

EMERGING NANOTECHNOLOGIES FOR DIAGNOSTICS, DRUG DELIVERY, AND MEDICAL DEVICES

Edited by
Ashim K. Mitra
Kishore Cholkar
Abhirup Mandal

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EMERGING NANOTECHNOLOGIES FOR DIAGNOSTICS, DRUG DELIVERY, AND MEDICAL DEVICES

Edited by

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CHAPTER 1

Therapeutic Applications of Polymeric Materials

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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.

Other most common and extensively studied biodegradable polymers include poly(ϵ -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).

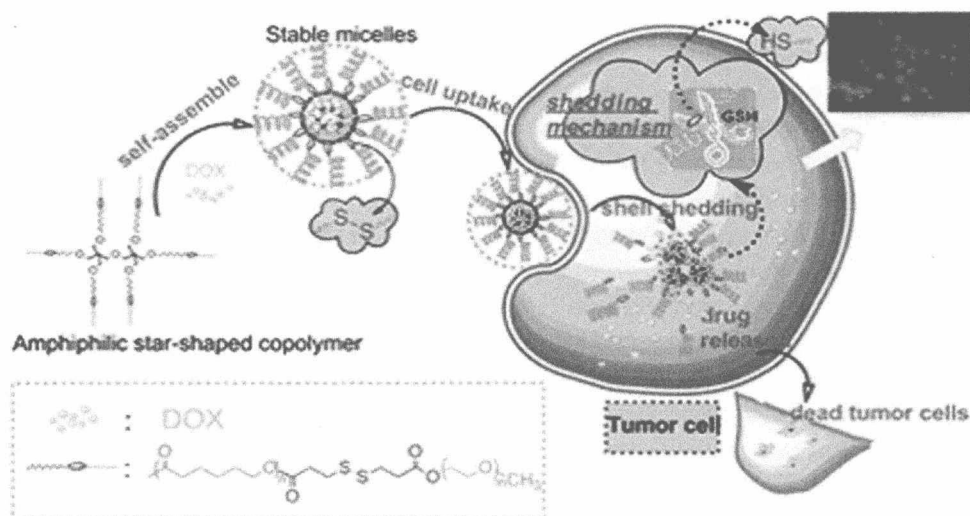


Figure 1.1 Scheme illustrating the spherical micelles based on poly(ethylene glycol)–SS–polycaprolactone incorporating drug [doxorubicin (DOX)] and entering tumor cell through the leaky vasculature and releasing the drug on shedding triggered by glutathione (GSH) inside the cell. (Reprinted with permission 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.)

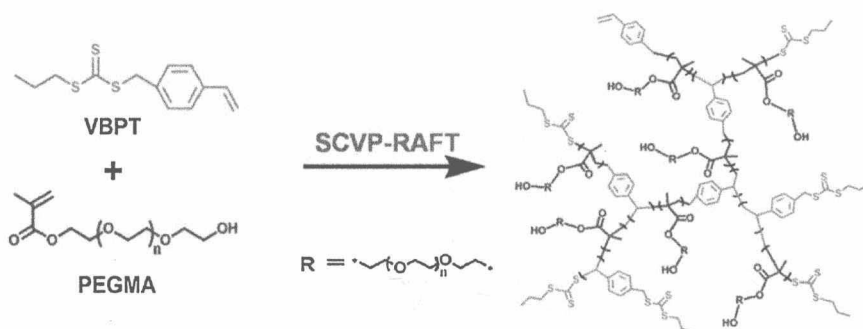


Figure 1.2 A schematic illustration of hyperbranched poly-(S-(4-vinyl) benzyl S'-propyltrithiocarbonate)-co-(poly(ethylene glycol) methacrylate)) (poly(VBPT-co-PEGMA)) constructed by SCVP-RAFT (self-condensing vinyl polymerization-reversible addition-fragmentation chain transfer polymerization) using 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,

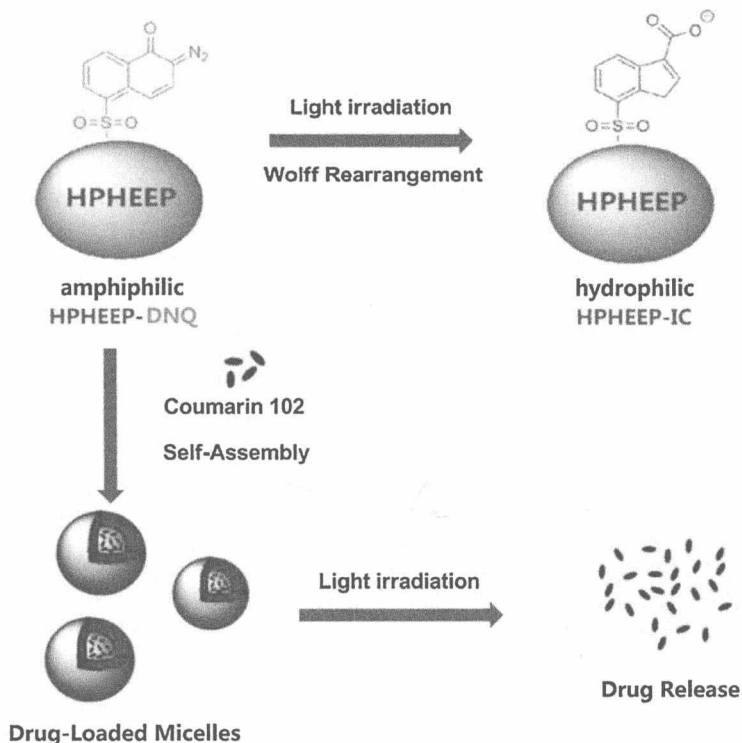


Figure 1.3 Photoresponsive behavior of hyperbranched polyphosphate (HPHEEP)–2-diazo-1,2-naphthoquinone-5-sulfonyl chloride (DNQ) and schematic illustration of the self-assembly and light-triggered drug release behavior of HPHEEP-DNQ micelles. (Reproduced with permission from Chaojian Chen GL, Liu X, 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— α -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 voriconazole, rapamycin, dexamethasone, resolvin analog, acyclovir derivatives and peptides like cyclosporine [7,33–39]. Results indicated that solubility of