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Polymeric drugs: Advances in the development of pharmacologically active polymers

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Abstract

Synthetic polymers play a critical role in pharmaceutical discovery and development. Current research and applications of pharmaceutical polymers are mainly focused on their functions as excipients and inert carriers of other pharmacologically active agents. This review article surveys recent advances in alternative pharmaceutical use of polymers as pharmacologically active agents known as polymeric drugs. Emphasis is placed on the benefits of polymeric drugs that are associated with their macromolecular character and their ability to explore biologically relevant multivalency processes. We discuss the main therapeutic uses of polymeric drugs as sequestrants, antimicrobials, antivirals, and anticancer and anti-inflammatory agents.

Keywords

Polymeric drugs; Drug delivery; Polymer therapeutics; Dendrimers; Multivalency; Polymeric sequestrants; Antimicrobials; Antivirals; Gene delivery; SiRNA delivery; Cancer; Tumor delivery

1. Introduction

Synthetic and natural polymers play a vital part in pharmaceutical research and development. Pharmaceutical applications of polymers range from inert bulk excipients to sophisticated drug delivery technologies. Currently, polymers are overwhelmingly used in applications in which they are expected to be pharmacologically inactive and simply to aid in the delivery of existing small molecule or macromolecule drugs. Undoubtedly, polymers provide a range of benefits in drug delivery applications that result in improved drug delivery, including controlled release of drugs, adjustable pharmacokinetic and biodistribution profile, and improved drug safety (Scheme 1).

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In contrast to pharmacologically inert polymers used in most drug delivery applications, polymeric drugs are polymers that exhibit pharmacological activity that can be harnessed for therapeutic benefits [2]. Polymeric drugs have a long history, going back to the 1960s when the first example of a polymeric drug entered clinical trials. Successful examples of polymeric drugs followed both rational discovery processes as in the case of polymeric sequestrants and antimicrobial agents or were the result of serendipitous discoveries as in the case of several excipients and materials previously assumed inert [3].

Despite their current niche status, polymeric drugs can bring multiple potential benefits to drug discovery not readily available with traditional small molecule drugs. Most biological targets explored for therapeutic interventions are macromolecular in nature. Binding to such targets and activation or inhibition of related signaling pathways is often determined by complex set of multivalent interactions. Unlike traditional small molecule drugs, polymers are macromolecules that fall into the size range of proteins and their repeating unit nature allows for easy incorporation of multivalent features on size scales not accessible to small molecules.

This review provides a perspective on the current state-of-the-art of the field of polymeric drugs. We focus on the design principles of synthetic polymers as applied to the current main disease areas of applications.

2. Multivalency as key feature of polymeric drugs

Biological multivalent interactions are defined as simultaneous binding between multiple ligands on one molecular or biological entity (e.g. proteins, polymer, cell, virus) and multiple corresponding receptors on another. Multivalent interactions are characteristic features of many biological processes, including attachment of viruses and bacteria to the surface of a host cell, interactions between antigens and macrophages, cell–cell interactions, and binding between transcription factors and DNA [4,5]. These interactions are reversible and occur in both activation and inhibition biological processes. In contrast to weak monovalent receptor-ligand binding, multivalent interactions generally amplify signaling transduction followed by significantly pronounced downstream activity. Such augmentation is due to enhanced affinity, cooperativity, and favorable entropy [1,4,6].

Outside of exploiting multivalency in simple applications such as polymeric sequestrants, polymeric drugs that contain multiple ligands to mimic the multivalent ligands in nature offer significant therapeutic potential (Scheme 2). Targeting multivalent receptors using small molecule drugs often requires high doses or frequent dosing regimens. More importantly, many multivalent receptors are simply not accessible for monovalent small molecule drugs. In situations where receptors require chelation mode or clustering actions for binding, small molecule (i.e., monomeric) drugs generally exhibit only marginal activity [7]. Some receptors have more than one binding pocket where monovalent drugs can only access the primary binding sites [8]. Polymeric drugs presenting multiple ligands however, can easily act simultaneously on multiple receptors or different binding subsites of one receptor. Even when the receptors are physically not close enough to be bridged by a synthetic macromolecule, a polymeric drug can still offer benefits via the mechanism of

statistical rebinding. As soon as one ligand dissociates from the receptor, the adjacent ligands on the same polymer chain can bind the receptor. This process is more energy efficient than recruiting another small molecule, resulting in longer residence time of the polymeric drugs. In addition, polymeric drugs can also create steric stabilization effect in which the bulky nature of the polymers can prevent the interactions with detrimental biological entities (e.g. viruses) [9,10]. All these unique advantages of multivalent polymeric drugs may lead to faster, longer and superior pharmacological effect compared with small molecule drugs.

In order to take advantage of multivalency in designing polymeric drugs, one has to take into account a number of key factors, including i) the binding affinity, strength and length of a single ligand to the target receptor; ii) the number, spatial distance and three-dimensional arrangement of multiple ligands in one polymeric system; iii) the presentation and accessibility of the ligands; and iv) the potential changes to the polymer after multivalent interactions between the ligands and the target receptors [4,6]. Most of these considerations can be addressed by selecting proper molecular weights, structure and architecture of the polymers, and by appropriate selection of linkers and spacers to achieve maximum therapeutic outcomes [11]. The most widely used polymer scaffolds include linear polymers, dendrimers, dendronized polymers, polypeptides, and nanogels [12]. Among all the polymeric scaffolds, linear polymers with multiple pendent ligands were the first applied as multivalent polymeric drugs due to their flexibility and ease of controlling the ligand density and polymer chain length. Chemical structures of selected examples of polymeric drugs discussed in this review are summarized in Scheme 3.

3. Polymeric drugs in cancer treatment

Remarkably, the first anticancer polymeric drug, a copolymer of divinyl ether and maleic anhydride (DIVEMA) (Scheme 3D), entered clinical trials in the early 1960s [13]. Although it failed due to its severe systemic toxicity, DIVEMA marked the start of a new chapter as the earliest polymeric drug discovered for its anticancer activity [14]. Yet, despite the early efforts and even with clinical advances in related fields of polymer–drug conjugates and polymer–protein conjugates, there are currently no anticancer polymeric drugs used in the clinical practice.

3.1. Polymeric drugs with anticancer activity

The early development of DIVEMA has inspired testing of anticancer activity of variety of synthetic polymers, including poly(maleic anhydride), poly(acrylic acid–maleic anhydride) copolymers [15], poly(acrylic acid), poly(vinyl sulfate), and poly(amido amine)s [16,17]. Many of these polymers exhibited significant antitumor activity and prolonged survival in animal models either by direct toxicity to tumor cells or indirectly by activation of the immune system. Although some of these polymers entered (and failed) clinical trials, most of them remained in preclinical stages of development due to concerns about their toxicity, low efficacy, and ambiguous mechanism of action.

Discovery of cancer-specific biomarkers and their ligands promoted improved, multivalency-based design of anticancer polymeric drugs with enhanced therapeutic effect.

For example, the Kopeček lab developed a series of polymeric drugs that induce apoptosis by cross-linking antigens on the cell surface [18–21]. CD20 is a known biomarker on Raji B cells of non-Hodgkin lymphoma (NHL) and clustering of this non-internalizing receptor initiates apoptosis. A pair of oppositely charged pentaheptad peptides (CCE and CCK) that form antiparallel coiled-coil heterodimers was applied as a specific bio-recognition cross-linker [18]. CD20+ B cells were first bound with Fab' fragment of CD20 antibody with a CCE peptide tail (Fab'-CCE), followed by further exposure to multivalent CCK-grafted N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer (CCK-P). The self-assembly of CCE-CCK hybrid coiled-coil heterodimer triggered the cross-linking and clustering of the receptors (Scheme 2), resulting in cell death. Intravenous administration of Fab'-CCE followed by CCK-P enhanced the survival in SCID mice bearing human B cell NHL xenografts [19]. The approach was further explored by using hybridization of complementary morpholino oligonucleotides (MORF) to mediate the biorecognition [20]. The two components in the system, Fab'-oligoMORF1 conjugate and multivalent oligoMORF2-grafted HPMA copolymer, either administered consecutively or simultaneously, greatly reduced tumor burden in various organs and significantly prolonged survival in a systemic B cell NHL mouse model.

Other polymeric drugs that utilize ligand multivalency have been reported. Lamanna et al. have conjugated an apoptotic peptide that mimics the natural tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) by using adamantane-based dendrons as multivalent scaffolds [22]. The dendronized peptides exhibited markedly enhanced binding affinity to human TRAIL receptor 2 (TR2) when compared with the peptide alone. The binding affinity was highly correlated with the dendron generation and the number of the peptide ligands, as the trimer exhibited 1500-fold higher affinity than the monomer. The multivalent design was essential for triggering selective apoptosis in TR2+ BJAB lymphoma cells, as the monomer caused only marginal cell death. Maynard et al. have developed a linear norbornene copolymers substituted with two different oligopeptides that synergistically inhibited cell adhesion via limiting integrin-extracellular matrix protein interactions, showing promise for cancer treatment [23]. Development of polymeric drugs that inhibit chemokine receptor CXCR4 has been reported by several labs recently and promoted for their antimetastatic properties. The Kopeček lab reported multivalent HPMA copolymer with a CXCR4 inhibiting peptide BKT140 and showed considerably higher inhibitory activity than the free peptide [24]. The Oupický lab reported multivalent polymeric CXCR4 inhibitors based on cyclam-containing poly(amido amine)s with promising activity in experimental model of pulmonary metastasis in mice [25].

3.2. Polymeric drugs as carriers for combination cancer treatment

Cancer involves dynamic changes in the genome and a complex network of interactions among cancer cells and multiple cell types that form tumors. As a result, combination treatments have been proven highly effective due to their ability to affect multiple pathways involved in cancer [26]. The use of polymeric drugs both for their pharmacologic activity and for their ability to deliver existing drugs emerged as a viable strategy to combination cancer treatment. The most developed and understood dual use of polymeric drugs in combination cancer treatment is based on the work of the Kabanov lab on Pluronic block

direct copolymerization of an FDA-approved bicyclam CXCR4 antagonist Plerixafor (AMD3100) and a bisacrylamide linker. The more recent second generation PCX used a Boc-protected monocyclam CXCR4 antagonist to replace Plerixafor to create a linear polycation with multiple pendent CXCR4 ligands in the side chain (Scheme 3C). As a polymeric drug, PCX showed greatly enhanced CXCR4 inhibiting potency compared with the parent monomer drug, due to better presentation of the drug and the multivalent interactions (most likely due to statistical rebinding as illustrated in Scheme 2). PCX displayed anti-metastatic activity in an experimental metastatic mouse melanoma model [25] and was the first reported polymeric drug with the potential to mobilize hematopoietic stem cells in vivo [45]. In addition, both generations of PCX could form nanosized polyplexes with therapeutic nucleic acids via electrostatic interactions to mediate transfection and deliver gene therapy simultaneously. These dual-function delivery vectors represent great promise to enhance antimetastatic efficacy of a variety of cancer gene therapy methods.

4. Polymeric sequestrants

A variety of potentially harmful molecules either from the environment or diet, or generated endogenously can accumulate in the human body and cause diseases [49]. Effective and safe elimination of these species using polymers as functional sequestrants represents effective and clinically proven therapeutic strategy. Due to their macromolecular multivalent nature, such polymeric drugs demonstrate outstanding capacity and efficiency in removal of multiple target molecules. The polymers can exhibit high binding selectivity adjustable by changing their size, structure, and presence and distribution of functional groups. When given orally, these polymeric drugs are typically not absorbed in the gastrointestinal (GI) tract, resulting in no or minimal toxicity [49–52]. In this section, we will summarize recent advances of polymeric drugs that act as molecular sequestrants. The chemistry of these polymeric sequestrants is highly dependent on the structure of the substrate, the charge balance and complexity of the target molecule. The main types of current polymeric sequestrants are summarized in Scheme 5.

4.1. Polymeric sequestrants of inorganic ions

Excessive exposure to and accumulation of ions such as potassium, phosphate, iron and cadmium in human bodies could lead to lethal conditions such as electrolytic disorders and heavy metal intoxication. These ion-overload conditions are particularly severe in patients with kidney dysfunction, with failure to regulate ion absorption and elimination. The sequestration of these ions by polymeric drugs can be achieved via a number of different mechanisms including coordination interactions, ion-ion interactions, hydrogen bonding, and ion-aromatic interactions [53,54]. Incorporating more than one mechanism of interactions is often applied to improve binding specificity.

One of the earliest examples of polymeric sequestrants is Kayexalate®, which was approved by the FDA in 1958. It is a cation-exchange resin of sodium polystyrene sulfonate (Scheme 3E) to treat hyperkalemia (high levels of potassium in the blood that cause abnormal heart rhythm). The cross-linked polymer resin containing sodium is given orally or rectally, and used to exchange for excessive potassium in the GI tract. The formed insoluble potassium

polystyrene sulfonate complexes are removed by fecal excretion, preventing potassium re-absorption into the blood and lowering serum potassium levels [55].

Hyperphosphatemia represents another severe electrolytic disorder with excessive serum phosphate levels in patients, especially those with kidney failure and undergoing dialysis. It is challenging to maintain a fine balance between dietary restriction of phosphorus and adequate daily protein uptake [56–58]. The administration of phosphate binders provides a more efficient and patient-friendly alternative treatment strategy to achieve optimal phosphate equilibrium. Several phosphate binders based on cationic metals such as lanthanum, aluminum, magnesium and calcium showed clinical efficacy, however many of them induced neurologic toxicity or metal ion overload [58,59]. The development of amine-based polycations represents a safer approach to reduce dietary phosphates in the GI tract. Sevelamer hydrochloride (Renagel®) was the first polycationic drug approved by the FDA (1998) to treat hyperphosphatemia by oral administration. It is composed of a copolymer of allylamine crosslinked with epichlorohydrin (Scheme 3F). The multiple amine groups in the polycation become partially protonated in the intestines and sequester abundant phosphate anions via ion-ion interactions and hydrogen bonding [60,61]. A number of similar amine-based polymeric sequestrants became available on the market as oral formulations, including sevelamer carbonate (Renvela®), colestilan (BindRen®) and bixalomer (Kiklin®) [62,63]. Despite their wide clinical applications, these polycationic sequestrants interact with a broad range of anionic substrates in the GI tract such as bile acids and various vitamins, which may lead to vitamin deficiency and other side effects. To enhance binding specificity, several polymeric sequestrants are under development. Inoue et al. have synthesized a cross-linked poly(allylamine) named TRK-390 that showed superior binding selectivity for phosphate, with low binding to fatty acids and bile acids [64,65]. Vidasym Inc. has developed a novel polymeric phosphate binder VS-501 that overcomes safety concerns and effectively decreases phosphate without disrupting calcium homeostasis [66]. In addition, chitosan loaded in chewing gum has emerged as a novel salivary phosphorous binder as an alternative and currently under clinical development [67].

Iron overload, also known as hemochromatosis, gives rise to a number of pathological conditions including liver cirrhosis, diabetes, cardiomyopathy and arthritis. Patients have been traditionally treated with frequent or continuous intravenous or subcutaneous dosing of deferoxamine (DFO), a small molecule iron chelator. Low patient compliance prompted development of multiple alternative approaches by conjugating small molecule iron-chelators to polymers to either improve pharmacokinetics and safety profiles or enhance coordination interactions. Several research groups have attempted to attach DFO to various biocompatible polymers, including dextran, hydroxyethyl-starch [68], PEG [69] and hyperbranched polyglycerol [70] to prolong the blood circulation time. Zhou et al. have developed a series of brushed or dendritic polymeric iron sequestrants terminated with hexadentate ligands formed from hydroxypyridinone, hydroxypyranone, and catechol and showed high selectivity for iron(III) [71,72]. Later studies revealed that polymeric sequestrants based on the hydroxypyridinone hexadentate (CP254) provide the optimum coordination interactions with iron (III) to form highly stable complexes [72,73]. Similar approaches using polymers modified with various iron-chelating motifs were reported and shown in vivo iron-binding capability in rats when given orally [74,75]. This strategy has

also been extended to other metals such as aluminum, cadmium, and lead [54,76–78]. Haratake et al. have recently reported the synthesis of a hydrophilic porous polymer with phosphonic acid groups and evaluated its capability to sequester radioactive strontium-90 as post-exposure first-aid treatment in rats *via* oral administration [79]. In spite of all the advances mentioned above, the market is still awaiting the first polymeric drug product for heavy metal ion detoxification.

4.2. Polymeric sequestrants of bile acids

Cardiovascular diseases are the leading cause of death around the globe. High cholesterol levels in the blood, especially high level of low-density lipoprotein (LDL) cholesterol, is associated with elevated risk of cardiovascular disease. Bile acids are effective targets for lowering the cholesterol since cholesterol is transformed into bile acids in the liver and clearance of bile acids promotes biosynthesis of more bile acids from circulating cholesterol to maintain normal levels [50, 80,81]. In contrast to ion sequestration where the binding mostly relies on electrostatic interactions and coordination bonding, organic small molecule substrates exhibit more structural complexity, making it possible to achieve higher binding affinity and specificity [52,54]. Cholestyramine (Questran®) was the first approved orally given bile-acid sequesterant based on anion exchange resin composed of ammonium-modified styrene-divinylbenzene copolymer. A number of polycationic bile acid sequestrants have become available since then, including colestipol (Colestid®), colestilan (BindRen®) (also approved as phosphate sequesterant), and colextran based on cationized dextran [82,83]. Although these polymeric drugs exhibited satisfactory therapeutic outcomes, the clinical efficacy is relatively low due to their weak competition against active bile acid transporter system in the GI tract [50]. This has inspired the development of colesevelam hydrochloride (Welchol®), which has become the most successful polymeric sequesterant of bile acids. Colesevelam is based on hydrophobically and cationically modified crosslinked poly(allylamine) (Scheme 3G). The presence of the hydrophobic decyl groups provides secondary binding force and considerably enhances the potency. Colestimide (Cholebine®) is another successful example of such design. Today, continuing efforts are dedicated to advancing the binding capacity and affinity, as well as the safety of the polymeric bile acid sequestrants. When designing bile acid sequestrants, a few considerations need to be taken into account: i) presence of cationic groups at a proper density to ensure the electrostatic interactions with the anionic bile acids; ii) presence of hydrophobic moieties to attract the steroid skeleton of bile acids.

4.3. Polymeric sequestrants of nucleic acids

Circulating nucleic acids could potentially cause a number of pathological conditions such as inflammation. The adverse effects can be caused by nucleic acids produced as a result of endogenous processes like cell metabolism, cell death or as a result of exogenously introduced nucleic acids. Most current approaches to nucleic acid sequestration take advantage of abundant positive charges on polycations to bind and remove the negatively charged nucleic acids. The first study that explored the potential of polycations as nucleic acid sequestrants was in removal of therapeutic RNA aptamers used as anticoagulants during surgery [84]. An efficient antidote was required to counteract the aptamer activity after surgery. Complementary oligonucleotides that form stable double-stranded complexes

showed promise but there were concerns about the manufacturing costs and presence of circulating RNA complexes [85,86]. An alternative strategy was to use polycations as polymeric sequestrants to capture the circulating aptamers. A library of polycations that have been traditionally used for gene delivery was screened for aptamer binding affinity. Several candidates including G3 PAMAM dendrimer and cyclodextrin-containing polycations showed high efficacy to reverse the aptamer anticoagulant activity both *in vitro* and *in vivo* via intravenous injection in a pig model [87]. These initial studies also showed that some polycations can be used as anti-inflammatory agents that inhibit activation of multiple nucleic acid-sensing toll-like receptors (TLRs) triggered by extracellular nucleic acid release by dead or dying cells. Systemic administration of the TLR-inhibiting polymers prevented fatal liver injury triggered by proinflammatory nucleic acids in mice [88]. Other irregular immune pathogenesis could also be overcome by the polycations, including systemic lupus erythematosus caused by binding of extracellular DNA and anti-DNA antibodies [89,90]. A recent report showed that topical administration of G3 PAMAM dendrimers could efficiently sequester nucleic acids that cause increase in fibroblast activation and granulation tissue contraction, resulting in decreased pathological scarring during wound healing [91]. In addition, the application of polycations as antithrombotic agents that rapidly remove prothrombotic nucleic acids together with other polyphosphates was also demonstrated *in vivo* and proposed as a novel strategy to prevent thrombosis after injury [92].

4.4. Polymeric sequestrants of peptides and proteins

Polymeric sequestrants have been designed to incorporate multiple recognition moieties and binding pockets for capturing circulating large complex molecules like proteins via a number of non-covalent interactions. These interactions often lead to high avidity and specificity. Due to the charge heterogeneity of proteins, the selection as well as the density and presentation of the binding moieties on the polymer are often critical for the potency of polymeric drugs. Here, we summarize the recent investigations of polymeric drugs that function as protein sequestrants.

The development of polymeric sequestrants for proteins has been mainly focused on targeting various toxins, many of which are based on multivalent design of glycopolymers, glycodendrimers and glycoclusters [93]. The Bundle lab developed a highly potent macromolecular carbohydrate ligand (named starfish) that binds with Shiga toxin produced by *Escherichia coli* [7,94]. The multivalent interactions between the ligand and toxin significantly amplify the inhibitory activity. The ligand was later utilized as part of polymeric drugs to further boost its pharmacologic activity and to improve pharmacokinetics after i.v. injection [95,96]. Following similar approach, several labs have prepared a variety of polymers with an inhibitory peptide of anthrax toxin as polymeric sequestrants and showed substantial increase in the efficiency when compared with the single ligand [97–100]. Recently, Hoshino et al. designed a series of polymeric sequestrants bearing various compositions of hydrophobic, anionic and cationic functional groups and studied their structure-activity relationship both *in vitro* and *in vivo* following i.v. administration for binding melittin, a toxic peptide from bee venom toxin [101,102]. This study confirmed that optimization of polymer is vital for the efficiency as well as the bio-compatibility. The

balance of negative and positive charges presented on the polymer was especially important for the polymer selectivity to bind the target peptide without associating with plasma proteins and cell membranes. A number of polymeric sequestrants for *Clostridium difficile* toxin have also been developed based on simultaneous multivalent interactions with multiple binding pockets displayed on the toxin molecule [103,104]. Among these, Synsorb 90 and tolevamer have been clinically tested for preventing diarrhea associated with *Clostridium difficile* infection in the GI tract. However, neither Synsorb 90 nor tolevamer succeeded in recent Phase III clinical trials. The development of tolevamer was halted due to significant drop out of patients in the treated group and the failure of Synsorb 90 was due to insufficient efficacy compared with standard antibiotic treatment [52,105,106].

α -Gliadin is a component of gluten that has been identified as the major cause of celiac disease (CD), a chronic systemic inflammatory disorder in which the body becomes intolerant to gluten [107]. No effective pharmacological therapies are currently available for CD patients [108]. Pinier et al. synthesized copolymers of 2-(hydroxyethyl) methacrylate and styrene sulfonate and used them as α -gliadin binder to reduce inflammation via oral administration in a gluten-sensitized mouse model and *ex vivo* using tissues from CD patients [109]. Follow-up studies further systematically investigated the mechanism of interactions by analyzing copolymers with different compositions [110–112]. BL-7010 is a polymeric drug candidate based on these copolymers that is currently in Phase I/II clinical development by BioLineRx Ltd.

5. Polymeric drugs with antiviral activity

Viruses utilize concerted action of multiple surface epitopes to dock to the host cells and to facilitate cellular entry, replication of their own genetic material, and assembly of new virus particles to complete a typical viral replication cycle. Unlike small-molecule antivirals that can intervene at different stages of the viral replication (e.g. entry inhibitors, fusion inhibitors, reverse transcriptase inhibitors, integrase inhibitors) [113], antiviral polymeric drugs have been developed mainly based on interfering with the virus interactions with the host cell. Due to the high molecular weight and multivalent binding, polymers exert their antiviral activity by steric shielding of the viral surface or competitive inhibition of the interactions [52,54]. The latter could be achieved *via* receptors essential for viral docking and entry, either through polymer binding to the virus or the host cell, both of which leads to decreased viral entry (Scheme 6).

5.1. Polymeric drugs against influenza

The Whitesides lab reported linear polyacrylamides with pendent sialic acid (SA) groups that strongly inhibited agglutination of erythrocytes by influenza virus caused by the multivalent interactions between SA and its receptor hemagglutinin (HA) [10]. The polymeric inhibitors with various molecular weights exhibited a thousand- to a million-fold higher binding affinity with the viral surface than the monomer. A follow-up study using a library of acrylic acid copolymers with SA side chains attached *via* different linkers showed that hydrophobic linkers greatly enhanced the multivalent binding and the antiviral activity [114]. Promising *in vivo* antiviral activity against H1N1 was reported subsequently [115]. Similarly, dendrimer nanogels with sizes similar to influenza virus were decorated with SA

to successfully inhibit interactions with the virus [116]. Honda et al. grafted 4-guanidino-Neu5Ac2en analogs on poly-L-glutamic acid backbone to engineer multivalent polymeric inhibitors that target sialidase, another important surface glycoprotein on influenza virus essential for infective activity [117].

5.2. Polymeric drugs against HIV

Multiple approaches have been investigated in order to develop polymeric drugs to treat or prevent infections caused by the human immunodeficiency virus (HIV). The best known product is SPL7013 (VivaGel®), a poly(lysine) dendrimer with broad antiviral activity against multiple HIV strains. SPL7013 is a G4 dendrimer with molecular weight 16 kDa that is substituted with 32 anionic naphthalene-3,6-disulfonate groups to block viral entry by interactions with positively-charged glycoprotein gp120 in the viral envelope [118–120]. Although the dendrimers exhibited promising anti-viral activity after vaginal administration in Phase I and II clinical trials [121–123], they ultimately failed to achieve their primary end point in Phase III. Currently, VivaGel® is still under clinical development for preventing recurrence of bacterial vaginosis. Meanwhile, condoms containing VivaGel® are already available on the market in selected countries, including Australia and Japan. Other types and generations of dendrimers presenting a number of different anionic ligands have been explored in HIV prevention and treatment [124–127]. In addition to interfering with the viral entry, some of the dendrimers were even shown to target later stages (reverse transcriptase/integrase) of the replication cycle [127]. In addition to dendrimers, negatively charged linear polymers have been also tested as blockers of HIV entry. Sulfonated polymers such as poly(vinyl sulfonate), poly(acrylamido-2-methyl-1-propanesulfonic acid), poly(anetholesulfonate), sulfated poly(vinyl alcohol), and sulfated poly(vinyl alcohol-co-acrylate) all produced effective anti-HIV activity by targeting gp120 (reviewed in [113]). Poly(naphthalene sulfate) (PRO2000) was shown to inhibit HIV-1 entry via binding with soluble CD4 [128]. HIV inhibition could also be achieved using polymers that contained carboxylate moieties such as copolymers of styrene and maleic acid [129]. Several of these polymers have entered clinical trials, but none of them succeeded clinically, mainly due to unsatisfactory efficacy [130].

In addition to anionic dendrimers, cationic dendrimers have also been successfully applied as antiviral agents. In particular, cationic dendrimers based on N-alkylated 4,4'-bipyridinium units (known as viologens) showed potent anti-HIV properties [131,132]. Structure-activity relationship study discovered that spherical dendrimers were more effective than comb-branched ones, and the selective HIV inhibitory activity was attributed to the interactions with positively charged residues of CXCR4, one of the two co-receptors for HIV-1 entry into CD4+ cells. A follow-up study further explored the ability of the viologen dendrimers for dual functionality as gene delivery vectors and CXCR4 antagonists *in vitro* [133].

6. Polymeric drugs with antimicrobial activity

Resistance to multiple types of antimicrobial agents has emerged as a critical global healthcare problem [134]. New therapeutic strategies are urgently needed to overcome the challenges of treating infections caused by rapidly growing multi-drug resistant bacterial strains and polymeric drugs have been explored to target these pathogens. Most polymeric

antimicrobials are designed to bind to the bacterial surface, either causing direct damage to the membrane, blocking interactions with host cells, or decorating the surface with biorecognizable moieties to opsonize the pathogen for phagocytosis (Scheme 7) [52].

Ever since the discovery of innate antimicrobial peptides (AMPs), considerable efforts have been made in the development of polymeric mimics of AMPs [135]. These peptides assume α -helix folding arrangement and their antimicrobial activity is attributed to the segregation of cationic and hydrophobic moieties on the opposing sides of the helix. The segregation is critical for efficient insertion and disruption of bacterial membranes [135,136]. Synthetic polymers have been designed to mimic the naturally occurring AMPs using copolymerization of cationic and hydrophobic monomers to prepare amphiphilic random copolymers [137,138] (Scheme 3H). Alternatively, such polymers could be synthesized by using monomers carrying one cationic and one hydrophobic moiety in the same molecule [137,139] (Scheme 3I). Unlike natural AMPs, the selectivity of synthetic polymeric mimics towards pathogens over human cells remains a major challenge [140]. A series of poly(methylacrylate)s with various molecular weights and amphiphilicity was synthesized and it was found that polymers with higher lipophilicity and lower molecular weight showed better selectivity for bacterial membranes. The structure-activity study shed light on how cationic groups assist in the initial association and how hydrophobic groups form strong interactions with the lipids in the bacterial membrane [141, 142] (Scheme 3L). Additional examples of poly(methylacrylate)s [143–148], poly(norbornene)s [137,149,150], poly(β -amino acid)s [138, 151–158] (Scheme 3J) and poly(hexamethylene biguanide)s [159] with balanced charges and amphiphilicity confirmed potential of this approach to polymeric AMP mimics that selectively target certain bacteria, including multi-drug resistant strains. Some of the best performing polymers were able to achieve comparable therapeutic activity as conventional antimicrobial agents without significant toxicity concerns *in vivo*.

Known for their membrane-disrupting activity, cationic polymers also received significant attention as antimicrobial agents. In particular, cationic dendrimers exhibited the most promising activity, as their spherical shape together with the multiple positive charges displayed on the dendrimer surface facilitates strong interactions with peptidoglycans on the bacterial surface, leading to membrane damage [160,161]. Few cases of molecular weight- and architecture-dependent selective antimicrobial activity were reported even with a branched PEI [162,163]. Thoma et al. recently documented antimicrobial activity of a simple linear poly(aminoethyl methacrylate) both *in vitro* and *in vivo* against *Staphylococcus aureus* [164] (Scheme 3K).

In addition to cationic moieties, a number of other biorecognition motifs were applied to the design of antimicrobial polymers to improve interactions with available targets on the bacterial surfaces [161,165]. For example, dendrimers were modified with specific sugars to mimic surface of host cells to bind with lectins found in the bacterial membrane, thus serving as anti-adhesive agents [161,166]. Dendrimers with hydroxyl end groups could bind to *O* antigens on the bacterial membrane, while dendrimers with carboxylic acid groups acted as polyanions that could chelate divalent ions (e.g. Ca^{2+}) in outer membrane of *E. coli* [167].

Another interesting approach to antimicrobial polymers is to use heterofunctional polymers to decorate the surface of bacteria to direct neutralizing antibodies to the pathogen to promote opsonization and elimination by macrophages. The Whitesides lab described application of such heterobifunctional polymer that presents vancomycin and introduces haptens to the surface of bacteria. The decoration of the bacteria surface allowed specific antibody recognition and boosted phagocytosis of multiple strains of Gram-positive bacteria [168].

Finally, the Alexander lab recently reported the use of bacterial redox systems to induce polymerization at cell surfaces and producing *in situ*-templated polymers that bind strongly to the pathogens. Such bacteria-instructed polymer synthesis could generate matching polymers for a variety of bacteria strains, representing a promising approach for designing highly selective antibacterial polymeric drugs [169].

7. Miscellaneous applications of polymeric drugs

7.1. Polymeric drugs to modulate hemostasis

Fibrin is a fibrous protein that is produced at the site of vascular injury to form a water-insoluble hydrogel as a scaffold for clot components. Transglutaminase XIIIa (FXIIIa) is a key regulator that stabilizes the clot by crosslinking through amide bonds to produce a tight fibrin network. Lai et al. have synthesized a polymer with pendent dioxolane groups capable of changing the clot structure by influencing the lateral aggregation of protofibrils. This resulted in a decrease in FXIIIa-mediated crosslinking and antithrombotic activity *in vitro* [170]. In contrast, the Pun lab recently reported a synthetic polymeric drug named PolySTAT that was designed to crosslink the fibrin matrix to modulate hemostasis after systemic administration [171]. PolySTAT mimicked the stabilizing effect of FXIIIa by incorporating fibrin-binding peptides to the side chain of linear water-soluble copolymers of 2-(hydroxyethyl) methacrylate (Scheme 3M). The multivalent approach of displaying 16 highly specific fibrin-binding peptides in single polymer chain allowed fast-acting, efficient and safe construction of crosslinked fibrin meshes. PolySTAT altered architecture of the fibrin network with enhanced density, stiffness and smaller pores when compared with FXIIIa. Systemic administration of PolySTAT showed enhanced hemostatic efficacy and survival in a rat model of trauma by reducing blood loss and preventing re-bleeding during fluid resuscitation. In addition, the polymeric drug also showed improved pharmacokinetic profile when compared with the peptide alone, providing prolonged blood circulation and hemostatic activity at the injury site without undesired side effects.

7.2. Anti-inflammatory polymeric drugs

Multiple sclerosis (MS) is a common inflammatory disease of the central nervous system. Although the cause of MS is not fully understood, the pathology is associated with overproduction of inflammatory cytokines and upregulated T cell infiltration [172]. The development of glatiramer acetate (Copaxone®), which was approved by the FDA in 1996, has marked a therapeutic breakthrough in MS [173–175]. Copaxone is a synthetic copolymer of glutamic acid, lysine, alanine, and tyrosine obtained by random ring-opening copolymerization (molecular weight ~ 5–9 kDa). The copolymer successfully reduces T-cell

migration to central nervous system and controls the pathogenesis of MS by antigen-specific desensitization of auto-reactive T-cells [176]. This approach has inspired further exploration of similar amino acid copolymers to treat a number of autoimmune diseases [177–182].

The Haag lab has demonstrated anti-inflammatory effect of a multivalent dendritic polyglycerol sulfates (dPGS) targeting leukocyte trafficking [183]. The authors showed that dPGS function as efficient inhibitors of selectins, cell adhesion molecules that play a crucial role in initiating and regulating leukocyte migration. The dendritic architecture of dPGS could be optimized to present 61 surface sulfate groups to facilitate high-affinity multivalent binding with L- and P-selectin and to mimic natural carbohydrate ligands. As the selectin receptor typically localizes to patches on the surface of leukocytes, dPGS could simultaneously bind multiple copies of selectin, leading to receptor clustering and proteolytic shedding [1]. In addition, dPGS also inhibited activity of complement factors C3 and C5, resulting in further reduction of inflammation. Subcutaneous administration of dPGS significantly lowered leukocyte extravasation and edema formation in a mouse model of contact dermatitis.

Rheumatoid arthritis is another disease area with successful reports of beneficial effects of polymeric drugs. Hayder et al. developed anti-inflammatory polymeric drugs based on dendrimers modified with azabisphosphonate groups to treat rheumatoid arthritis [184]. The authors showed that the dendrimers could selectively activate the amplification of natural killer cells [185], direct monocytes towards anti-inflammatory activation, upregulate the level of anti-inflammatory cytokines, and exhibit anti-osteoclastic activity. Importantly, intravenous administration of the dendrimers resulted in a highly effective and long-term (up to 3 weeks) anti-inflammatory activity.

8. Conclusions and future perspective

Although viewed with skepticism in traditional drug discovery, polymeric drugs offer potential advantages as therapeutics that stem from their ability to readily combine benefits of small-molecule drug discovery process with advantageous properties related to their macro-molecular character typically found in protein drugs. Commercial viability and regulatory feasibility of polymeric drugs have already been confirmed in multiple therapeutic areas as documented by several polymeric drug products on the market. The number of marketed polymeric drug products compares favorably with other applications of polymers in drug delivery that receive significantly higher attention in the field, such as polymeric micelles, nanoparticles, and polymer-drug conjugates.

This review article provided an overview of the main trends in the development of polymeric drugs as applied to sequestrants, anticancer, antimicrobial, antiviral, and anti-inflammatory agents. The identified trends point to further growth of polymeric drugs in therapeutic areas, which can be addressed with local delivery approaches and do not require systemic absorption and distribution. Such approaches include nonabsorbable oral sequestrants, topical antimicrobials and topical antivirals (Table 1). For polymeric drugs that require systemic distribution to achieve their therapeutic effect, parenteral routes of administration will continue to dominate the field until effective methods of enhancing oral

bioavailability of macromolecules are developed. Dual use of polymeric drugs in combination treatments such as the application of pharmacologically active polycations in nucleic acid delivery is likely to remain active area of academic research but the regulatory complexities of developing combination treatments will make clinical translation challenging.

We anticipate future growth and expansion of the field of polymeric drugs spurred mostly by the advances in methods of controlled polymerization that allow to prepare better defined polymers than in the past. The improved control over distribution of molecular weights, sequence and distribution of ligands, and molecular architecture are particularly significant developments. To take full advantage of the therapeutic potential of multifunctional polymeric drugs, new synthetic methods to prepare sequence-defined polymers will be needed to allow better control of the spatial localization of various functionalities present in the polymeric drugs [186]. Despite our general optimism, there are multiple challenges faced in further expansion and development of polymeric drugs as a therapeutic class. First, chemical heterogeneity of polymeric drugs, especially those relying on ligand multivalency and prepared by traditional conjugation approaches, presents substantial analytical challenge and complicates structure-activity relationship studies [187]. Second, many polymeric drugs are based on non-degradable polymers and their metabolism, elimination, and toxicology are not fully understood and appreciated. Third, the relative novelty of polymeric drugs makes their commercial development challenging in a current system set up for development of small molecule drugs and unfamiliar with the peculiarities and unique features of polymers.

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Scheme 1.

Soluble polymers in pharmaceutical applications. Adapted from [13].

Scheme 2.

Monovalent vs. multivalent receptor–ligand interactions. Adapted from [1].

Scheme 3.

Chemical structures of selected examples of polymeric drugs (adapted from [137]).

Scheme 4.

Dual-function polymeric drugs to deliver combination anticancer therapy, such as A) pluronics or TPGS to deliver chemotherapy and function as inhibitors of efflux pumps to overcome MDR, or B) polymeric CXCR4 antagonists (PCX) to deliver gene therapy and inhibit cancer metastasis.

Scheme 5.

General mechanism of actions of polymeric sequestrants for binding excessive A) ions, B) bile acids, C) nucleic acids and D) proteins.

Scheme 6.

Antiviral polymeric drugs inhibit viral entry by blocking interactions between the virus and the host cell.

Scheme 7.

Polymeric drugs exert antimicrobial properties by A) directly damaging bacterial membrane resulting in cell death; B) blocking interactions between the bacteria and the host cell; and C) decorating bacterial cell surface to be recognized for phagocytosis.

Table 1

Selected examples of clinical trials of polymeric drugs registered at www.clinicaltrials.gov as of September 2015.

Drug candidate	Sponsor	Condition	Stage	Route of administration
Fostrap (chitosan-based)	Nestlé Health Science	Hyperphosphatemia in patients with chronic kidney disease	0	Oral/chewing gum
CLP-1001 (cross-linked polyelectrolyte)	Sorbent Therapeutics, United States	Hyperkalemia in heart failure	2	Oral
Velphoro® (starch-based) ^a	Vifor Pharma, Switzerland	Hyperphosphatemia in dialysis patients with chronic kidney disease	3	Oral/chewable tablet
VivaGel® (dendrimer)	Starpharma, Australia	Recurrent bacterial vaginosis	3	Vaginal/muco-adhesive gel
BL-7010	BioLineRx, Switzerland	Celiac disease	1/2	Oral
Vepoloxamer (MST-188) (poloxamer188)	Mast Therapeutics, United States	Subjects with sickle cell disease experiencing vaso-occlusive crisis	3	Intravenous

^a Approved by FDA in 2013.