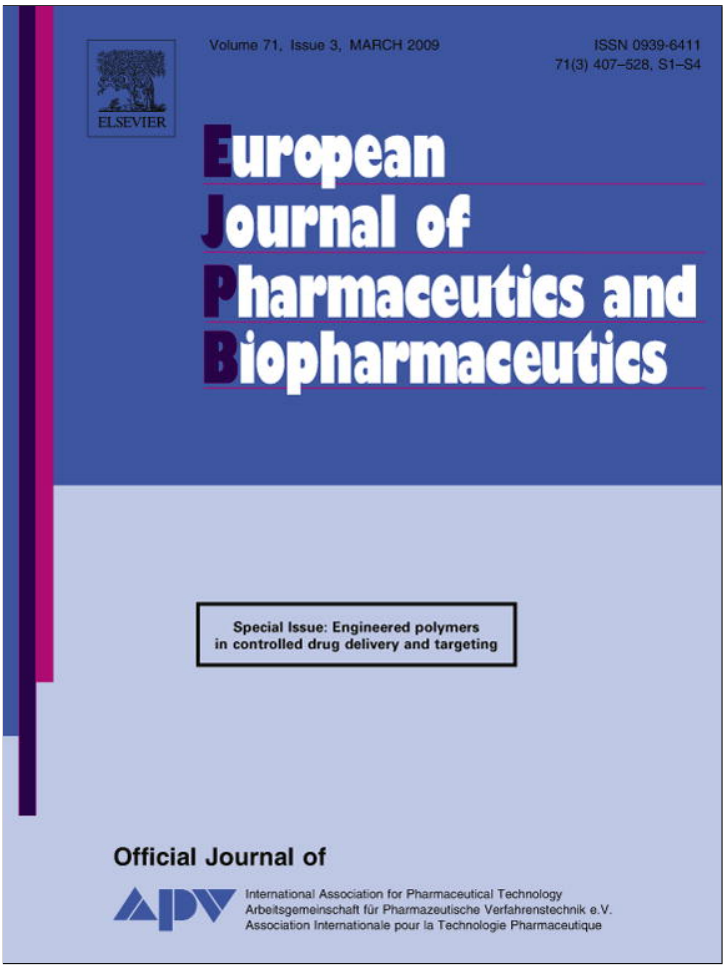

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Review article

Engineered polymers for advanced drug delivery

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ABSTRACT

Engineered polymers have been utilized for developing advanced drug delivery systems. The development of such polymers has caused advances in polymer chemistry, which, in turn, has resulted in smart polymers that can respond to changes in environmental condition such as temperature, pH, and biomolecules. The responses vary widely from swelling/deswelling to degradation. Drug-polymer conjugates and drug-containing nano/micro-particles have been used for drug targeting. Engineered polymers and polymeric systems have also been used in new areas, such as molecular imaging as well as in nanotechnology. This review examines the engineered polymers that have been used as traditional drug delivery systems and as more recent applications in nanotechnology.

1. Introduction

Modern drug delivery technology has been made possible by the advances in polymer science. These advances have resulted in polymers with unique properties. Initially, polymers were used as additives to solubilize and stabilize drugs or as mechanical supporters for the sustained release of drugs. Since that time, the roles of polymers have changed continuously. As new synthetic methods were developed, polymers with well-defined structures were produced. The availability of new monomers has allowed for the synthesis of polymers with different phenotypes and tailor-made properties. Input from other research areas, such as biochemistry, microfluidics, and nanotechnology, has made polymers and their drug delivery systems smarter and more effective.

As new polymers with innovative properties became available, selection of the right polymers for certain applications became critically important. This led to strong demands on more efficient and more functional drug delivery vehicles. As polymers with new properties were developed, more needs were found to develop polymers with even more intricate properties. It is most desirable if the polymers with advanced properties are synthesized with specific functions designed for drug delivery, such as drug solubilization and drug targeting, and for solving emerging problems. For this reason, it is beneficial to understand the current drug delivery technologies and the unique roles of polymers. This review is focused on two primary goals of presenting an overview of the advances in polymers and polymeric systems for drug delivery and describing an outlook over future technologies.

2. Polymers and polymeric systems for controlled drug delivery

2.1. Controlled release

For conventional formulations, the plasma concentration of a drug is directly proportional to the administrated dose. Fig. 1A displays the typical profiles of plasma drug concentration as a function of time after oral or intravenous administration. Those formulations are difficult to maintain the therapeutic dose for extended periods of time, which usually require multiple administrations to obtain therapeutic effect. In addition, systemic circulation of high drug concentration often induces the adverse effect, because in this case, drug delivery solely depends on simple diffusion or partition from blood stream to target site. Only one advantage of conventional formulations is that the cost of development is low.

The controlled drug delivery system has been developed to alleviate the shortcomings of conventional formulations. Primary concern of this system is the programmability. The simplest example is the sustained drug release, resulting in prolonged plasma drug concentration within a therapeutic window (Fig. 1B). For treating the imbalance of biological homeostasis, it is possible that a therapeutic agent can be released only when it is required (Fig. 1C). For example, dynamic release of the insulin from a polymer matrix should occur only in response to increased glucose concentration of diabetic patients [1]. Such a feedback control mimicking natural biological system could be achieved by the smart polymers to be described later. To extend the blood circulation time, drugs have

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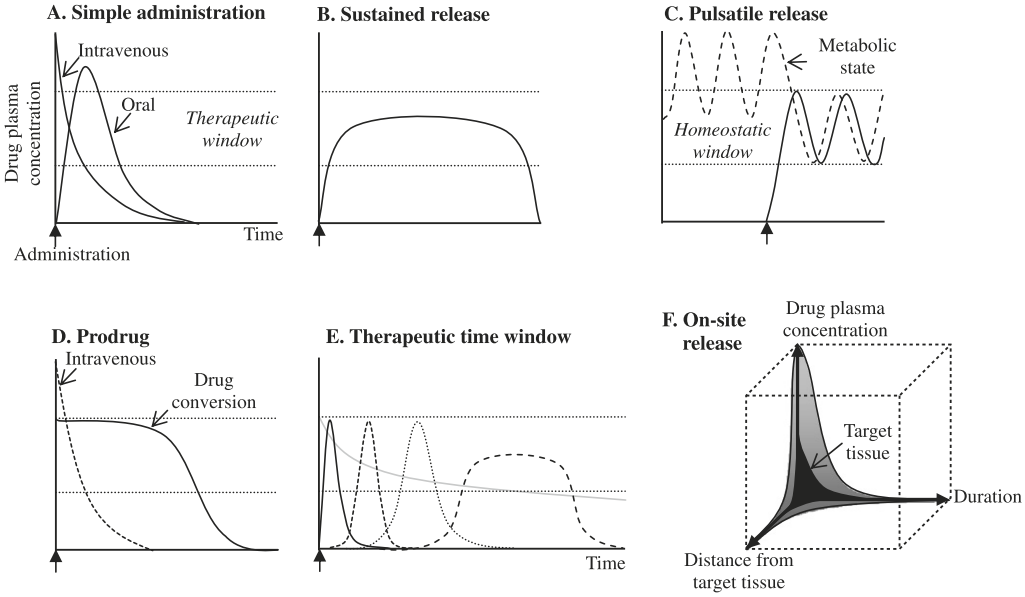

Fig. 1. Different types of controlled release systems. (A) Drug delivery based on simple diffusion and partition. (B) Sustained release to prolong the therapeutic period. (C) Pulsatile release to tightly maintain homeostasis. (D) Release profile and drug conversion of the polymer-drug conjugate as a prodrug. (E) Temporally controlled (or sequential) release profile of multiple drugs. (F) On-site release to maximize therapeutic efficiency and to minimize side effect.

been encapsulated in nano- or micro-particles. Polymer-drug conjugation has also resulted in an increase of the drug circulation time and drug stability in blood [2]. As shown in Fig. 1D, active drug can be generated by continuous or site-specific degradation of linkers by which drugs and polymers are chemically conjugated.

Progress of a certain disease usually recruits multiple biological components, such as growth factors, enzymes, and leukocytes. To treat this etiological trouble, conventional concept of the therapeutic window should be extended to therapeutic time window because the time frame, in occurrence of each component, becomes a key parameter. During stroke development, for example, ischemic brain induces several cellular events including provocation of excitatory amino acids and reactive oxygen species within an hour, formation of polymorphonuclear leukocytes within a day, and macrophage activation within a week [3]. The therapeutic time window can be applied for the tissue engineering based on drug delivery. To obtain specialized function in a body, normal tissues also require temporally specified stimulation during their development. For instance, many growth factors (fibroblast growth factor, insulin-like growth factor, platelet-derived growth factor, transforming growth factor-β, bone morphogenic protein, vascular endothelial growth factor, etc.) participate in bone regeneration [4]. As an extension of the pulsatile release system, a temporally programmed drug release system is an excellent solution to supply multiple drugs. In this system, multiple drug components are supposed to be sequentially released only when they are demanded (Fig. 1E).

In addition to the programmability, on-site drug release is another important advantage of the controlled release system. Usually, the on-site release can be achieved by targeting strategies. As shown in Fig. 1F, this system tightly controls the drug release to maximize the therapeutic efficiency and to minimize the side effect. Drug release is much limited to a target site at a high local concentration for a long time. Table 1 summarizes conventional drug formulation, sustained release system, triggered release systems (pulsatile and on-site release systems), and polymer-drug conjugate systems. In general, more controllability may accompany more complexity in system design. Therefore, how to choose an appropriate drug delivery system for a specific application and how to reduce the system complexity will be important questions on developing effective drug delivery systems.

Table 1
Comparison among controlled drug release systems.

	Simple diffusion/ partition	Controlled release		
		Sustained release	Triggered release	Prodrug
Formulation	Solution dispersion emulsion powder	Hydrogel micro-/ nanoparticles film	Smart polymer systems BioMEMS	Polymer-drug conjugate
Targeting	[a]N/A	[b]N/R	[c]Active/[d]passive	Active/passive
Drug release rate	Burst	[e]Gradual	[e]Burst	[e]Gradual
Programmability	No	Yes	Yes	Yes/no
Side effect	Relatively high	Mild	Low	Low/mild
Feedback loop	Open	Open/closed	Open/closed	Open
Design complexity (production cost)	Low	Moderate	High	High
Scalability	Easy	Relatively easy	Difficult	Moderate

[a] Not applicable.
[b] Not required.
[c] Targeting strategy mediated by ligand and/or stimuli-sensitivity.
[d] Enhanced permeation and retention effect.
[e] Controllable.

2.2. Smart polymers

Advancement in polymer science and engineering has developed new polymers for well-controlled delivery of therapeutic drugs. One of them will be the smart polymer (stimuli-sensitive polymer), which possesses active responsiveness to environmental signals and changes the physicochemical property as designed. Physical (temperature, ultrasound, light, electricity, mechanical stress), chemical (pH, ionic strength), and biological signals (enzymes, biomolecules) have been used as triggering stimuli. The signal can be either artificially supported by 'external' sources or

naturally promoted by the 'internal' environment of a certain pathophysiological condition. The most fascinating features of the smart polymer arise from versatility and tunable sensitivity. There are numerous monomers that have sensitivity to specific stimuli. Each monomer can be tailored to a homopolymer responding to one signal as well as to copolymers answering multiple stimuli. The versatility of polymer sources and their combination methods make it possible to tune up the polymer sensitivity responding to a given stimulus within a narrow range. By taking both advantages, smart polymer systems lead to more accurate and programmable drug delivery.

2.2.1. Temperature sensitivity

Representative polymers for each stimulus are listed in Table 2. One of the famous examples is the thermo-sensitive polymer. Temperature sensitivity is originated from the balance between hydrophobic and hydrophilic segments, which can be either monomer units or polymer blocks. Inter- and intramolecular interactions between hydrophobic segments results in polymer chain aggregation of physical cross-linking. For instance, poly(*N*-isopropylacrylamide) (PNIPAAm) is clearly soluble in water at room temperature, which ranges from 25 to 32 °C. Above the lower critical solution temperature (LCST), the solution becomes opaque and finally turns into gel [5,6]. The LCST can be tuned by copolymerizing hydrophobic monomers or controlling polymer molecular weight. More hydrophobic monomers and higher molecular weight lower the LCST. In addition, incorporation of hydrophilic monomers that form hydrogen bonds with thermo-sensitive monomers increases the LCST point. Block copolymers of poly(ethylene glycol) / poly(lactic-*co*-glycolic acid) (PEG/PLGA, ReGel®) [7–9] and poly(ethylene oxide)/poly(propylene oxide) (PEO/PPO, Pluronic®) [10,11] also have thermo-sensitivity. A solution of each copolymer can be injected into a body, and in turn, forms a soft gel at body temperature. Those thermo-sensitive polymers are very attractive for protein/peptide drug delivery because no organic solvent was used during formulation [12]. However, they can also solubilize very hydrophobic drugs such as paclitaxel, and have been an excellent formulation of poorly water-soluble drugs [12,13].

2.2.2. pH-sensitivity

In a healthy human, pH of body tissue is maintained around 7.4. However, there exist several mechanisms to modulate pH inside the body. At first, the gastrointestinal tract changes the pH along the tube, which is ~1–3 in the stomach and ~7 in the intestine [14], and the lysosomes inside the cells have a much lower value than neutral pH (e.g. ~5) by continuously pumping protons into the vesicle in order to digest foreign molecules. In some cases, solid tumors with malformed capillary blood vessels show low blood pressure, local hypoxia, and accumulation of acidic metabolites, which result in local fluctuation of pH ranging 5.7–7.8 [15,16]. Each mechanism has been used as a triggering signal for pH-responsive drug delivery. Basically, ionizable moieties such as carboxylic acid, amine, azo, phenylboronic acid, imidazole, pyridine, sulfonamide, and thiol groups can afford pH-sensitivity. Acrylic acid (AA) is a representative example. The AA at pH over its pK_a value (~4.5) becomes hydrophilic due to ionization. Foss et al. reported poly(AA)-*g*-PEG nanoparticles for oral insulin delivery. At pH 6, size of the nanoparticles became more than 600 nm, which was expected to avoid uptake by intestinal Payer's patch that plays a key role in intestinal immunization and in the removal of foreign substances [17]. Cationic polymer, e.g. poly(ethyleneimine), forms an ionic complex with therapeutic genes. After cellular uptake, the complex is located in endosomes derived by fusion between lysosomes and endocytotic vesicles [18,19]. Many primary, secondary, and tertiary amino groups in the cationic polymer induce osmotic unbalance, thanks to proton buffering effect, which finally results in dissociation of therapeutic genes and endosome rupture. The pH-sensitive polymers used for anti-cancer drug delivery should have a narrow pH range for modulating their physical property. Otherwise, pH-sensitive drug carriers can induce either severe toxicity by drug burst or poor therapeutic efficacy by incomplete drug release at a target site. PEG-*b*-poly(L-histidine) (PEG-PHis), for instance, spontaneously generated micelle structure at high pH over the pK_b of histidine (6.5–7.0) and loaded anti-cancer drug, doxorubicin inside the micelle core [20]. At pH 6.8, doxorubicin-loaded PEG-PHis micelle could effectively eliminate multidrug-resistant MCF-7 cells [21], which might be expected to work in vivo

Table 2
Representative smart polymers and their applications.

Stimulus	Polymer	Application	Reference
Temperature	Poly(*N*-isopropylacrylamide)	Hydrogel	[5]
		Doxorubicin release	[6]
Ultrasound	Polyanhydride, polyglycolide, polylactide poly(hydroxyethyl methacrylate-*co*-*N*,*N*'-dimethylaminoethyl methacrylate)	Ultrasound-enhanced biodegradation	[125]
		Ultrasound-enhanced drug release rate	[126]
Magnetic field	Poly(ethylene-*co*-vinylacetate)	Prompted BSA release from matrix in magnetic field	[127]
Oxidation	PEG-*b*-poly(propylene sulfide)-*b*-PEG	Oxidation-sensitive polymer vesicle disintegration	[128]
Light	Poly(*N*,*N*-dimethylacrylamide-*co*-4-phenyl-azophenyl acrylate)	Photo-sensitive active site-gating of streptavidin	[129]
	poly(*N*,*N*-dimethyl acrylamide-*co*-4-phnyl-azophenyl acrylamide)	Photo-sensitive active site-gating of streptavidin	[129]
Electricity	Poly(ethylenediamine-*co*-1,10-bis(chloro-carbonyl)decane)	Electric-sensitive capsule	[130]
	polyethyloxazoline/poly(methacylate)	Electrically erodible matrix for insulin delivery	[131]
Mechanical stress	Dihydrazide-crosslinked polyguluronate poly(methyl methacrylate)/poly(vinyl alcohol) or /cellulose ether	Pressure-sensitive hydrogel	[132]
		Pressure-sensitive adhesive	[133]
pH	Poly(acrylic acid)-*g*-PEG	Oral insulin delivery	[17]
	PEG-*b*-poly(L-histidine)	Doxorubicin release	[21]
Ionic strength	Poly(NIPAAm-*co*-benzo-18-crown[6]-acrylamide)	Ba^{2+}-sensitive membrane pore	[134]
Enzymes	[a]PEG-peptide linker-doxorubicin	Doxorubicin release by lysosomal enzyme-mediated peptide degradation	[32]
	[a]Poly(*N*-(2-hydroxypropyl)methacrylamide)-peptide linker-doxorubicin	Doxorubicin release by lysosomal enzyme-mediated peptide degradation	[33]
Biomolecules	PEO-*b*-poly(2-glucosyloxyethyl acrylate)	Glucose-sensitive micelle for insulin delivery	[135]
	Thiolate PEG-*b*-poly(L-lysine)	Glutathione-sensitive micelle for anti-sense DNA delivery	[29]
	[b]Poly(RCOOH-*co*-butyl acrylate-*co*-pyridyl disulfide acrylate)	Glutathione- and pH-sensitive copolymers for oligodeoxynucleotide delivery	[136]

[a] Peptide linker = GFLG.
[b] R = $-CH_3$, $-CH_2CH_3$, or $-CH_2CH_2CH_3$.

condition due to the slightly different pH of breast tumor tissue compared to normal tissue.

2.2.3. Biomolecules sensitivity

Polymers responding to biomolecules have been an interesting subject because they can provide high specificity superior to polymers responding to physical or chemical stimuli. Famous example will be glucose-sensitive polymers utilizing phenyl boronic acid [22,23], glucose oxidase (GOx) [24,25], or concanavalin A (ConA) [26–28] for insulin delivery to treat diabetes. Those systems looked fascinating in that the insulin release could be tightly regulated by a closed-loop feedback system. Unfortunately, their practical application was much limited. Proteins such as GOx or ConA were hard to immobilize, which resulted in protein leakage from a polymer system followed by a host immune reaction. Also, many monosaccharides could competitively bind to the glucose binding sites. Another important molecule is glutathione which regulates cellular redox state and predominantly exists inside a cytoplasmic compartment. Due to its excellent reduction activity, disulfide bonds in a polymer can be easily cleaved by glutathione. When oligodeoxynucleotide (ODN) and small interfering ribonucleic acid (siRNA) were linked to a PEG end by a disulfide, micelles can be produced, and after endocytosis, good therapeutic efficiency could be achieved in vitro [29–31]. Recently, enzyme-sensitive polymer and polymeric systems have much highlighted because most diseases accompany impaired enzyme function. For example, polymer-drug conjugates such as PEG-doxorubicin [32] and *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymer-doxorubicin [33] linked via peptide bridges were designed to localize doxorubicin at a tumor site. The peptide linkers were supposed to be enzymatically degraded inside lysosomal compartment, which provoked a high concentration of doxorubicin at target cells. Polymeric micelles responding to protein kinase A (PKA) were also reported [34–36]. PKA substrate peptides tagged to those micelles can be phosphorylated by PKA, which increased the density of negative charge leading to dissociation of therapeutic genes from the polymer backbone. Since there are numerous enzymes that regulate homeostasis in a body, the enzyme-sensitive polymer will be a useful tool for drug delivery to specific organelles, cells, tissues, and organs.

In spite of extensive researches on the smart polymers, it is not easy to find a commercialized product based on any smart polymer. The major limitation recurs to the biocompatibility issue. In 1972, Bischoff published a review article titled "Organic polymer biocompatibility and toxicology [37]." He reported about hydrolysis and free radical- or oxidation/reduction-mediated breakdown of implanted polymers. In addition, he demonstrated blood clotting, host-rejection, carcinogenesis, and phagocytosis by reticuloendothelial system, which was induced by polymers inside living subjects. Currently, typical research protocol to develop a new polymeric drug delivery system follows synthesis or selection of monomer(s), polymer synthesis/characterization, drug-loading/release tests, cytotoxicity test, and therapeutic effect/biodistribution monitoring from animal experiments. Most of the research primarily focuses on how to design a polymer with more sensitivity responding to a given stimulus in vitro. There has been no remarkable advancement in the biocompatibility issues because researchers followed the same footsteps of previous workers. Therefore, questions about the biocompatibility of polymers and polymeric systems designed for human application are still unsolved, with the most important questions to be clarified soon.

2.3. Drug-polymer conjugates (prodrug)

Many drug-polymer conjugates have been developed since the first form was reported in 1970. As addressed before, conjugation of macromolecular polymers to drugs can significantly enhance the blood circulation time. Especially, protein or peptide drugs which are liable to be quickly metabolized inside a body can maintain their activity by conjugation of water-soluble polymer PEG (PEGylation). For example, it was reported that PEGylated L-asparaginase increased plasma half-life up to 357 h [38]. Without PEG, the half-life of natural L-asparaginase is known to be only 20 h. There already exist many PEGylated protein drugs under clinical investigation [2]. However, the major huddle is the difficulty on separating active form of PEGylated protein/peptide drugs from inactive forms, in which PEGs are often conjugated to the active site of them.

Another important function of polymer conjugation is to solubilize poorly soluble drugs. Modification of a small-molecular drug unavoidably leads to loss of bioactivity due to the structure-activity relationship. Moreover, bioactivity of poorly water-soluble drugs frequently originates from their high hydrophobicity. Nevertheless, there are many strategies to chemically modify the structure without activity failure [39]. Conjugating water-soluble polymers to functional groups that already exist in the drug structure can significantly enhance the drug solubility. By acid/base- or enzyme-mediated hydrolysis, original structure of a drug can be retrieved. Representative examples are the HPMA copolymers conjugating doxorubicin [40] and paclitaxel [41], and many other polymer-drug conjugates are examined under clinical phases [2]. However, these polymer-drug conjugates still require chemical modification of existing drugs so that they cost more and purification steps are unavoidable. Besides, polymer conjugation creates new chemical drugs, which need additional FDA approval although the used drug is already approved.

2.4. Parallel synthesis

Recently, a powerful tool for developing polymeric biomaterials was introduced. Parallel synthesis is similar to combinatorial synthesis for preparing a large number of compounds in a few simple steps and at a very fast rate. The parallel synthesis takes advantages over conventional combinatorial synthesis in that numerous polymers of sufficient amounts can be prepared separately. The significance of parallel synthesis on development and discovery of new polymeric biomaterials was reviewed by Kohn et al. [42]. Traditional "Combichem" strategy has been usually used to find small-molecular organic drugs. In this case, active drugs can be separated from randomly mixed compounds by specific affinity to target biomolecules or cells, which is primarily based on a chemical structure-activity relationship. In contrast to small molecules, synthetic polymers require multiple parameters for biomedical application, which include high purity to avoid impurity-related variables, molecular weight and its distribution, hydrophobicity, degradability, topology, and so on. Therefore, parallel synthesis in which each polymer is produced in its own reaction vessel is a very useful, and maybe the only possible method to prepare a library of synthetic polymers at high speeds [42,43].

Due to the benefit of parallel synthesis on biomedical study, a number of research papers using the parallel synthesis to discover new polymers have been reported. Brocchini et al. constructed for the first time a small-scale polyacrylate library (112 polymers) from 14 tyrosine-derived diphenols and 8 diacids to find polymers optimized for medical implants [44,45]. In a series of reports, they confirmed the potential of parallel synthesis for biomedical research. Another important field supported by the parallel synthesis is the gene delivery based on polymeric vector. Lynn et al. constructed a biodegradable poly(β-amino ester) library using 7 diacrylates and 20 amines [46]. All those polymers contained secondary amino groups to enhance the transfection efficiency promoted by 'proton sponge' effect. Cell-based high-throughput

screening (HTS) was greatly helpful to monitor the ability of prepared polymers for gene transfer. Subsequent studies revealed relationships of polymer structure to in vitro/in vivo transfection efficiency and biocompatibility [47].

Combinatorial approaches for developing small-molecular drugs [48], therapeutic oligonucleotides [49] or peptides [50] have advanced significantly in comparison with development of biomedical polymers. The major difference is the difficulty in prediction of the effects of biomaterials on living tissues or cells. Therapeutic efficiency of drugs is primarily determined by their structure. In oligonucleotides and peptides, the sequence of nucleotides or amino acids is the major determinant of their activity. Polymers for biomedical application, however, require many parameters, such as well-defined structure and composition, polymer properties (mechanical, thermodynamic, etc.), biocompatibility (toxicity, immunogenicity, biodegradability, etc.), interaction with cells/tissues, and biodistribution. In the early stage of biomedical research, polymeric biomaterials were usually supposed to be biologically inert. But, recent studies have suggested that biomaterials should have proper interactions with target cells or tissues. The concept of 'polymer genomics' is an example of the renewed understanding of interactions between biomaterials and cells [11]. Thus, it is very important to develop HTS methods to monitor those parameters from polymer libraries [42,43]. The high-throughput experiment is now a rate-determining step in the systemic approach of biomedical polymers to informatics. Also, limitations of the parallel synthesis, such as synthetic methods, catalyst systems, and controllability of reaction, should be improved for practical applications.

3. Targeting strategies

3.1. Enhanced permeability and retention (EPR)

It was found that under certain circumstances, blood vessel walls might become leaky. In tumors, blood vessels are poorly aligned defecting endothelial cells with wide fenestration and lacking smooth muscle layer. The defective vascular architecture is created by rapid vascularization because tumor cells develop so fast and demand a large supply of nutrients and oxygen. Macromolecules or leukocytes can be drained through the leaky blood vessels and be retained, which is the enhanced permeation and retention effect (EPR effect) [36,51]. The vascular permeability of tumor tissues can also be enhanced by the actions of secreted factors such as kinin and VEGF [52,53]. As a result of such increased vascular permeability, micelles, liposomes, and polymeric particles ranging from 10 to 500 nm in size can be selectively delivered to tumor tissue [54]. If these particles load anti-cancer drugs, they can also selectively deliver those drugs to the tumor tissue. PEG-modified liposomes encapsulating an anti-cancer drug (doxorubicin) provide a good example of EPR-based cancer therapy with reduced systemic toxicity, which has been used in clinical applications [55–57]. It is well known that polymeric micelles consisting of PEG-PLGA block copolymers can circulate in the bloodstream for a long period and localize to solid-tumor sites by the EPR effect [21,58,59].

Cancer therapy based on the EPR effect is, however, still being argued. Recently, some studies have revealed that drug delivery to a target tumor cannot be achieved only by the EPR effect. This is why, after accumulation, it is difficult for drugs or drug carriers to interact with tumor cells or to access the deeper place of tumor tissues [60,61]. Moreover, a large amount of drug-loading carriers should be administered to achieve a therapeutic dose because just small portions of initially given carriers are expected to be accumulated at the tumor site [62].

3.2. Targeting ligands

An active targeting strategy can improve the efficacy of the therapy and diminish side effects associated with drugs. To increase the delivery of a given drug to a specific target site, targeting ligands are conjugated to carriers, such as liposomes, micelles, and particles. These ligands include antibodies, carbohydrates, aptamers, and small molecules.

Since monoclononal antibodies (mAb) were developed in 1975 [63], many researchers have conjugated mAbs to drugs or to drug carriers. Kabanov et al. first introduced the ligand into a micelle [64]. Conjugation of brain-specific antibodies into haloperidol-containing micelles exhibited 5- to 20-folds higher neuroleptic action than non-targeting micelles and free drug did. Torchilin et al. developed diacyl lipid-PEG-conjugated polymer micelles which were conjugated with an anti-cancer mAb [65]. The anti-cancer mAb on the micelle effectively recognized and bound various cancer cells in vitro and increased the accumulation at tumors in mice in comparison to micelles without mAb. Moreover, paclitaxel-loaded micelles conjugating anti-cancer mAb showed a 4-fold higher amount of drug accumulated in the tumor than plain micelles did. Kocbek et al. reported that mAb-attached PLGA nanoparticles (immuno-nanoparticles) had the ability to recognize and target specific antigens to invasive breast tumors [66]. Whereas normal nanoparticles were taken up by both cells, the immuno-nanoparticles entered only breast tumor cells co-cultured with human colon adenocarcinoma cells, which demonstrated the ability to target specific cells.

Since carbohydrates such as galactose, lactose, and mannose were known as specific ligands to liver cell receptors, they have been used to target drug delivery for treatment of liver diseases. Kopecek and Duncan also reported hepatocellular carcinoma overexpressing asialoglycoprotein receptors (ASGPR) which bound to carbohydrate [67]. Terada et al. developed galactosylated liposomes containing PEGylated matrix metalloproteinase cleavable peptide-conjugated dioleoylphosphatidylethanolamine for hepatocellular carcinoma-selective targeting [68]. Jeong et al. synthesized poly(γ-benzyl L-glutamate)-PEG diblock copolymer conjugating galactose for application of liver-specific targeting [69]. Paclitaxel-loaded nanoparticles made from galactosylated block copolymer showed significantly higher uptake in ASGPR-expressing tumor cells. The Kataoka research group developed sugar-conjugated PEG-poly(D,L-lactic acid) (PDLLA) micelles and investigated their specific interaction with ricinus communis agglutinin lectin molecule, which is a representative cell surface receptor [70–72].

Aptamers are oligonucleotides (DNA or RNA) or peptide molecules that can bind to specific target antigen [73]. Aptamers have many favorable characteristics such as non-immunogenicity, stability in a wide range of pH 4–9 and temperature, and tumor specificity. Moreover, aptamers synthesis is an entirely chemical process without biological systems, which allows us to easily scale-up for clinical trial. Farokhzad et al. developed aptamers-conjugated biodegradable PEG-PLGA and PEG-poly(lactic acid) (PLA) micelles encapsulating docetaxel to target the prostate-specific membrane antigen (PSMA) that was expressed on surface of prostate tumor cells [73,74]. These micelles showed specific affinity to PSMA-expressed prostate LNCaP epithelial cells with 77-folds binding increment when compared to the control group. The aptamer-conjugated PEG-PLGA micelles encapsulating docetaxel resulted in significantly increased in vitro cytotoxicity over normal PEG-PLGA micelles. Injection of the aptamer-conjugated PEG-PLGA micelles encapsulating docetaxel into tumor-bearing mice exhibited low systemic toxicity as determined by mean body weight loss.

Folate has been extensively investigated for targeting various tumor cells overexpressing folate receptors, such as lung, kidney,

ovary, breast, brain, uterus, and testis. The folate in target drug delivery systems is primarily due to convenient and easy conjugation step and to the high affinity for the folate receptor after conjugation [75,76]. Yoo et al. introduced folate-conjugated PEG-PLGA or PEG-poly(ε-caprolactone) (PCL) micelles for tumor targeting [77]. Folate-conjugated PEG-PLGA micelles encapsulating doxorubicin effectively bound KB cells (human nasopharyngeal epidermal carcinoma cell line) in vitro and showed an enhanced cytotoxicity when compared to non-targeting micelles.

3.3. Smart polymeric systems

As described above, smart polymers have suggested distinctive systems to enhance the efficacy of drug delivery and the therapeutic efficiency. Passive targeting based on the EPR effect uses a unique physiological property of a disease (physiological targeting), while the conjugation of targeting moiety to drug carriers is a biochemical targeting strategy. Smart polymeric systems also provide a targeting strategy, which is activated and triggered by a specific environmental signal (triggered targeting). As shown in Fig. 2, each targeting strategy may not be separated from each other. Combined targeting methods can result in a synergy effect to maximize disease treatment. For example, a pH-sensitive micelle tagged by biotin showed excellent selectivity to target tumor cells only when the environmental pH was less than 7.2 [78]. In the micelle, biotin was embedded inside a hydrophilic PEG shell under normal physiological pH, which popped up at low pH. However, the primary goal of micellar drug carrier might be to prolong drug circulation time, which would be localized at tumor site by the EPR effect. Therefore, combination of those strategies can provide a powerful therapeutic effect in vivo condition.

4. Recent progresses in polymeric systems

4.1. Polymeric systems for drug delivery

A number of polymers have been developed for controlled and targeted delivery as described up to now. Those polymers based on synthetic or natural sources should be fabricated to a specific delivery system such as hydrogel, microcapsule, or nanoparticle, which depends on various requirements like biocompatibility, high loading capacity, extended circulation time, and ability to accumulate in required pathological sites in the body [79].

Since the first synthetic hydrogel was reported by Wichterle and Lim in 1954, hydrogels have been widely used in biomedical applications, especially as a drug carrier. Hydrogels are polymeric networks that absorb large quantities of water without dissolving in water ('swelling') [80]. In a hydrogel-based drug delivery system, swelling ratio is a very important parameter because it is determined by the mesh or pore size that has great influence on the drug transport property. The swelling ratio is known to be controlled by network structure, hydrophilicity, and cross-linking ratio. Recently, smart hydrogels such as superporous hydrogels (SPHs) were developed, which showed fast swelling rate due to much larger pore sizes than the typical mesh size of conventional hydrogels. The pore size of SPHs generated by the gas-blowing technique ranges from less than 1 μm to more than 1000 μm [81–83]. The SPHs possessing such a unique porous structure were used as a wicking agent to decrease disintegration time (fast-disintegrating tablets) [84,85]. Omidian et al. have developed a SPH by hybridization of polyacrylamide and sodium alginate, which provided superior mechanical and elastic properties in swollen state to those of conventional hydrogels [86,87].

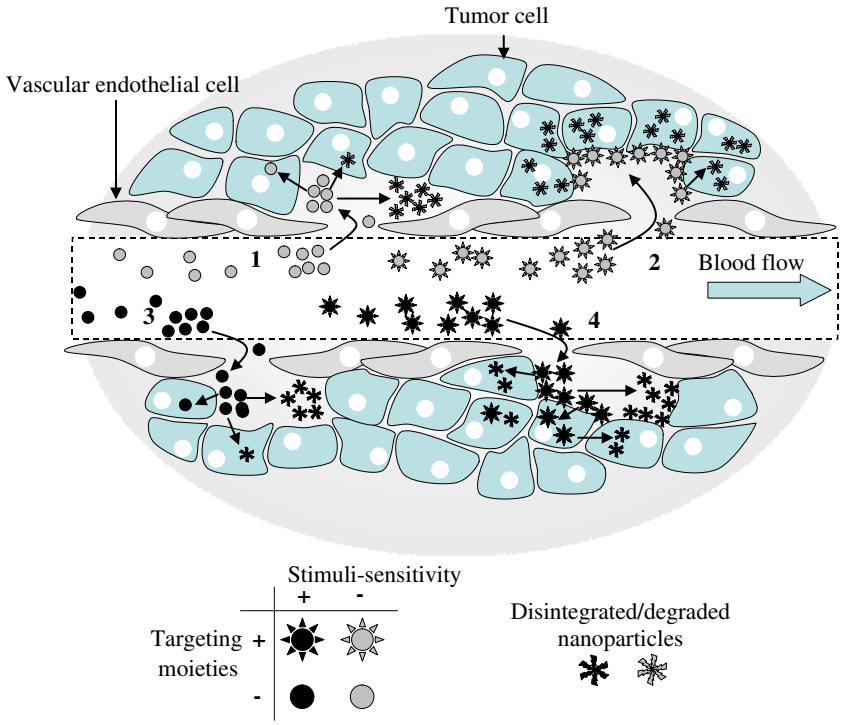

Fig. 2. Targeting strategies for cancer therapy. (1) Passive targeting can be achieved by enhanced permeation and retention (EPR) effect mediated by leaky vascular structures. Accumulation of macromolecular drugs or nanoparticles increases local drug concentration by degradation of drug carriers at the extracellular space or inside cells after endocytosis. (2) Active targeting mediated by targeting ligands specifically localizes drug carriers at desired cells or tissues. Due to the ligands, primary action mechanism is drug release inside cells after endocytosis. (3) Smart polymer systems loading therapeutic drugs also can be localized by EPR effect. Depending on disease, disintegration or degradation of drug carrier to release drugs can occur. (4) Combination of targeting ligands and smart polymer systems provides more effective release of encapsulated drugs. By environmental signals, drugs can be liberated at the extracellular space or inside target cells according to predetermined program.

Polymeric microspheres have been used especially to formulate protein drugs. Among several different preparation techniques, the water-in-oil-in-water (W/O/W) multiple emulsion is one of the most convenient methods to encapsulate water-soluble proteins, firstly reported by Ogawa et al. [88,89]. However, the major drawback of this technique is that proteins undergo physical and chemical denaturations during fabrication [90–92]. To improve protein stability and drug-loading efficiency, the solvent exchange method has recently been reported [93,94].

Many nano-sized drug delivery systems such as liposomes, polymeric micelles, nanoparticles, dendrimers, and nanocrystals have been developed. The polymer micelle system has been extensively studied to deliver various therapeutic drugs. The system consists of a hydrophilic shell and a drug-containing core, which can be spontaneously generated in an aqueous solution from amphiphilic copolymers. Major advantages of the polymer micelle are prolonged drug circulation time, drug stability, and escape from the reticuloendothelial system due to their nanometer size. The most attractive property is that the micelle can be used to solubilize and formulate extremely hydrophobic drugs. However, currently used systems have limitations of low drug-loading efficiency and amount as well as low aqueous stability. To overcome those problems, Huh et al. reported hydrotropic polymer micelles. Hydrotropic polymers were specially designed to enhance the aqueous solubility of paclitaxel, which is a highly potent anti-cancer drug, but poorly soluble in water (<0.3 μg/mL). A hydrotropic polymer micelle consisting of poly(2-(4-(vinylbenzyloxyl)-*N*,*N*-diethylnicotinamide) and PEG block copolymers showed paclitaxel loading amount of 37.4% (w/w), which was significantly higher than a conventional polymeric micelle based on PEG-PLA [95]. Moreover, the hydrotropic polymer micelles presented excellent stability in buffer up to one month. On the other hand, self-aggregated nanoparticles based on hydrophobically modified glycol chitosan also showed high stability in an aqueous environment. The nanoparticles did not change their size up to 10 days in vitro and high accumulation of tumor in tumor-bearing mice [96,97].

4.2. Polymeric systems for molecular imaging

Advancement in imaging technology has shifted conventional invasive and anatomical diagnosis to non-invasive and physiological/molecular imaging technique. High spatial resolution of imaging modalities, as well as continuously accumulated knowledge on physiological events in molecular level, has led the molecular imaging to one of the most promising technologies in the 21st century. Applying the molecular imaging technique to clinical imaging modalities, such as magnetic resonance imaging (MRI), positron emission tomography (PET), fluorescent optical imaging, and ultrasound imaging, however, has been hampered by poor sensitivity and specificity of current imaging probes. Small molecules that are directly labeled with a wide range of chemicals have been limited in use due to their lack of specificity, instability, toxicity, and rapid clearance. Recently, the combination of polymer chemistry and imaging realm has led to novel polymeric probes for clinical diagnosis. Polymeric probes for molecular imaging take all the advantages of polymer-based drug delivery systems, which can significantly increase plasma half-life and blood stability, reduce systemic toxicity, and especially improve contrasting ability by the introduction of targeting moiety [98].

On the other hand, shortcomings of conventional contrast agents can also be solved by chemically conjugating polymers to them. In general, imaging probes are liable to be aggregated or degraded in vivo, which results in poor imaging quality. Introducing hydrophilic polymers like PEG to those probes provides a good solution to avoid aggregation or degradation. Since first introduced by Saeed et al., PEG-coated iron oxide has been widely investigated for MRI application, especially MRA (MR angiography), because of prolonged circulation time and stability in blood [99]. Mohs et al. examined effect of the PEG chain length on blood pool contrast enhancement profiles in MRI contrast agents. Longer PEG chains showed more persistent contrast enhancement in the kidney, which indicated that the length of PEG might affect renal clearance of the probes [100]. PEGylated imaging probes have been widely applied to many imaging modalities such as optic or nuclear imaging instruments. For example, PEGylated quantum dot (QD) showed high solubility, high stability, and low toxicity compared to bare QD [101–103]. Not only PEG but also other polymers such as dextran, dextran derivatives, albumin, poly(vinyl alcohol) have been studied for modification of clinical and preclinical MRI imaging probes. Feridex® is one of the most commonly used dextran-coated iron oxide MRI imaging probes, which presents excellent images of hepatocellular carcinoma because it can be taken up by reticuloendothelial system (RES) of liver [104].

The other challenge in molecular imaging is to develop more specific probes, which may provide high contrast with low signal-to-noise ratio. Targeting strategies and smart polymer systems as introduced before may suggest an excellent solution because polymer probes can be highly localized at a specific site. RGD-derived peptides, biotin, annexin V, or folate have been widely used as affinity ligands for MRI, PET, and optic fluorescent imaging [85,102,105,106]. For example, ^{64}Cu-labeled PEGylated RGD peptide, ^{64}Cu-DOTA-PEG-E[c(RGDyK)]$_2$, showed excellent PET images for lung cancer because the RGD peptide could strongly bind to α_v-integrins over-expressed during angiogenesis [105]. In addition, polymer probes based on smart polymers are supposed to provoke a strong signal only when they confront expected environmental stimuli. Such systems can be categorized by 'activatable probes,' which are activated by local stimuli conducted from a specific disease or abnormal pathophysiology in a limited area. Polymeric activatable imaging probe was first coined by Weissleder et al. in 1999 [107]. They used near-infrared (NIR) fluorescent dyes to label a polymer system because the NIR of 650–900 nm could much reduce light scattering, auto-fluorescence, and absorption by tissues rather than shorter wavelength light [98]. Many polymeric activatable probes based on PEG-grafted polymers (PGCs) and NIR fluorophores have been investigated for imaging breast cancer, lung cancer, rheumatoid arthritis, atherosclerosis, and apoptosis [108–111]. Polymeric nanoparticles were also used to visualize cellular events. Based on polymer nanoparticles, Kwon's group reported activatable probes for imaging apoptosis and phosphorylation by protein kinase A (PKA) in living cells [112,113]. A polymeric nanoparticle consisting of deoxycholic acid modified poly(ethyleneimine), NIR fluorophore, and caspase-3 peptide substrate successfully visualized the apoptosis event of HeLa cells. For imaging of phosphorylation by PKA, a polymeric imaging probe was prepared, which was a polyionic complex conjugating PKA substrates. PKA activity could be monitored by increased NIR fluorescence intensity from living cells.

In the drug delivery and molecular imaging fields, 'theragnosis' is one of the emerging fusion technologies. The term, 'theragnostics,' was first used by PharmNetics president John Funkhouser, which meant a precise diagnosis to achieve successful therapy for a specific disease [114]. Since that time, the concept of theragnostics has been gradually modified. The advance in pharmacogenomics had definitive impact on establishing the concept of theragnosis. Pharmacogenomics focuses on polymorphism-derived biomarkers, which are unique depending on individuals. By combining with nanotechnology, proteomics, genomics, and cytomics, drug delivery systems and therapeutic recipes can be personalized to each patient with a specific disease. In addition, diagnosis and prognosis of disease state before and after treatment can also be specialized person by person. The final goal of theragnosis is to

develop an effective therapeutic regimen and to completely follow up the post-therapeutic progress in every single patient. Also, theragnosis aims at establishing clinically applicable bioinformatics by integration of information from diverse biomarkers as well as clinical and demographic factors [115–117]. Such renovation of the concept not only results from the advance in technologies, but demand on safer and more effective drugs, 'personalized medicine.' On March, 2005, FDA released guidelines of 'Guidance for Industry: Pharmacogenomic Data Submissions' and 'Class II Special Controls Guidance Document: Drug Metabolizing Enzyme Genotyping System,' which described an outline of the personalized medicine. In contrast to the uncertainty and risk of the 'one-size (dose)-fits-all' medicine, the final goal of personalized medicine is "the right dose of the right drug for the right indication for the right patient at the right time." Therefore, theragnosis and related personalized medicine will possess a great part of the drug delivery in future.

4.3. Polymeric device for drug delivery

Micro- and nanofabrication have revolutionized the biology and medicine realm, especially drug delivery, with numerous enabling technologies. The biomedical microelectromechanical system (BioMEMS) has been widely used to prepare polymeric micro/nanoparticle, microneedles, microfluidics, and implantable devices for controlled drug delivery. Micromachining technique is generally produced by a photolithography process adapted from standard semiconductor processing technology – applying a photosensitive coating to the substrate surface, exposing the coated substrate to light through a mask containing an image of the pattern to be transferred, immersing the substrate in a developer solution, selectively depositing or etching material in the pattern areas, and preparing the master. Polymeric devices in BioMEMS can be fabricated by casting or soft lithography processes, in which the negative and/or positive image of desired structures is produced using micromachining technique. Many polymeric micro/nanoparticles fabricated using various soft lithography techniques such as microcontract printing, microtransfer molding, microfluid contact printing, and particle replication in nonwetting templates (PRINT) have been reported [118,119]. Those methods provided more effective preparation process on controlling the size and shape with lower cost, milder fabricating condition, and more versatility in materials than conventional methods.

Administration of polymeric particles typically requires hypodermic needle injection which induces patients' pain. To solve this problem, polymeric microneedles have been investigated. Depending on the injected drugs, solid or hollow microneedles can be prepared by microfabrication technology. Solid microneedles are able to deliver insulin, growth hormone, plasmid DNA, or vaccines, because they can be pierced into the skin to increase permeability as well as to provide a substrate on which the drug can be coated or encapsulated for rapid release [120,121]. Hollow microneedles are investigated for infusion of drug solution [122]. On the other hand, micropumps have been commonly used to deliver drugs at a determined rate. In those systems, microvalves have critical function control flow rate and microsensors are mainly used for monitoring change of physiological conditions such as pH, temperature, pressure, and flow rate of body fluids [123,124]. They have been individually developed before 'pharmacy-on-a-chip' emerges as a breakthrough in controlled drug delivery system. The pharmacy-on-a-chip that has its origin from 'lab-on-a-chip' can be swallowed or implanted, and programmable to deliver precise amounts of drugs at specific time period. The pharmacy-on-a-chip consists of biosensors (to detect physiological levels of metabolites), a battery (to obtain signals from biosensors, to emit electrical charge as well as to send electric power to pump and valves), a pump, and a valve (to release drug or to quit releasing).

5. Summary

Controlled drug delivery systems have been developed and progressed in parallel with the advancement of polymer science and engineering. Sustained and pulsatile release systems as well as polymer-drug conjugates were initially designed to overcome and improve drawbacks of conventional drug delivery systems, which made it possible to control spatiotemporal release of multiple drugs. The parallel synthesis provides a powerful tool for finding new polymers optimized to a specific biomedical application. Various targeting strategies and smart polymer systems promise programmability and on-site release of therapeutic drugs. Currently, controlled drug delivery systems integrate multiple components in a carrier and seek multiple purposes at a time. Moreover, interdisciplinary researches provide more integrated and more complicated polymer systems not only to obtain maximal therapeutic efficacy but also to achieve multi-functionality of a single drug carrier. It is difficult, however, to find clinically applicable products among numerous drug delivery systems. Because drug delivery systems are supposed to be administrated into a body, the safety issue should be always considered on developing a new system. As expected, many drug delivery carriers have faced significant problems in approval processes and clinical trials. Therefore, effort to make a safe and massively producible drug delivery system should be accompanied with study to develop a new and more efficient drug delivery system.

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