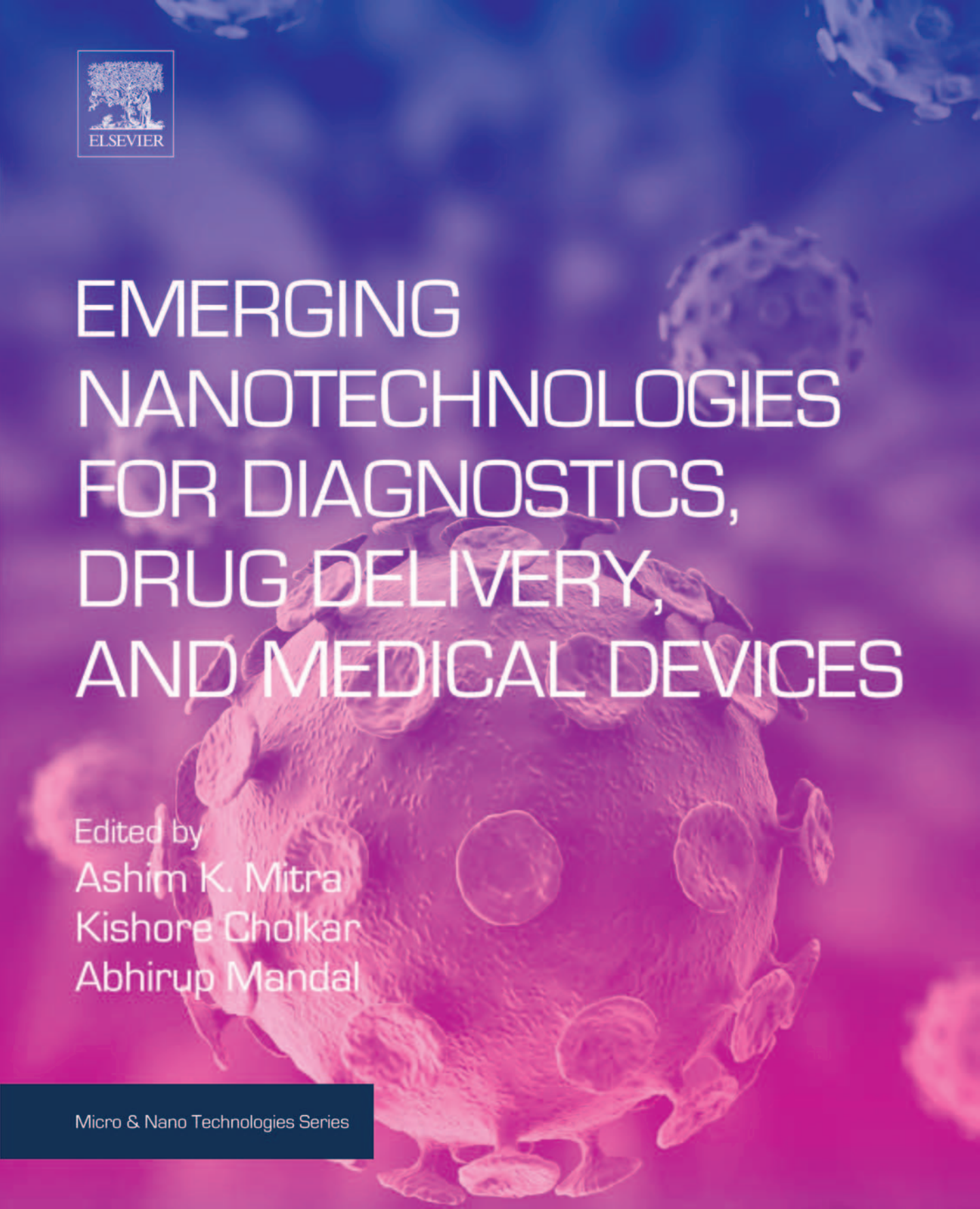
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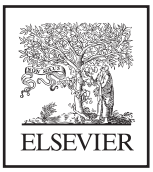

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Dr. Kishore Cholkar completed his PhD from University of Missouri—Kansas City, USA. During his academic career he was awarded with several travel awards. He is an active member of American Association of Pharmaceutical Scientists (AAPS), Association of Research in Vision and Ophthalmology (ARVO), Pharmaceutical Sciences Graduate Student Association (PSGSA), and United States Pharmacopeia and Ophthalmology group (OMICS). Moreover, Dr. Cholkar received the First Best Poster Award from Ophthalmology group in 2014 at Ophthalmology-2014 Conference, Baltimore, USA. He is the first author of more than 10 scholarly articles in peer-reviewed journals. One article, of which he was the first author, "Novel strategies for anterior segment ocular drug delivery" in the Journal of Ocular Pharmacology and Therapeutics, was in the top 10% of papers in Pharmacology and Toxicology of 2013 with approximately 50 independent citations. Another article of Dr. Cholkar's work is "Development and validation of a fast and sensitive bioanalytical method for the quantitative determination of glucocorticoids—quantitative measurement of dexamethasone in rabbit ocular matrices by liquid chromatography tandem mass spectrometry" in the Journal of Pharmaceutical and Biomedical Analysis of 2010 with 37 independent citations. "Ocular drug delivery systems: An overview" has been independently cited 75 times since its 2013 publication in World Journal of Pharmacology. Dr. Cholkar has more than 300 citations for his work with *h* index of 9 and i10 index of 9. In addition, Dr. Cholkar actively

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Abhirup Mandal is currently a PhD candidate at University of Missouri—Kansas City School of Pharmacy. He is also a pharmacist by training, with a Bachelors of Pharmacy degree from the Manipal College of Pharmaceutical Sciences, India. Abhirup has worked extensively in improving drug development and delivery strategies with comprehensive knowledge in analytical techniques, formulation of small molecule— and macromolecule-based nanocarriers, in vitro 3-D cell culture models, uptake and transport experiments, and brain and ocular microdialysis techniques. His research accomplishments include transporter-targeted drug delivery, prodrug development, and formulation approaches for improving brain and ocular drug absorption. He has published more than 13 peer-reviewed scientific research and review articles in reputed international journals including Advanced Drug Delivery Reviews and Journal of Controlled Release. He is an active member of American Association of Pharmaceutical Scientists (AAPS) and has presented more than 10 abstracts in various scientific meetings. He was awarded the Graduate Student Research Award in Drug Discovery and Development Interface at the AAPS 2016 annual meeting.

CHAPTER 1

Therapeutic Applications of Polymeric Materials

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Contents

1. INTRODUCTION

Polymers are one of the most important agents in pharmaceuticals. Polymers provide a wide range of applications in diverse biomedical fields such as, but not limited to, drug delivery, tissue engineering, implants, prostheses, ophthalmology, dental materials, and bone repair [1,2]. For better understanding, polymers may be broadly classified as biodegradable and nonbiodegradable. Biodegradable polymers represent a most important class due to their biocompatibility with biological fluids (blood/serum), tissues, and cells with minimal/no toxicity [3]. Moreover, such polymers degrade over time due to hydrolysis and therefore require no surgical procedure for their removal. Examples include polylactic acid (PLA), polyglycolic acid (PGA), polylactic glycolic acid (PLGA), and polycaprolactones (PCL). Nonbiodegradable polymers can achieve long-term near-zero-order drug release kinetics. Examples of such polymers include polyvinyl alcohol (PVA), ethylene vinyl acetate, and polysulfone capillary fiber. Although biocompatible, these polymers are not biodegradable polymers. On the other hand, various natural and synthetic polymers have applications in drug delivery, imaging, and diagnosis. Examples include polyesters, polyamides, poly(amino acids), polyorthoesters, polyurethanes, and polyacrylamides [4]. Among them, thermoplastic aliphatic polyesters like poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and especially their copolymer poly(lactic-*co*-glycolic acid) (PLGA) are of significant interest due to their biocompatibility, process ability, and biodegradability.

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Other most common and extensively studied biodegradable polymers include poly(E-caprolactone) (PCL), chitosan, gelatin, and poly(alkyl cyanoacrylates).

Early studies by Duncan et al., reported the development of first polymer–drug conjugates with applications for biomedical field [2,5]. Since then, several polymer–drug conjugates have been developed and commercialized. Polymeric systems may offer advantages such as improved drug stability, reduced toxicity, and enhanced targetability. Moreover, these polymers have been introduced in medical practice [6]. Biocompatible, biodegradable polymers and copolymers have demonstrated therapeutic potential in three major areas: (1) diagnostic applications, (2) therapeutic delivery, and (3) theranostics [6].

Polymer-based diagnostic agents are employed in diagnostic techniques such as fluorescence, imaging, magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), and ultrasound diagnosis [6]. Moreover, polymeric systems have been intensively investigated as carrier systems for active pharmaceutical ingredient/s [2]. Polymeric systems may offer protection and improve the half-life for highly unstable drugs such as resolvins [7]. Moreover, half-lives for biologics such as DNA and RNA and protein stability may be enhanced. Moreover, it can provide protection against in vivo degradation and premature inactivation [2]. Several stimuli (pH and temperature)-responsive smart polymeric drug delivery vehicles have been designed to achieve targeted drug delivery. Such polymeric systems exhibit improved efficacy and aid in optimizing the dose. Current investigations are being focused on applications of polymers in therapeutics [2]. For example, polymer synthesis methods allow designing the polymer architecture, which in turn plays an important role in biological activity [8,9]. Various ligands can be conjugated to polymer backbone, which may result in targeting a specific receptor and transporter site.

A drug delivery system must release the drug at or into the target as well as maintain therapeutic drug levels for a desired duration [10] in blood stream, allowing for distribution to tissues by the enhanced permeability and retention (EPR) effect. Additionally, active targeting may be achieved by the polymer carrier, a polymer–drug conjugate, or the drug [10].

2. POLYMERS AS DRUG DELIVERY SYSTEMS

In recent years, various engineered nanoscale materials have been developed or are currently under investigation for drug delivery applications. Polymer blends are of significant interest in the biomedical field due to its wide variety of applications [11–14]. Compatibility of the copolymers and their interaction with the active pharmaceutical ingredient (API) play an important role in deciding the phase separation of the blend, which in turn plays an important role in the release behavior of the drug from the blend. The release rate may be tailored by varying ratio of the polymers in the copolymers blend [15]. Biocompatible and biodegradable nanomicelles based on block

copolymer (BCP) are certainly one of the most promising nanostructures, for controlled delivery of poorly water-soluble drugs such as doxorubicin (DOX), paclitaxel, and clofazimine. These micellar drug formulations offer various advantages such as increased circulation time, improved water solubility, and tumor tissue targeting via the enhanced permeation and retention (EPR) effect [16]. The EPR effect exploits the increased porosity of the vasculature immediately surrounding a tumor. Polymeric nanomicelles (diameters 10−100 nm) can enter the tumor cells through endothelial cell lining of healthy capillary walls and can be retained in the lymphatic system [16]. In spite of these advantages, progress in the development of these systems have been hampered by slow and incomplete drug release (degradation times ranging from days to months) [17,18]. Extensive research is going on at present to overcome slow drug release, enhancing therapeutic efficacy and responding to changes in the environmental condition.

In particular, degradation in response to external stimuli is highly advantageous due to enhanced release of encapsulated drug molecules at the target site. Stimuli-responsive polymers are defined as polymers that undergo physical or chemical changes in response to surrounding environment [19].

Incorporating disulfide bond at the junctions of hydrophobic and hydrophilic blocks has emerged as a unique pathway to control the intracellular drug release. In particular, reductive-sensitive shedding nanomicellar systems are of great interest due to a high imbalance of glutathione (GSH) level between intracellular and extracellular environments [20,21]. The presence of a high redox potential difference between the oxidizing extracellular space and reducing intracellular space makes the disulfide bond a potential candidate as intracellular drug delivery tool [22]. Furthermore, the tumor tissues are reducing and hypoxic rendering disulfide-containing BCP specifically suitable for anticancer drug delivery. The other common strategy is to include disulfide linkage thereby cross-linking through S−S bonds. Fig. 1.1 illustrates doxorubicin incorporated into spherical nanomicelles. It is composed of polyethylene glycol (PEG)-SS-PCL, which permeates the tumor cell through the leaky vasculature and releasing the drug S−S cleavage by GSH intracellularly. Polymer properties may be tuned by changing the polymer architecture from linear or cross-linked to a partially or highly branched structure [6]. Owing to the unique properties, hyperbranched polymers (HBPs) with biocompatible and biodegradable polymers have demonstrated great potential for therapeutic applications [23−26].

The drug product, genetic segment, or the diagnostic agent may be encapsulated or conjugated with HBPs [6]. Zhu et al. synthesized a hyperbranched poly-((*S*-(4-vinyl) benzyl *S*′-propyltrithiocarbonate)-*co*-(poly(ethylene glycol) methacrylate)) (poly(VBPT-*co*-PEGMA)) with multiple thiol groups via SCVP-RAFT (self-condensing vinyl polymerization-reversible addition-fragmentation chain transfer polymerization) copolymerization (Fig. 1.4) [27,28]. The authors demonstrated that thiol-containing anticancer drugs may be conjugated to this biocompatible HBP via disulfide linkages after aminolysis reaction to achieve a redox-responsive drug release (Fig. 1.2).

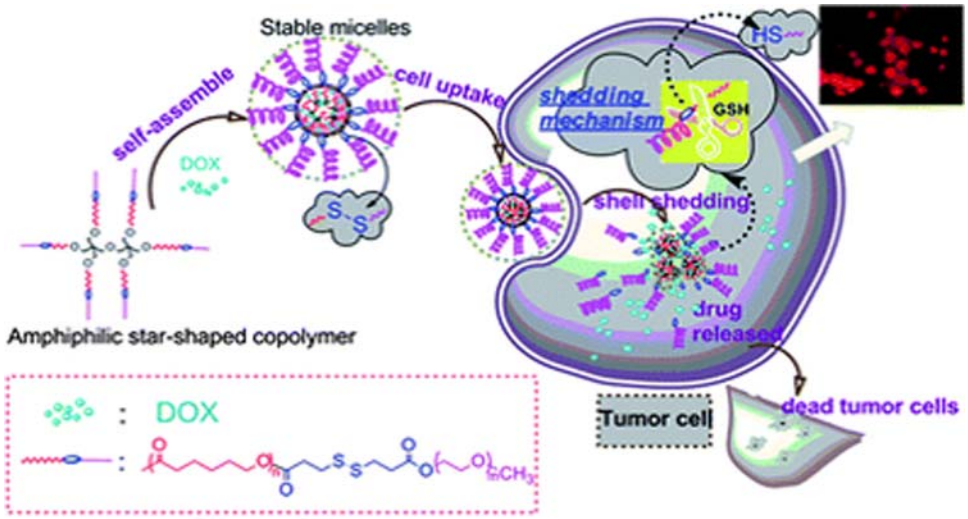

Figure 1.1 Scheme illustrating the spherical micelles based on polyethylene glycol—SS—polycaprolactone incorporating drug [doxorubicin (DOX)] and entering tumor cell through the leaky vasculature and releasing the drug on shedding triggered by glutathione (GSH) inside the cell. *(Reprinted with permission from Royal Society of Chemistry. Tian-Bin Ren YF, Zhang Z-H, Li L, Li Y-Y. Shell-sheddable micelles based on star-shaped poly(ε-caprolactone)-SS-poly(ethyl glycol) copolymer for intracellular drug release. Soft Matter 2011;7:2329—31.)*

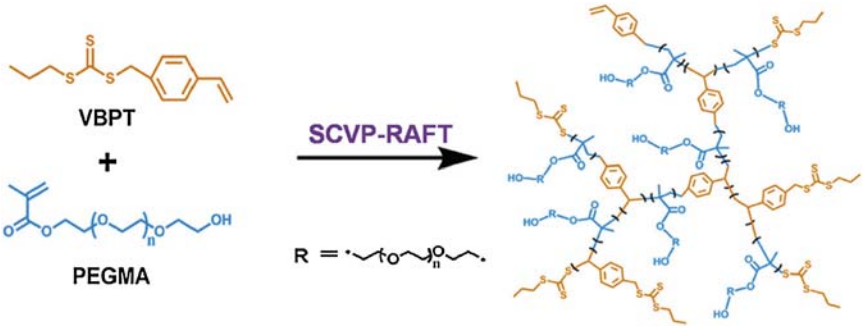

Figure 1.2 A schematic illustration of hyperbranched poly-(*S*-(4-vinyl) benzyl *S*′-propyltrithiocarbonate)-*co*-(poly(ethylene glycol) methacrylate)) (poly(VBPT-*co*-PEGMA)) constructed by SCVP-RAFT (self-condensing vinyl polymerization-reversible addition-fragmentation chain transfer polymerization) using VBPT and PEGMA monomers. *(Reproduced from Zhuang Y, et al. Facile fabrication of redox-responsive thiol-containing drug delivery system via RAFT polymerization. Biomacromolecules 2014;15(4):1408—18. Copyright 2014 American Chemical Society.)*

PEG-based HBP has also been explored for drug delivery as these systems may exhibit enhanced encapsulation efficiency and controlled drug release. This technology also offers postpolymerization modification, which may add stimuli-responsive features depending upon the functionality. Ji and coworkers have synthesized photoresponsive,

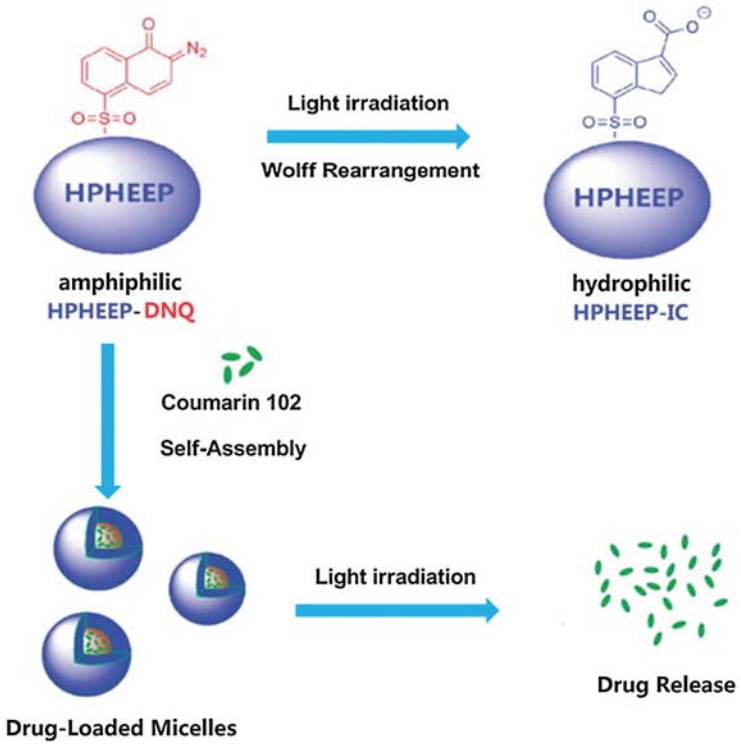

Figure 1.3 Photoresponsive behavior of hyperbranched polyphosphate (HPHEEP)—2-diazo-1,2-naphthoquinone-5-sulfonyl chloride (DNQ) and schematic illustration of the self-assembly and light-triggered drug release behavior of HPHEEP-DNQ micelles. *(Reproduced with permission from Chaojian Chen GL, Liu X, Pang S, Zhu C, Lv L, Ji J. Photo-responsive, biocompatible polymeric micelles self-assembled from hyperbranched polyphosphate-based polymers. Polym Chem 2011;2:1389—97.)*

biocompatible, and biodegradable hyperbranched polyphosphate (HPHEEP) via terminal modification, hydrophobic 2-diazo-1,2-naphthoquinone-5-sulfonyl chloride (DNQ) [29]. The resulting polymer can self-assemble into nanomicelles in water. The photochemical reaction of DNQ moieties under ultraviolet exposure results in destabilization of the nanomicelles to achieve photoresponsive drug release (Fig. 1.3) [6].

2.1 Polymer—Drug Conjugates

Another extensively studied nanoscale material for drug delivery is polymer—drug conjugates [12]. Small-molecule therapeutic agents, especially anticancer drugs, have the following disadvantages. They have poor aqueous solubility, short circulation half-life, may cause embolism, and off-target distribution, resulting in toxicity to normal cells [30]. The conjugation of small-molecule drugs to polymeric nanocarriers can overcome these problems. Polymer—drug conjugates can extend the in vivo circulation time and reduce

cellular uptake to the endocytic route. The initial clinical trials with PEG were carried out in the early 1990s [31]. It can improve the plasma stability and solubility of the drug while reducing immunogenicity. Various PEGylated drugs are in clinical practice. For example, Adagen (PEG—adenosine deaminase) is indicated in immunodeficiency disease; Pegasys (PEG—a-interferon 2a) is prescribed to treat hepatitis B and C infections; and Oncaspar (PEG—L-asparaginase) can be recommended to treat acute lymphoblastic leukemia [30]. Besides PEG, other linear polymers that have also been studied as polymeric drug delivery carriers include polyglutamic acid, polysaccharide, and poly(allylamine hydrochloride).

2.2 Polymers in Ocular Drug Delivery

Natural and synthetic polymers have been introduced in ocular drug delivery. Natural polymers include starch, sodium alginate, sodium hyaluronate, xanthan gum, gelatin, gellan gum, guar gum, collagen, chitosan, and albumin. On the other hand, synthetic polymers include, but not limited to, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, poly(acrylic acid), carbomers, sodium hyaluronose, chitosan, cyclodextrins, polygalacturonic acid, xyloglucan, xanthan gum, gellan gum, poly(ortho esters), hydroxyl ethyl cellulose, PVA, PGA, PLA, PCL, and poly(lactide-*co*-glycolide). These polymers may be straight chain or branched. Moreover, such polymers may be blended to achieve the desired drug release profile from the polymeric matrix. Mostly, such polymers are designed to encapsulate the active pharmaceutical ingredient for sustained or controlled drug release. In general, block copolymers may include diblock or triblock. However, Mitra et al. synthesized pentablock copolymers with different ratios of polymer block in the polymeric chain [32]. Such polymers may be custom tailored with respect to API to achieve desired drug loading and release. Moreover, these polymers can be applied in the preparation of nanoparticles and thermosensitive hydrogels. Nanoparticles prepared with pentablock copolymers encapsulated both small and large molecules. Thermosensitive polymers exhibit liquid or solution properties at room temperature (25°C) and transition to gel at physiological temperatures (34—37°C). Such a polymer can be applied to encapsulate drug-loaded nanoparticles for sustained drug release. In vivo studies were conducted in New Zealand albino rabbits to demonstrate biocompatibility and biodegradability. This study reveals that pentablock copolymer turns into a gel depot followed by slow degradation (Fig. 1.6). Interestingly, pentablock hydrogel encapsulating pentablock blank nanoparticles injected into rabbit eye demonstrate a depot over 90 days. Moreover, the depot did not appear to interfere with the field of vision.

Other amphiphilic polymers such as vitamin E tocopheryl polyethylene glycol (Vit. E. TPGS), octoxynol-40, and hydrogenated castor oil-40/60 have been evaluated for ocular drug delivery. These polymers have the ability to spontaneously generate nanomicelles in aqueous environment. Studies were conducted to encapsulate hydrophobic drugs such as voclosporin, rapamycin, dexamethasone, resolvin analog, acyclovir derivatives and peptides like cyclosporine [7,33—39]. Results indicated that solubility of

these highly hydrophobic drugs was significantly improved in aqueous solution because of the drug encapsulation in the polymeric nanomicelles. The hydrophilic corona of nanomicelles aids in solubility. Hydrophobic interactions of the drug within the nanomicelle core stabilize and improves drug solubility. Biocompatibility studies on ocular cell lines demonstrated the delivery system to be safe and well tolerated.

In vivo studies conducted in New Zealand albino rabbits demonstrated that nanomicelles carried the drug to deeper anterior ocular tissues. Interestingly, the drug was detected in the back of the eye tissues (retina/choroid) with topical drop administration. These results indicate that nanomicelles follow conjunctival—scleral pathway to reach retina from topical dosing [34,35,38,39]. Such a technology can offer a platform for delivery of small and macromolecular drugs to posterior ocular tissues.

2.3 Polymers in Tissue Engineering

Tissue engineering/regeneration hypothesizes that a progenitor cell is recruited or delivered at an injured site to regenerate the damaged tissue. A synthetic porous three-dimensional polymeric scaffold has been engineered that enhances functional tissue regeneration by facilitating progenitor cell migration, proliferation, and differentiation. Such scaffolds may be prepared from natural or synthetic polymers. Natural polymers such as chitin, gelatin, elastin, fibrinogen, silk fibroin, and collagen have been utilized as scaffolds in tissue engineering. These polymers can be molded to scaffolds like hydrogel scaffolds (Fig. 1.4), PET grafts, and electrospun PCL mats (Fig. 1.5). Chitin is a biopolymer (*N*-acetyl-glucosamine monomer) extracted from shellfish. Depending upon the processing method *N*-acetyl-glucosamine and *N*-glucosamine units may be randomly or block distributed throughout the biopolymer chain. In a biopolymer if the fraction of *N*-acetyl-glucosamine units is higher than 50%, the biopolymer is called chitin. Chitin and its derivatives have applications as wound dressing materials, drug delivery systems, and candidates for tissue engineering. Hydroxyapatite (HA) or other calcium-containing materials amalgamated with chitin are commonly referred as "composite." These materials have application in orthopedics and periodontics. For example, a combination of polymer with HA provided maximum osteoconductive behavior of HA in vivo. The matrix progressively resorbs and allows bone growth to occur inside the implant [40,41]. nHA [$Ca_{10}(PO_4)_6(OH)_2$] displays high surface area to volume ratio and mimics apatite like structure and composition of hard tissues like bone, dentine, and enamel [42—44]. This material is nontoxic, noninflammatory, nonimmunogenic, nondecomposable, osteoconductive. Moreover, it demonstrates stability in body fluids and forms chemical bonds with surrounding hard tissues [45,46]. β-Chitin/HA and α-chitin/HA nanocomposite scaffolds were synthesized from a mixture of β-chitin hydrogel and nHA by freeze-drying technique [47,48]. Biocompatibility for such nanocomposite scaffolds was studied with MG

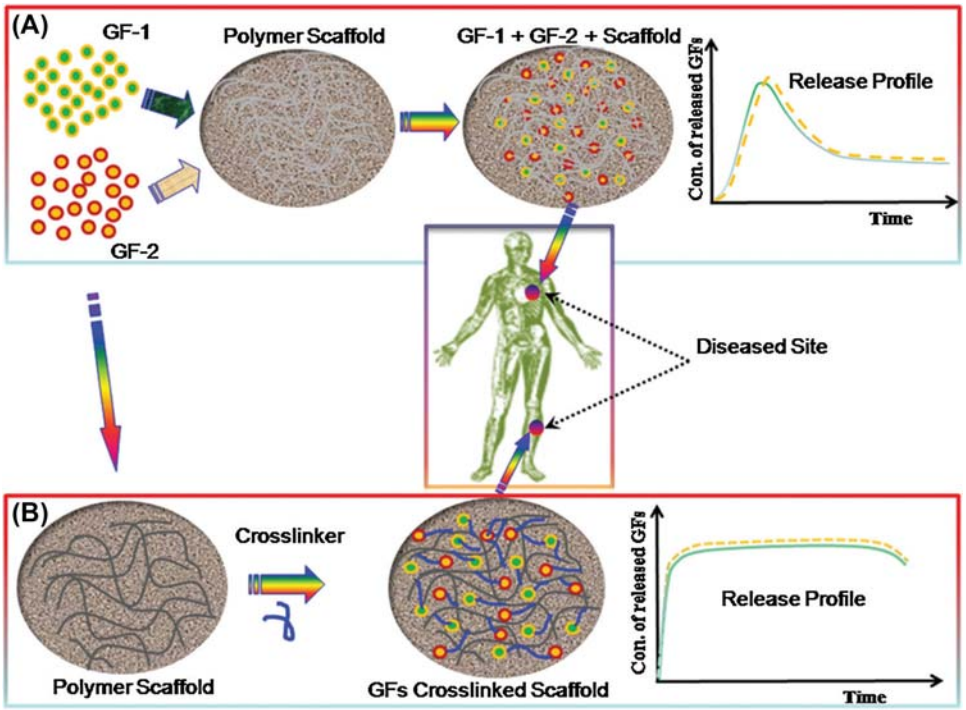

Figure 1.4 Schematic illustration of methods for immobilization of bioactive factor molecules [growth factors (GFs)] into hydrogels scaffolds. (A) Noncovalent immobilization of two different types of GFs loaded into hydrogels directly via entrapment before implantation and their expected release profile. (B) Covalent immobilization of two types of GFs modified and thereafter covalently cross-linked to the hydrogels via cross-linkers before implantation to the diseased site and their sustained release profile. *(Reproduced from Shuai X, et al. Micellar carriers based on block copolymers of poly(epsilon-caprolactone) and poly(ethylene glycol) for doxorubicin delivery. J Control Release 2004;98(3):415–26.)*

63 cells. The results indicated that cells were viable and exhibited enhanced attachment and proliferation onto the nanocomposite scaffolds. This result essentially signifies that nanocomposite scaffolds may serve as potential candidates for bone tissue engineering. Natural polymers, synthetic polymers, combination or blend of polymers and their application in tissue engineering are presented in Table 1.1.

3. POLYMERS IN IMAGING AND DIAGNOSIS

Polymers consist of multiple similar units bonded together and have been widely employed in therapeutic and diagnostic applications. Based on the monomer units, the polymers display various physical and chemical properties. Because of the mechanical and functional properties, many biological and synthetic polymers have become the important materials for medical applications such as vascular or urinary catheters, vascular

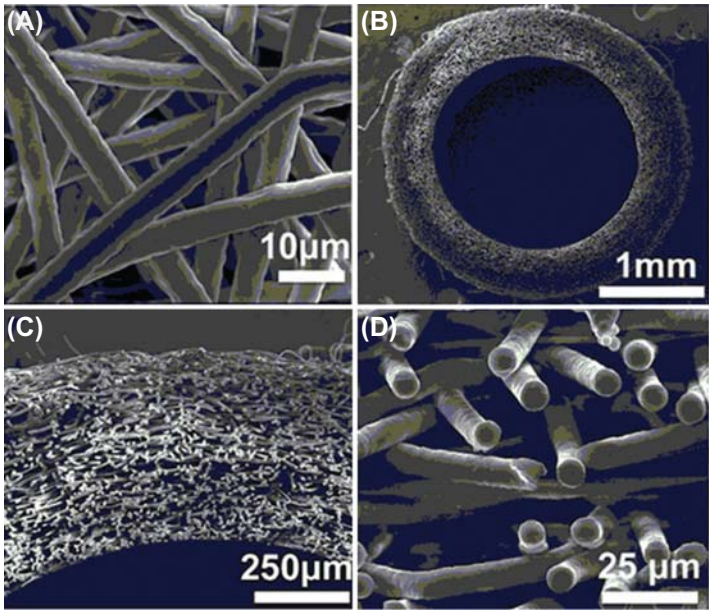

Figure 1.5 Scanning electron microscope images of electrospun polycaprolactone mats with thicker fibers (A) and cross-sections of the tubular thicker fiber grafts (B—D). *(Reproduced with permission from Wang Z, et al. The effect of thick fibers and large pores of electrospun poly(epsilon-caprolactone) vascular grafts on macrophage polarization and arterial regeneration. Biomaterials 2014;35(22):5700—10. Copyright 2014, Elsevier.)*

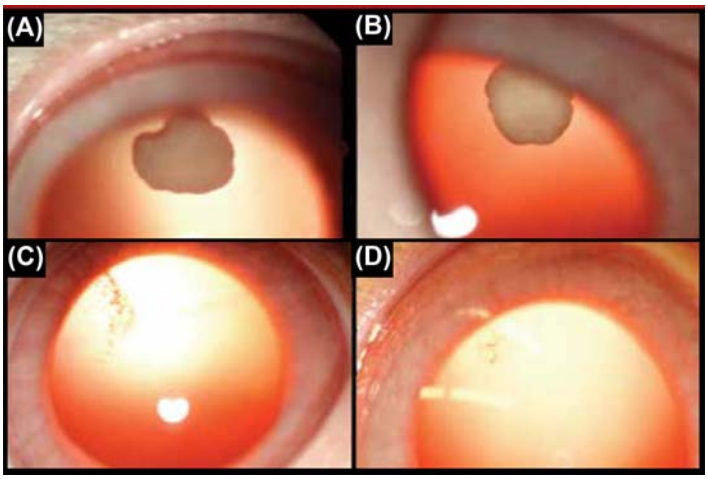

Figure 1.6 Gel forming pentablock copolymer; depot formation after intravitreal injection into rabbit eye. Images taken on (A) day 1, (B) day 21, (C) day 42, and (D) day 49 show the gel biodegrading over time.

Table 1.1 List of natural polymer scaffolds and their applications

Polymer	Application	Remarks/conclusions	References
Gelatin/poly(lactic acid-*co*-glycolic acid) (PLGA) bilayered nanofibers	Fabrication of meniscal tissue engineering scaffold	In vitro, the meniscal cells derived from New Zealand white rabbits menisci seeded in the scaffolds demonstrated cell proliferation. The bilayered gelatin/PLGA scaffold revealed concurrent effects of mechanics and cytocompatibility. Moreover, such scaffold appears to be a promising scaffold for future meniscal repair strategies	[84]
Collagen-BDDGE (1,4-butanediol diglycidyl ether)-elastin core-shell scaffold	Tendon regeneration	A prototype of the core module implanted in a rat tendon lesion model demonstrated safety, biocompatibility, and ability of the scaffold to induce tendon regeneration. Results indicate that such a device may support and induce in situ tendon regeneration	[85]
Fibrinogen-based nanofibers	Differentiation of human mesenchymal stem cells for cartilage development	Human adipose-derived mesenchymal stem cells established significant chondrogenic differentiation and may generate quality cartilage when cultured on 2D and randomly oriented fibrinogen/poly-lactic acid nanofibers relative to 3D sandwich-like environments. The adhering cells demonstrated well-developed focal adhesion complexes and actin cytoskeleton arrangements. This confirms proper cellular interaction with either random or aligned nanofibers	[86]
Electrospun fibrinogen-PLA nanofibers	Vascular tissue engineering	Development of a new type of hybrid fibrinogen-polylactic acid (FBG-PLA) nanofibers with improved stiffness, combining the good mechanical properties of PLA with the excellent cell recognition properties of native FBG	[87]
Silk fibroin nanofibrous scaffold	Bone tissue engineering application	Results confirm the positive correlation of alkaline phosphatase activity, alizarin staining, and expression of runt-related transcription factor 2, osteocalcin, and type 1 collagen representing the biomimetic property of the scaffolds. Developed composite demonstrated to be a potential scaffold for bone tissue engineering application	[88]

Agarose/silk fibroin blended hydrogel	In vitro cartilage tissue engineering	The hydrogels demonstrated immunocompatibility, which was evidenced by minimal in vitro secretion of tumor necrosis factor-α (TNF-α) by murine macrophages. Results suggest promising attributes of blended hydrogels and nonmulberry silk fibroin-agarose blends as alternative biomaterial for cartilage tissue engineering	[89]
Electrospun silk-fibroin nanofiber	Skin tissue engineering	Histologic findings in only electrospun SF scaffolds evidenced significant proliferation of fibroblasts in deeper layer and more differentiation of keratinocytes in superficial layer. Results suggest that 3D electrospun SF scaffolds may be suitable for skin tissue engineering	[90]
In situ cross-linking and mineralization of electrospun collagen scaffolds	Bone tissue	Among the catecholamines, matrix containing norepinephrine displayed superior mechanical, photoluminescence, and biological properties than matrix loaded with dopamine. Such smart multifunctional scaffolds may potentially be utilized to repair and regenerate bone defects and injuries	[91]
Thermosensitive collagen hydrogel	Constructing tissue engineering complex	Thermosensitive collagen hydrogel-poly-L-lactic acid fiber joint-constructed complex extracellular matrix had good biocompatibility and dynamic culture. Such construct may promote the distribution of bone marrow-derived mesenchymal stem cells on the surface and inside the structure, thus promoting cell proliferation, so it could be used for the in vitro construction of tissue engineering complex	[92]
Acellular collagen scaffold	Urethral regeneration	Spontaneous repopulation of urothelial and smooth muscle cells on all grafts was demonstrated. Cellular organization increased with time; however, 20% of both fistula and stenosis could be observed postoperatively. This off-the-shelf scaffold with a promising urethral regeneration has a potential for clinical application	[93]

Continued

Table 1.1 List of natural polymer scaffolds and their applications—cont'd

Polymer	Application	Remarks/conclusions	References
Biomimetic porous PLGA scaffolds	Kidney tissue regeneration	Results suggest that the tissue-engineering techniques can be an effective alternative method for treatment of kidney diseases. Moreover, the extracellular matrix incorporated poly(lactic-*co*-glycolic acid) scaffolds may be one of the promising materials for biomedical applications including tissue engineered scaffolds and biodegradable implants	[94]
Cell-free methacrylated hyaluronic acid/ poly(lactide-*co*-glycolide) (HA-MA/PLGA) scaffolds	Regeneration of full-thickness cartilage defects	Expression of inflammatory factor interleukin-1β was downregulated, although TNF-α is remarkably upregulated. With the anti-inflammatory, bioactive properties and good restoration of full-thickness cartilage defect in vivo, the oriented macroporous HA-MA/PLGA hybrid scaffold has a great potential for practical application in in situ cartilage regeneration	[95]
Nanohydroxyapatite/ poly(L-lactic acid) (HA/PLLA) spindle composites	Bone tissue engineering	The in vitro tests indicate that HA/PLLA biocomposites have good biodegradability and bioactivity when immersed in simulated body fluid solutions. All the results suggested that HA/PLLA nanobiocomposites are appropriate to be applied as bone substitute in bone tissue engineering	[96]