrophobic, non-degradable material. It induces only little inflammation in the body and shows some tissue ingrowth [47]. It is mainly applied as vascular graft.

2.3. Poly(vinyl chloride) (PVC)

PVC has an ethylene backbone with one covalently bound chlorine. Its fabrication and application requires stabilizers and plasticizers, which are the main reason for medical concerns against this polymer. Stabilizers, most frequently Ca/Zn are necessary to prevent autocatalytic cleavage of HCl and degradation of the polymer during thermal processing [48]. Plasticizers, most frequently phthalates, turn the rigid PVC to a soft polymer, which is used for extracorporeal tubings or blood storage bags. Direct cytotoxicity in vitro has been reported for the combination of tin-based stabilizers and phthalate based plasticizers [49]. There are concerns about phthalate plasticizer di(2-ethylhexyl) phthalate (DEHP), which presents a high amount of the PVC, is released to the ambience and dissolves in the lipid bilayers of cells. Hormone-like effects, birth defects and infertility have been described for DEHP in rodents. These toxic effects were observed upon oral uptake, but not upon parenteral administration, because enteral lipases are seen necessary for toxification of DEHP [50].

Published data on complement activation of PVC with various plasticizers or alternative tube materials are contradictory, but DEHP plasticized PVC apparently activates more complement than reference materials [51–53]. Also the coagulation activation via the contact system is slightly elevated for PVC [52,54].

2.4. Silicone

Silicones consist of an –Si–O– backbone with different chain lengths and crosslinks, which determine mechanical properties from liquid oil via a gel structure to rubber elastomer. The side chains may be modified, but in the most common poly(dimethylsiloxane) (PDMS) they are methyl groups. Silicones are hydrophobic and biostable elastomers without need of plasticizers. The biological response differs for various applications: There is high tolerance in ophthalmologic

applications [55,56], fibrous capsule formation at breast implants [57,58], and synovitis as late complication in intraarticular implants [59]. An association with hematologic cancers and connective tissue diseases is assumed especially for silicon oil residues [60,61].

2.5. Methacrylates

Methyl methacrylates polymerize to very rigid polymers (PMMA) by radical polymerization and therefore find application in dentistry and in orthopedics. They are used for

Table 1
Abbreviations and applications of the polymers in the text.

Abbreviation	Full name	Application	Ref.
BTHC	Butyryl-trihexyl-citrate	Alternative plasticizer of \nearrow PVC in blood bags	[76]
DEHP	Di(2-ethylhexyl)phthalate	Most frequent plasticizer of \nearrow PVC	[50]
DINCH	Di-iso-nonyl-1,2-cyclohexanedicarboxylate	Alternative plasticizer for \nearrow PVC	[50]
ePTFE	Expanded PTFE	Gore-Tex [®] , used for vascular grafts, surgical meshes, ligament and tendon repair	[120,121,148,160,161,174]
EVAl	Ethylene vinyl alcohol copolymer	Hemodialysis membrane component	[81]
HDI	Hexamethylene diisocyanate	Diisocyanate for polyurethane formation	[119]
HDPE	High density PE	Stiff polyolefin used for packaging, inner lining of catheters or aws graft for craniofacial contour augmentation	[46,70,173]
HXPE	Highly crosslinked PE	Obtained by gamma sterilization of \nearrow UHMWPE	[125,126,199]
IPDI	Isophorone diisocyanate	Diisocyanate for polyurethane formation	[119]
LDPE	Low density poly (ethylene)	Soft polyolefin mainly for packaging	
PA	Poly(amide)	Nylon, used as suture material, ligament and tendon repair, balloon of catheters, dialysis membranes	[70,71,81,85,112,148]
PAN	Poly(acrylonitrile)	Dialysis membranes	[81,85]
PC	Poly(carbonate)	biostable polyester for dialysis membranes and containers	[81,85]
PCL	Poly(caprolactone diol)	Diol for polyurethane formation	[119]
PDLA	Poly (D-lactic acid)	Degradable polyester of D-lactic acid, similar spectrum as \nearrow PLLA	
PDMS	Poly(dimethylsiloxane)	Silicones are highly inert elastomer, used for catheters, nucleus pulposus substitute, plastic surgery, intraocular lenses, glaucoma drainage devices and dialysis membranes	[47,55,84,93,141,178]
PDS	Poly(dioxanone)	Degradable polymer, frequently as co-polymer with \nearrow PLLA with comparable applications	
PE	Poly(ethylene)	Stable polyolefin, used as \nearrow LDPE, \nearrow HDPE or \nearrow UHMWPE	
PEEK	Polyether ether ketone	Hard stable polymer for orthopedic applications or inner lining of catheters	[68,70]
PEG	Poly(ethylene glycol)	Hydrophilic linear polymer used as antifouling coating on catheters, hydrogel or as pore former in dialysis membranes	[81,94,177]
PEO	Poly(ethylene oxide)	Antifouling coating of catheters	[94]
PEPA	Polyester polymer alloy	Hemodialysis membrane	[81,85]
PES	Polyether sulfone	Hemodialysis membrane	[81,85]
PET	Poly(ethylene terephthalate)	Biostable polyester Dacron used for membranes, vascular grafts, surgical meshes, ligament and tendon repair	[120,148,160]
PGA	Poly(glycolic acid)	Degradable polyester with similar application spectrum as \nearrow PLLA	
pHEMA	Poly(hydroxyethyl methacrylate)	Antifouling coating and hydrogel for intraocular lenses, frequently in copolymers with PMMA	[56,106]
PLGA	Poly(lactic-co-glycolic acid)	PLLA/PGA copolymer with similar application spectrum as \nearrow PLLA	
PLLA	Poly(L-lactic acid)	Degradable polyester of L-lactic acid for orthopedic fixation tools, ligament and tendon repair, vascular stents	[134,148,154]
PMMA	Poly(methyl methacrylate)	Hard methacrylate as bone cement, as intraocular lens, or for dialysis membranes	[81,85,143,178]
PMP	Poly(methylpentene)	Material for oxygenator membranes without plasma leakage	[89,90]
PP	Poly(propylene)	Polyolefin for containers, suture material and surgical meshes, oxygenator membranes	[73,87,88,112,120,121]
PSf	Polysulfone	Component of hemodialysis membranes	[81,85]
PTFE	Poly(tetrafluoroethylene)	Inert and hydrophobic polymer with application mainly in the expanded form \nearrow ePTFE	
PVA	Poly(vinyl alcohol)	Linear hydrophilic polymer as antifouling coating or for hydrogel formation nucleus pulposus or vitreous body replacement	[141,177,181]
PVC	Poly(vinyl chloride)	Low-cost, highly plasticized polymer for tubings or blood bags	[50,75,76]
PVDF	Poly(vinylidene fluoride)	Suture material or surgical mesh	[112,120,122]
PVP	Poly(vinylpyrrolidone)	Hydrophilic, soluble polymer as antifouling coating or in dialysis membranes	[81,85,105,106]
SIBS	Poly(styrene-b-isobutylene-b-styrene)	Coating of drug eluting stents	[154]
UHMWPE	Ultrahigh molecular weight PE	Stable and low friction polymer for joint prostheses	[124]

application with polymerization in situ. This polymerization process is exothermic and can cause tissue damage, so that low amounts should be applied and saline irrigation for cooling may be necessary. While the polymer is biologically inert, there can be reactions against the monomer and rest-monomers in the polymer [62]. Due to the optical properties (Plexiglass[®]) and inertness in the eye, they are also used as intraocular lenses.

The hydrophilic side chains in the hydroxyethyl methacrylate monomer lead to the polymerization to a hydrogel (pHEMA). This has good protein repellent anti-fouling properties and is used for various applications like hemocompatible coatings [63,64] or as lubricant coating on contact lenses [65].

2.6. Polyesters

Biostable and biodegradable polyesters are used in biomedicine. Biostable polyesters containing aromatic groups are polycarbonates (PC), poly(ethylene terephthalate) (PET, dacron). They are used in form of membranes, filaments and meshes.

Polyesters of small aliphatic glycolic acid or lactic acid present the most common degradable polymers poly(glycolic acid) (PGA), poly(L-lactic acid) (PLLA) and poly(D-lactic acid) (PDLA). Polydioxanone (PDS) is a further degradable polyester composed of multiple repeating ether-ester units. Non-enzymatic hydrolysis of is the main mode of degradation of these polymers, and the degradation products catalyze the further degradation [8,11,66]. The degradation rates partly depend on the monomer structure, but it is also highly influenced by molecular weight, crystallinity, fiber structure and substituting groups [17]. PGA, PLLA, and PDLA rapidly entered clinical application because their monomers and degradation products are physiological metabolites, however, there are sometimes concerns about the acidic character of these degradation products causing restrictions in the permitted amount [11,67]. These polymers are available in different shapes from solid body for orthopedic applications, via meshes to drug eluting coatings on vascular stents.

2.7. Polyethers

Ether bondings are biostable. Polyether ether ketone (PEEK) as hard material for orthopedic applications [68] and polyether sulfone (PES) for dialysis membranes [69] are main representatives of this polymer class in biomedicine.

2.8. Polyamides

Naturally, all proteins consist of units linked by amide bonds, and highly repetitive proteins like collagen or silk fibroin can be classified here. The most important synthetic polyamide with clinical application is nylon. For its high tensile strength it is used for suture materials. Polyamide block copolymers containing soft segments for better elasticity combine the flexibility of polyurethanes with the strength of nylon and therefore became the material of choice for the balloon of catheters for angioplasty [70,71].

2.9. Polyurethanes

Polyurethanes are synthesized with multiple chemistries and properties. Polyester-, polyether-, and polycarbonate-based polyurethanes with aromatic or aliphatic components are in medical use, where aromatic formulations have the better biostability. Thermoplastic polyurethanes do not need plasticizers, but retain their elasticity by the mixture of hard and soft segments. The polycarbonate based polyurethanes have excellent stability against oxidation and biodegradation as PVC does, however, there are concerns about release of bisphenol A with estrogen-like activity. Polyether based polyurethanes, especially aliphatic formulations show rapid softening in the body, making them more comfortable for the patient [72].

After these general statements about possibilities and trends of polymers in biomedicine, in the following some specific applications shall be reviewed. Due to the plethora of applications and materials, this review is restricted to main materials, the specific demands of the various applications and the approaches to solve them. Review articles, given in the references have more in depth information.

3. Biomedical applications of polymers outside the body

3.1. Containers

Numerous polymer devices are not inside the body, but they are used for packaging of drugs and devices. Plastic ampullas and prefilled syringes are convenient to use, but adsorption and migration of the bioactive substance into the polymer, pH shifts, oxygen permeation, optical properties and the release of leachable components have to be considered carefully for the individual applications [46,73]. The interaction may affect not only the drug, but also the function of the polymer container. Polyolefins, HDPE or PP are the most frequent polymer for compressible vials, but frequently also multilayer containers are used to achieve required properties of inertness, oxygen- or UV protection. For prefilled polymer syringes, cyclic olefin polymers and copolymers (Daikyo Crystal Zenith[®]) found wide application due to their mechanical and optical properties, inertness and stability at steam sterilization; the stopper and the tip cap are usually made of elastomers [73,74].

PVC containing the phthalate plasticizer DEHP is used for many extracorporeal perfusion tubes to provide medicines, or also in blood leading tubes in extracorporeal dialysis or extracorporeal oxygenation. Also blood donations and blood products are typically stored in bags of this polymer. Due to the lipophilic nature of the plasticizer, it transfers from the polymer surface to the lipids and membranes of the red blood cells. It was found that the plasticizer in the blood bags reduces the hemolysis of red blood cells by about 50% compared to non-plasticized blood containers and improves the quality of the blood product [50]. Because of the intense contact and elevated thrombogenicity of PVC, tubings of extracorporeal circulation therefore are frequently heparinized to reduce the coagulation [75].

In reaction to the phthalate concerns, alternative plasticizers partly are applied for storage of red blood cells, such as

butyryl-trihexyl-citrate (BTHC) or di-iso-nonyl-1,2-cyclohexanedicarboxylate (DINCH) [50,76]. For platelet storage, also alternative polymers like polyolefins are used [77], and polyethylene and polyurethanes are used for tubings. The tubings of the peristaltic pumps are typically made of silicone.

3.2. Hemodialysis membranes

Hemodialysis membranes are produced as bundles of hollow fibers with a blood contacting surface of 1.0–1.5 m². Besides the technical requirements of permeability for substances smaller than albumin and the request to prevent the passage of impurities of the dialysate into the blood, the intense blood contact poses high challenges on the blood compatibility of the membranes. Early dialysis membranes were made of cellulose, where hydroxyl groups were soon substituted by acetyl derivatives or modified with other supportive additives to prevent activation of the complement system and associated leukocyte activation and leukocyte sequestration into the lung [78–80].

Synthetic membranes mainly are composed of a hydrophobic base material and hydrophilic components; the coprecipitation membranes of polyarylsulfones, polysulfone (PSf) or PES and polyvinylpyrrolidone (PVP) are most prominent. But also multiple other membrane materials are used, such as polyamide (PA), polycarbonate (PC), and polyacrylonitrile (PAN), PMMA, polyester polymer alloy (PEPA), ethylene vinyl alcohol copolymer (EVAL), and molecular-thin nanoporous silicon membranes [81–84]. The hydrophilic component PVP or poly(ethylene glycol) (PEG) in the membrane is pore-forming agent and also improves antifouling properties and blood compatibility.

The process of removal of uremic substances during hemodialysis is controlled by diffusion along concentration gradients, pressure gradients (convection) and adsorption to the membrane. Thus, effective pore size, low membrane thickness and binding capacity for uremic substances determine the efficiency of a membrane. Especially PMMA membranes have high binding capacity for β_2 -microglobulin or for activated complement factors and prevents their entry into circulation [81,85]. A most narrow distribution of the pore size has to be achieved to provide a sharp cut-off only slightly below albumin 50–60 kDa [86].

3.3. Extracorporeal membrane oxygenation

Membranes for extracorporeal membrane oxygenation, ECMO have slightly different mode of action than dialysis membranes. In order to achieve good exchange of O₂ and CO₂, microporous hollow fiber membranes of hydrophobic PP with pores of less than 1 μ m diameter are applied [87,88]. Gas transfer occurs at a direct blood-air interphase at these pores, guaranteed by the interface tension at the highly hydrophobic material, however, protein adsorption and water evaporation changes the interphase properties and plasma leakage happens. Recently membranes of polymethylpentene (PMP) have been developed, which

have a very thin film covering the pores, thus avoiding problems of pore occlusion by deposited proteins or plasma leakage and therefore do not require round-the-clock monitoring by a perfusionist or respiratory therapist [89,90]. Silicon hollow fibers as pore-free membranes with good gas permeability and good hemocompatibility promise further safety of plasma and gas leakage, however, they are still in an evaluation phase [91,92].

4. Temporary in vivo applications

4.1. Vascular catheters

Vascular catheters must be non-thrombogenic and must not induce an inflammatory response in the vessel wall. Mechanical flexibility along with non-kinking and non-collapsing properties is required. Central venous catheters with longer persistence in the body usually have antimicrobial fitting and properties which prevent the formation and adhesion of bacterial biofilms.

Plasticized PVC was one of the first polymers used for catheters. It is mainly avoided nowadays due to the plasticizers and is used only for short-term applications as peripheral venous catheters. Thermoplastic polyurethanes are the key polymers for catheters as they do not need plasticizers. Multiple polyester-, polyether-, and polycarbonate-based polyurethanes with aromatic or aliphatic components have been prepared for catheter application [71,72]. Silicone vascular catheters are inserted for long term access (weeks to months), frequently as access for hemodialysis. Silicon is softer than the polyurethanes, therefore also thick-lumen catheters have no risk of vascular injury [93].

The surface of the catheter may be modified by grafting long chain hydrophilic molecules like PEG or exposing them from the bulk polymer to reduce protein adsorption. Active anticoagulant properties frequently are endowed by immobilization of heparin with various methods. Antimicrobial properties are provided by incorporation of silver nanoparticles, silver sulfadiazine, chlorhexidine or others [94–96].

HDPE or PTFE are usually used as inner lining of interventional catheters to provide good sliding on the guide wire. Guide wires also may be PTFE coated. Alternatively, polyimide or PEEK is used as inner lining of load bearing catheters due to their high mechanical resistance. Polyamide block copolymers are frequently used as the outer layer of these catheters, because they combine the flexibility of polyurethanes with the strength of nylon [70]. The balloons of interventional catheters are typically made of polyester or the polyamide nylon 11 and nylon 12 due to their tensile strength. The catheters usually get a lubricant surface fitting to improve the placement.

4.2. Urinary catheters and ureteral stents

Urinary catheters are mostly made of latex, polyurethane or silicone. Due to a high prevalence of latex allergy and the high

friction of latex, pure latex catheters are rarely used any more. General problems with urinary catheters are urinary tract infections, catheter encrustation and blockage, which also is promoted by colonization with bacteria *Proteus mirabilis* and damage of the mucous membrane of the urinary tract [97–99]. The catheter must have sufficient strength to allow insertion, prevent occlusion by kinking or collapse and allow removal without detachment of the balloon from the shaft, but be sufficiently soft for the tolerance of the patient. The surface must be smooth with a low friction finish. Coating technologies therefore are generally applied.

Latex catheters coated with PTFE may stay in the patient up to 4 weeks, silicon catheters or silicon coated latex even longer. Also hydrogel coatings, e.g. of pHEMA allow long maintenance of the catheter. Antimicrobial fittings are provided by silver containing hydrogel coatings or nitrofurazone or minocycline/rifampicin impregnation. Although these systems could decrease the risk of minor contamination, results are disappointing concerning symptomatic infections in clinical studies [100–103]. Copolymerization of acrylate polymers with different aliphatic and aromatic structures recently showed promising antimicrobial results in vitro and in vivo, which await transfer to clinics [104].

Polymer ureteral stents in the upper urinary tract face similar problems of bacterial infection and encrustation with significant morbidity as the catheters in the lower urinary tract [105,106]. Silicone is the best biocompatible material with lowest tendency for encrustation, but low mechanical stiffness and high friction make application difficult. Optimized polyurethane formulations (Perculfex[®], Tecoflex[®], Hydrothane[®], ChronoFlex[®], Sof-Flex[®]), polyester (Silitek[®]), polyethylene-vinyl acetate and Styrene/ethylenebutylene/styrene block copolymers (F-Flex[®]), and PMMA/pHEMA co-polymers have been developed as polymers with improved mechanical properties than silicone. Stents are coated with glycosaminoglycans (GAGs, heparin or pentosan polysulfate), phosphorylcholine, PVP or hydrogels for reduced bacterial colonization, encrustation and enhanced comfort for the patients [105,106].

4.3. Wound dressings

Wound dressings are a very wide field for polymers in temporary, mainly external contact with the body. Wound healing is a complex biological process, involving inflammation, clearing of cell debris, cell migration, proliferation and differentiation, and remodeling which may be disturbed at different steps in the case of delayed wound healing of chronic wounds. Advanced active polymer wound dressings have been developed with release or adsorption properties to support physiological processes or remove detrimental influences. They are also more comfortable for the patient than traditional gauze dressings [107–109]. Mechanical protection and a barrier function are achieved with minimized adherence to the wound avoiding traumatization during movements or removal. The dressing has to provide permeability for oxygen and water vapor for a proper ambient of wound healing without bacterial superinfection. Hemostatic properties are preferred for the wound dressings, especially in the case of hemorrhagic traumatization [109].

A wide range of synthetic, biological and hybrid materials are applied in multiple shapes to match different types of wounds

[110]. Transparent semipermeable films of nylon, polyurethanes with acrylate based coatings or natural polymers like chitosan provide a mechanical protection and barrier with support of a moist environment at the wound, but they are not suitable for infected or heavily exuding wounds [107,111]. Foam dressings of synthetic polyurethane foams or natural polysaccharide alginate foams are highly absorbing and permeable for water vapor and they are therefore recommended for exuding wounds. Hydrocolloids are a combination of hydrogel forming components like carboxymethyl-cellulose, gelatin, pectin, alginates and elastomers, which provide the mechanical stability. They are suitable for moderately exuding wounds and can be fitted also with drug release properties for antimicrobials, antibiotics or growth factors. Pre-swollen hydrogels of collagen or elastin, hyaluronic acid, alginate, chitosan, or synthetic hydrogels of PVP or methacrylates as wound dressing are highly flexible, but usually need a mechanical support. As they do not absorb much liquid any more, they are not suitable for heavily exuding wounds, but they rehydrate dry tissue, facilitate autolytic wound debridement and also may be used for drug release.

5. General surgical implants

5.1. Suture materials

Suture materials and staples are a domain of polymers in general surgery. Tensile strength, friction/trauma to tissue, degradability and stability of knots are main parameters for the selection of suture materials. Still a number of biological suture materials is in use. Degradable biological suture materials are collagen based materials, catgut; non-degradable bio-polymers are silk or cellulose (cotton). Synthetic resorbable materials are PGA, polyglactic acid (Vicryl), PDS, poliglecaprone 25 (Monocryl); non-resorbable suture materials are nylon, polyethylene, polypropylene (Prolene), polyester, polybutester, and Polyvinylidenfluorid (PVDF) [112]. Generally fast healing tissue, such as peritoneum and inner organs is treated with resorbable suture material, whereas slow-healing tissue and tissue with high mechanical exposure, such as skin or tendons, are treated with non-resorbable material. The biological degradable materials degrade by proteolysis with significant tissue response, whereas hydrolytically degrading synthetic polymers show less tissue response. Also for the non-resorbable suture materials, the biopolymers silk or cotton cause more intense inflammation than the synthetic polymers [113].

5.2. Tissue adhesives and sealants

Tissue adhesives are an alternative to sutures with lower adhesion strength than sutures, but forming an a priori tight occlusion of the wound [114,115]. Adhesives find wider application in modern surgical techniques of laparoscopy and robotic surgery or for organs like liver or lung, where the puncture defects of the needle are already problematic. A technological challenge is the adhesion to the wet substrate.

The main biological sealants are fibrin glues with the main two components fibrin and thrombin mixed at the site of the

wound; factor XIIIa supports crosslinking and aprotinin prevents fibrinolysis. However, there are also collagen-, gelatin-, and polysaccharide- (chitosan, alginate, heparin or chondroitin sulfate) based adhesives [116–118]. Due to the limited strength of these adhesives, they are mainly used to prevent bleeding and they are combined with sutures. Cyanoacrylate glues (2-octyl cyanoacrylate, n-butyl-2-cyanoacrylate) are the most frequently applied synthetic glues, mainly in superficial wounds in cosmetic surgery to avoid stitches. They provide higher strength than the fibrin glues. Photopolymerized PEG-based hydrogels find application for bigger wounds in thoracic surgery. Dendrimers with reactive end groups have application in ophthalmic surgery. Polyurethanes of polycaprolactone diol (PCL) either with isophorone diisocyanate (IPDI) or with hexamethylene diisocyanate (HDI) are fully degradable tissue glues [119], however the curing time of the polyurethane adhesives and sealants usually is too long for practical application [116]. Due to the adhesion to wet surfaces, even mussels and mussel-inspired adhesive found attention [116].

5.3. Surgical meshes

Reconstructive meshes in general surgery support organs or tissue to prevent a prolapse or hernia. The main classifications of the surgical meshes are according to the mesh size or the weight of the mesh, because this is more relevant for the biological response than the material [120,121]. The main polymers for non-resorbable meshes are expanded PP, ePTFE, PET or PVDF, however, also they show significant signs of degradation at the surface and even fragmentation. Among these materials PVDF meshes usually induce less foreign body response than PP meshes do [122,123]. Large pores (< 1 mm) generally show less inflammation and bridging scar formation than small pores do.

6. Orthopedic implants

6.1. Joint prostheses

In orthopedic surgery, joint prostheses most frequently have a pairing of metal on UHMWPE [124]. UHMWPE is a semicrystalline polymer with superior strength, creep- and wear resistance; however, it still is the weaker component of the pairing due to wear, oxidation and fatigue fractures. Long lived free radicals in the polymer induced by gamma sterilization caused significant ageing of the UHMWPE devices upon storage in oxygen containing ambience. While other means of sterilization are possible, gamma sterilization is generally preferred, because it induces crosslinkings and improves the mechanical stability of the polymer [125,126]. This highly crosslinked PE is referred to as HXPE. Antioxidants, like vitamin E are added to the UHMWPE to quench free radicals and improve mechanical properties as a plasticizer [127].

Sub-micrometer debris particles are the main problem of UHMWPE, as they induce a chronic inflammation, bone resorption, osteolysis, and loosening of the implant [128,129].

No other polymer could take the role of UHMWPE for replacement of big load bearing joints; there are only metal-on-metal or ceramic-on-ceramic pairings as alternatives. In small joint replacement flexible silicon spacers dominate [130]. However, inorganic pyrolytic carbon (Pyrocarbon) with graphite-like structure finds increasing attention for small joints or as interposition material because of its inertness, low friction behavior and a Young's modulus close to bone [131,132].

6.2. Osteosynthesis material

Stabilizing and load transferring applications at bone must be strong enough to withstand the forces, but they also should have elastic properties similar to the bone for a homogeneous load transfer and to prevent stress shielding of the bone, which would lead to bone resorption. Cortical bone has a Young's modulus of about 20 GPa [133]. Most metals have a higher modulus, but carbon fiber reinforced polymer composites can reach such values and therefore they are applied for some load bearing applications. A technical disadvantage of thermoset reinforced polymers, like epoxy resins, is that they cannot be contoured to the bone in the way as metal plates can, and there are concerns about leachable toxic rest monomers [134,135]. However, especially carbon reinforced PEEK is attractive and has application in spine surgery for fusion cages [68]; applications as osteosynthesis plates and endosseous nails of PEEK are in more experimental stages [68,134–138]. Polylactide based resorbable osteosynthesis plates also have been developed. Due to low mechanical strength, completely resorbable polymers are applied only at non-weight bearing bones in maxillofacial surgery. Reinforcement with phosphate bioglass fibers gives higher strength to expand the application spectrum [134].

Vertebral disc replacement may be necessary in the case of a disrupted or degenerative intervertebral disk. Either only the nucleus pulposus needs to be substituted or the total disc. While total disk replacement mainly is done by mechanical joint pairings [139,140], silicone elastomers and polyvinyl alcohol (PVA) hydrogels or PVA–PVP co-polymers are applied for nucleus pulposus replacement. They may be inserted as solid piece or injected and cure in situ [141,142].

6.3. Bone cements

Bone cements serve for anchorage of a joint prosthesis into the bone and should provide a homogeneous load transfer from the implant to the bone. PMMA is widely predominant for this application [143]. It is frequently equipped with the antibiotic gentamicin [144]. As PMMA does not promote bone adhesion, filling with hydroxyapatite particles has been suggested [145]. The polymerization

reaction of PMMA is exothermic and the heat may cause tissue damage. There are also concerns about the toxicity of monomers released during this phase. Zinc-based glass polyalkenoate (glass-ionomer) cements [146] lead to bone resorption and fibrous encapsulation and therefore are not suitable for general application. Calcium phosphate cements have excellent biocompatibility, but the mechanical properties do not allow application in load bearing situations; the main applications are in dentistry and cranial surgery [147].

6.4. Scaffolds for ligament and tendon repair

Various materials are used to bridge ligament and tendon defects where autologous material is missing or not strong enough [148]. Mammalian collagen scaffolds, obtained for small intestine submucosa, dermis, pericardium, kidney capsule or other tissues by intensive cleaning and removal of cellular components, cross-linking and sterilization are frequently used biopolymers for this purpose [148,149]. They contain more than 90% type I collagen, some type III collagen and elastin. Their mechanical stability is relatively low, even causing failure of surgery, but they have the clear advantage of interaction with the host tissue, cell adhesion, proliferation and matrix remodeling. Synthetic polymers for ligament or tendon repair are polypropylene, ePTFE, PET/Dacron, nylon. They provide better mechanical stability than the biological scaffolds, however their non-degradation and persistence in the body causes problems [148]. Foreign body reactions, inflammatory responses and synovitis are frequent [149]. A biodegradable polyurethane urea polymer (Artelon[®]) as a degradable synthetic scaffold material is on the market [150], resorbable polylactic acid and poly(lactide-co-glycolide) (PLGA) scaffolds are in an experimental phase [148]. However, the main developmental work in ligament or tendon repair is in the field of tissue engineering.

7. Vascular and cardio-vascular intervention

7.1. Vascular stents

Vascular stents in conjunction with balloon angioplasty have revolutionized angiology and cardiology as they maintain blood flow through stenotic vessels. First stents were only metal supports, partly with hemocompatible ceramic or inorganic carbon coatings [151–153]. With the appearance of drug eluting stents, which combat responsive proliferation of the vessel wall and restenosis of the target vessel, polymers came up as release platform. The coatings of first generation drug eluting stents were a polymer blend coating of poly(ethylene-co-vinyl acetate) and poly(*n*-butylmethacrylate) loaded with sirolimus or poly(styrene-*b*-isobutylene-*b*-styrene) (SIBS) loaded with paclitaxel, respectively. Both polymer coatings were thick with 12–16 μm , not degradable and did release only a small fraction of their drug cargo [154]. They were also not optimized for blood compatibility, attributing to the problem of late stent thrombosis. The second generation stent coatings were everolimus eluting fluoropolymer or zotarolimus eluting phosphorylcholine methacrylate with thickness of only 5–8 μm [155]. There is modification of the release kinetics by

drug-free top-layers. Coating technologies, which treat only the abluminal stent surface, prevent blood clotting by a non-hemocompatible polymer coating. Degradable polymers in use for drug eluting coatings are PLLA, PLGA block copolymers, or poly(lactide-co-*S*-caprolactone) copolymer [154,156].

Fully degradable stents, which vanish after the blood vessel has sufficiently remodeled are mostly made of the metals magnesium and its alloys or iron [16]. However, there are also polymer stents which can be fully degraded and metabolized by the body made of PLLA, PGA and their copolymer, PLGA. They have typical strut thickness of 170 μm and resorption time of 1–3 years [16]. The resorption time can be controlled by various factors like molecular weight and crystallinity of the polymer. While the performance of early polymer stents, either stable or degradable was poor due to different geometry, bio-incompatibility of the polymers and their degradation products [157], this has improved remarkably for drug eluting fully degradable stents [158]. As acidic degradation products induce inflammatory vessel wall response [157], there are concepts to quench them by incorporation of calcium phosphate nanoparticles [159].

7.2. Vascular grafts

Vascular graft materials are used as vascular prosthesis in aneurysm surgery, fur bypass surgery or as hemodialysis access. ePTFE has evolved as the leading material for this application [160,161]. Although graft patency is similar to the polyester Dacron, ePTFE has handling advantages [161,162]. Vascular access grafts of polyurethane are self-sealing and therefore allow immediate puncture in contrast to ePTFE grafts. They show similar patency as ePTFE grafts, but the rate of infectious complications is higher [163–165]. Although polymer vascular grafts for big vessels are rather successful, 5-year patency rates e.g. of femoropopliteal bypass grafts are only in the range 40–50% [162]. The patency of small caliber vessels is even less, and there are still no successful synthetic grafts below 6 mm diameter. Autologous venous grafts, despite defects at the donor site therefore are still first choice for bypass or hemodialysis vascular access. Tissue engineering of endothelialized vascular grafts for small diameter vessels or vessels, which can remodel and grow, is a major field of research [166].

7.3. Polymeric heart valves

There are two main types of artificial heart valves, either mechanical tilting disk-and-ring constructs of metal or pyrolytic carbon or bioprosthetic valves made of decellularized and cross-linked porcine heart valves or bovine pericardium. The mechanical valves have better long-term stability than the bioprosthetic valves, but they require permanent anticoagulation of the patient [167]. There are only few studies of polymer prosthetic heart valves [168,169]. Thermoplastic polyurethanes, polycarbonate urethanes and polysiloxane-based polyurethanes provide good flexibility at low thrombogenicity and resistance to degradation or calcification [170]. However, still blood clotting and deterioration of the polymer valves by calcification are the leading

problems. Their application therefore is mainly for temporary applications in cardiac assist devices [170].

8. Plastic, reconstructive and cosmetic surgery

Reconstructive surgery applies the surgical techniques and materials described before for the general and orthopedic surgery. Tissue augmentation for the correction of contour deficiencies is a specific domain of plastic surgery. Crosslinked silicone elastomer is used as onlay material on bone and soft tissue for contour augmentation, in chin and malar cosmetic surgery. For breast implants or tissue expanders, silicone elastomer is usually the outer shell of saline or silicone-gel filled implants. There is chronic inflammation around the implant with fibrous encapsulation and potential association with anaplastic large cell lymphoma [58,171]; the mechanism of this encapsulation is still not completely clear, but a textured surface seems to reduce the encapsulation and contracture [57,172].

A HDPE with interconnected pores (Medpor) is typically used for craniofacial contour augmentation and restauration of nose, orbital rim and floor and also for ear reconstruction [173]. Vascular and fibrous tissue ingrowth provides integration and fixation of the implant [47]. Also ePTFE is used as facial augmentation material [174].

9. Ophthalmology

9.1. Contact lenses

Contact lenses are the most frequently applied biomaterials on the eye. In the contact with the eye, the material must be sufficiently hydrophilic to sustain the normal hydration of the tear film and resist deposition of tear proteins and lipids. Early polymer lenses were made of rigid PMMA, being hard and oxygen impermeable, both properties are harmful to the cornea epithelial cells [175,176]. The introduction of silicon acrylates allowed the formation of rigid gas permeable contact lenses. Siloxane containing hydrogels are used for the formation of soft oxygen permeable contact lenses for up to one month permanent wear [176]. Such hydrogel contact lenses are currently also considered as drug release systems, e.g. in the treatment of glaucoma [177].

9.2. Intraocular lenses

Intraocular lenses (IOLs) after cataract surgery are the most frequently implanted polymer devices in ophthalmology. They traditionally were made of PMMA, and this material still has outstanding biocompatibility for this application; however, due to its stiffness these lenses need large incisions for implantation, and they are less frequently used today. Alternatives are silicone, foldable hydrophobic acrylates, copolymers of acrylate and methacrylate or foldable hydrophilic acrylates, mixtures of pHEMA and acrylic monomers. Also biohybrid polymers, containing collagen (Collamer) are available with good biocompatibility [56,178]. All lenses are

equipped with a chromophore to absorb UV light; some also absorb blue or violet light to protect the retina [179]. Highly hydrophilic poly(ethylene oxide) (PEO) as antifouling coatings, but also fluorinated omniphobic coatings are applied on lenses to reduce cell adhesion and opacification [178]. Stability to silicon oil, which may be used for ocular endotamponade in vitrectomy surgery, tendency for opacification of the posterior capsule and opacification by calcification are issues to consider [56].

9.3. Other polymer devices in ophthalmology

In the frame of retinal detachment treatment, the vitreous body of the eye is generally removed and needs to be substituted. Gases octafluoropropane and sulfur hexafluoride are most frequently used for this. Silicon oil is the most frequently used polymer for it and it is the first choice for complex retinal detachment, however, it must be removed after healing because of side effects like retina toxicity, cataract progression and glaucoma [180,181]. Hydrogels of crosslinked PVA, PVP, PEG, and poly(acrylamide) and also responsive hydrogels have been suggested, but there is no long-term experience yet [177,181].

Glaucoma drainage implants are inserted to drain the anterior eye chamber in cases where glaucoma is refractory to medical treatment and trabeculectomy. Materials are polypropylene, polyethylene, or silicone, where silicone seems to be associated with less complications [55,182].

10. Dentistry

10.1. Composites

Dental polymers have high requirements concerning esthetics, toughness, and polymerization mode besides the biocompatibility. Materials must support high load and shear forces, and forces of thermal expansion and shrinkage. As mentioned before, leachable unreacted monomers deteriorate the biocompatibility. Polymerization associated shrinkage has to be avoided for tightness of the filling. Composite filling materials consist of polymerizable resin, filler, and the filler–resin interface. [183–185]. The filler is usually inorganic with particle size in nanometer or micrometer range. It increases the modulus of the polymerized composite, modulates the temperature behavior and the polymerization shrinkage. Usually fillers are silanized for improved bonding in the polymer network. The resin usually consists of dimethacrylate or monomethacrylate monomers, and different formulations with different viscosity, curing time, improved volume shrinkage and shrinkage stress are the current developments [185]. Free radical addition polymerization with photoinitiation is the mostly applied [183], but self-curing one- or two component systems are still in use and have advantages for certain applications [186].

11. Neurosurgery

11.1. Peripheral nerve guidance conduits

Nerve guidance conduits are used for the repair of peripheral nerve damages, where direct repair by neurorrhaphy is not possible and where the gap should not be bridged by an autologous graft. The conduit provides mechanical stability; it guides the axonal sprouting and prevents fibrous tissue ingrowth. Stability, flexibility and guidance properties by 3D tubular structure are basic requirements. The materials must be semipermeable to allow passage of oxygen, nutrients and metabolites, but maintain a milieu of neurotropic factors. While there is still big research in this field, several conduits have received FDA approval and are in clinical use [187]. Processed and decellularized allograft nerve tissues with removed immunogenicity but maintained extracellular matrix components and growth factors are commercially available as biological grafts [67,188–190]. Tubular sheaths of PVA hydrogel are used as synthetic non-resorbable conduits and allow bridging up to 6.35 cm, however, neural compression can occur due to the lack of absorption [67,191]. Resorbable PGA is the most widely used material for conduits and has indication for bridging of defects up to 3 cm, although there are concerns about the acidic degradation products [67]. Poly (D,L lactide-co-ε-caprolactone) is a successor product with slower degradation and less acidic degradation products and got approval for tubes up to 10 mm diameter. It has advantage of transparency, but disadvantage of high stiffness [67,190]. In the field of biopolymers, various devices with type I collagen are on the market suitable for gaps up to 4 cm [67]. Agarose, chitosan, keratin, silk or synthetic poly(hydroxybutyrate) or polyurethanes are experimental polymers for nerve guidance conduits [192–194].

11.2. Central nervous system

Possibilities for regeneration in the central nervous system are much more limited than peripheral nerve repair because of the high complexity. However, there are various approaches to regenerate the dopaminergic cells of the *substantia nigra* using hydrogels as scaffold material [195–198]

12. Conclusion

Numerous types of polymers are currently in use in virtually all fields of medicine. The different polymer classes with tailored formulations like adjusted molecular weight, cross-linking degree, degree of crystallization, co-polymers and blends and additional bioactive surface functionalization allow this wide range of applications. While engineering-related properties like stiffness, tensile stability and elasticity are usually primary characteristics for selecting a polymer, also toxicity and biocompatibility aspects have to be taken into account. Biodegradation as a more advanced property of some polymers finds application in an increasing number of fields from suture materials via orthopedic stabilizing materials to

vascular stents, because these devices may disappear after they fulfilled their function. Responsive degradation of polymers upon defined triggers also allows controlled drug release applications. These concepts currently present the most active fields of research and products should soon appear on the medical device market.

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