Polymers as Drugs—Advances in Therapeutic Applications of Polymer Binding Agents

This manuscript is dedicated to the 75th birthday of Professor Bob Grubbs for his life-long extraordinary achievement in research and education.

Eric F. Connor,[1] **Inez Lees**,[2] **Derek Maclean**[2]

[1]308 Willow Hill Court, Los Gatos, California, 95032
[2]Relypsa, Inc, 100 Cardinal Way, Redwood City, California, 94063
Correspondence to: D. Maclean (Email: dmaclean@relypsa.com)

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ABSTRACT: Polymer drugs are those in which a polymer agent has a direct therapeutic effect on the body. A major investigated area of polymer drugs is their use as binding agents, or sequestrants, which can neutralize or remove undesired components from the body. By taking advantage of the unique properties of crosslinked, insoluble polymers, new polymer drugs continue to be developed for oral use, acting in the gastrointestinal tract and excreted in the feces. Soluble polymer binders may be administered by a variety of routes and act at diverse sites of therapeutic action. This article reviews the properties of polymer drugs, particularly sequestrants, with an emphasis on recent advances in polymer properties which may enhance the utility of this class of drugs. © 2017 Wiley Periodicals, Inc. J. Polym. Sci., Part A: Polym. Chem. **2017**, *55*, 3146–3157

KEYWORDS: polymer binders; polymer drugs; polymer pharmaceuticals; polymer sequestrant; synthetic macromolecular drugs

INTRODUCTION Polymers have a wide range of applications in the field of therapeutic development. This article describes polymer drugs in which a polymeric species directly effects the desired pharmacology, and the polymer itself is considered to be the active pharmaceutical ingredient. This is in contrast to the wide usage of polymers that function as excipients (e.g., coatings, viscosifiers, surfactants, etc.), that improves the performance of the pharmaceutical product (active pharmaceutical ingredient) without direct, intrinsic pharmacologic effect.[1]

Polymer-containing drugs also include conjugates, where a polymeric moiety is covalently attached to a pharmacologic agent, as well as polymer complexes in which active moieties may be physically encapsulated within a polymer matrix. In these cases, the primary role of the polymer is to modulate the pharmacokinetic properties of the active agent, by, for example, preventing clearance or enhancing delivery to the desired site of action. We will briefly describe such applications of polymer-containing nanoparticle and microparticle technologies, as well as polymer-drug conjugates.

The main focus of this review will be on polymers which are designed to exert a therapeutic effect, primarily through binding to certain species in the body. Such polymer binders, or sequestrants, are arguably the clearest embodiment of the polymer-as-drug concept as they utilize intrinsic properties of polymers (such as avidity and multiple binding sites) to bind and retain target entities.

Insoluble, often crosslinked polymer binders are typically administered orally and act in the gastrointestinal (GI) tract. The bound entity is then cleared from the body in the feces, along with the polymer. This application is clearly limited to the binding of agents which are accessible in the GI tract. As such agents are often transported between the GI and systemic circulation, local binding by polymer sequestrants can exert pharmacological effects elsewhere in the body. This strategy has been in therapeutic use for many decades. We will describe representative applications of these insoluble polymer binding agents, with an emphasis on cases where recent innovations in polymer design have resulted in the potential for enhanced application of the polymer drug.

Soluble polymer binders have also seen a high degree of interest for therapeutic development, although few examples have reached wide commercial application. In contrast to the insoluble binders, soluble drugs may be administered by a variety of routes, for example, sub-cutaneous, intra-venous, topical, or oral. This flexibility provides the potential to directly access a large number of biological targets, and such drugs have been developed for a correspondingly wide range of clinical indications, such as anti-infectives, cell surfactants,

and immune modulators. We will describe examples of recent advances in soluble polymer drugs.

Other classes of therapeutic binding agents are outside the scope of this article, such as inorganic molecular sieves (e.g., potassium-binding zirconium silicates),[2] activated carbon therapies,[3] or non-covalent assemblies (such as ammonia-binding liposomes).[4]

An illustrative summary of mechanisms by which polymer drugs provide therapeutic effects is shown in Figure 1. In all of these cases, the ability to control polymer properties has proven a useful component of the toolbox for polymer therapeutic scientists seeking to improve patient health, compliance, and safety.

POLYMERS FOR PHARMACOKINETIC MODULATION

Pharmacokinetic properties have a key role in determining the efficacy and toxicity of drugs. Polymers have a long history of use for modifying the exposure of drugs to the body, through means such as controlling dissolution, reducing plasma concentration, extending systemic half-life, and enhancing tissue targeting.

As well as polymer coatings and other excipients (not discussed herein), polymers may be either directly conjugated to an active moiety (thereby directly affecting the drug's properties and distribution), with either permanent or reversible linkage, or non-covalently incorporated with the drug to control in vivo exposure. Examples include the use of poly(ethylene glycol) (PEG) and poly(lactic-*co*-glycolic acid) (PLGA). PEG has been conjugated to a wide range of drugs (small molecules, peptides, proteins) to increase the molecular weight and decrease clearance, or otherwise mask the drug from the action of undesired in vivo processes.[5] PLGA has been used to form polymer matrices which can encapsulate drugs. The slow erosion of the resulting PLGA particles (typically in micrometer range) by hydrolysis or dissolution results in the release of the drug into systemic circulation.[6]

Nanoparticles have been used to control drug delivery through the ability of various materials to form spherical particles (e.g., micelles or liposomes) which act as "nanocontainers," binding to or encapsulating various therapeutic agents. In oncology or inflammation, the enhanced permeability and retention (EPR) effect is proposed to offer unique benefits for nanomedicines.[7] In EPR, leaky blood vessels are hypothesized to allow selective access of particles in the nanometer range, and poorly functioning lymphatic drainage in the same tissue reduces particle clearance. Thus the overall effect is tissue-selective retention of nanoparticles. Larger polymer conjugates (e.g., using 20–40 kDa PEG) may also benefit from the EPR effect.[5] Nanoparticles are typically constructed from amphiphilic materials which act as surfactants to form monolayer or bilayer particles. Amphiphilic polymeric micelles or liposome analogs ("polymersomes") can be constructed by controlled block copolymerization to achieve the tightly controlled weight

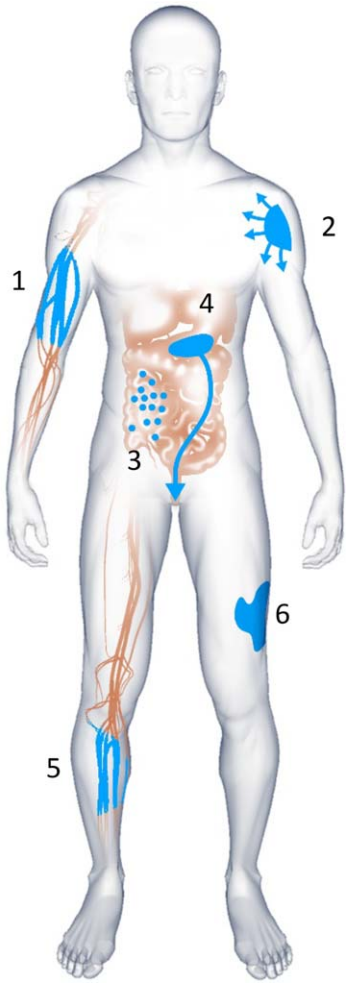

FIGURE 1 Mechanisms of therapeutic polymers. 1. Intravenous polymer conjugates or nanoparticles control drug pharmacokinetics; 2. Sub-cutaneous polymer depot formulation controls delivery of active moiety; 3. Soluble oral polymer drugs neutralize infective or immunogenic agents in GI tract; 4. Insoluble, orally-active polymer sequestrant causes fecal removal of undesired agents; 5. Polymer drugs act as blood bulking agents or in vivo surfactants; 6. Polymer drugs act as topical anti-infectives. [Color figure can be viewed at wileyonlinelibrary.com]

distribution required to support effective nanoparticle formation,[8] with beneficial effects observed in animal[9,10] and clinical studies.[11] However, recently concern has been raised about the broad clinical applicability of this approach due to the failure of three separate polymer bound chemotherapy drugs in late-stage clinical studies (BIND-014, CRLX101, and NK105).[12–14]

These uses of polymers for drug delivery have been the subject of numerous reviews[15,16] and will not be further discussed here. Instead, this article highlights therapeutic applications in which polymers act directly as the drug agent, and the biological activity is due to the polymeric species itself, that is, "polymer drugs."

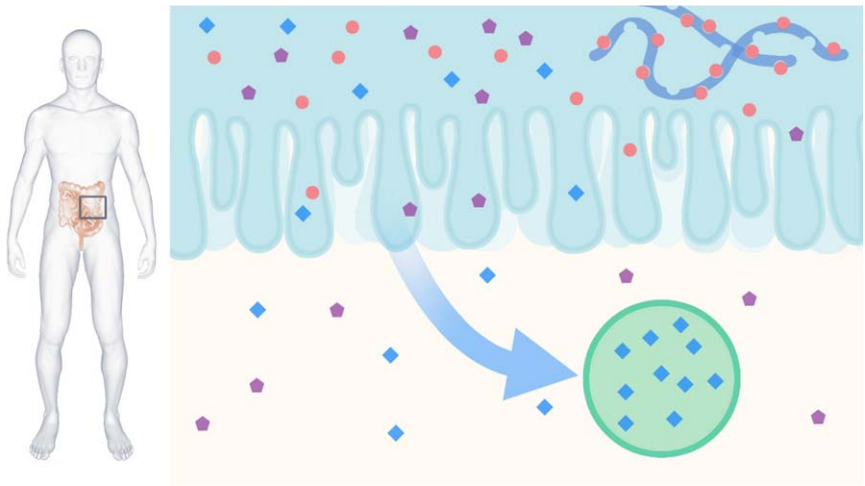

FIGURE 2 Polymer sequestrants for removal of undesired agents from the body. Soluble factors (colored dots) may pass between the blood stream (above) and GI tract (below) through the intestinal epithelia. Insoluble polymers (green circle) may selectively bind soluble factors in the GI tract resulting in elimination via feces and lowering of systemic concentration. Soluble polymers may bind factors in the blood stream and affect exposure to tissues. [Color figure can be viewed at wileyonlinelibrary.com]

POLYMER DRUGS

Polymeric drugs may be broadly divided into soluble and insoluble materials. Polymer drugs which are soluble in biologic fluids may be administered orally or parenterally. Insoluble polymer drugs are typically non-systemic[17] and include polymeric sequestering agents which bind undesirable moieties in the GI tract but are not themselves absorbed, resulting in their removal from the body by the fecal route together with the bound moiety. Development of gut-restricted, insoluble polymers is potentially advantageous as consideration of systemic drug absorption, distribution, metabolism, and excretion is not required.

Aspects of polymer design and application for each of these classes of polymer drug is presented below, with emphasis on recent developments in the field.

Polymer Binders

Polymer sequestrants for binding of inorganic ions (such as potassium and phosphate) and bile acids have been used clinically for many years.[18] The high density of functional groups that can be achieved with crosslinked hydrogel polymers provides high absorption capacity for the targeted removal of species from the GI tract. Figure 2 illustrates the mode of action of polymer sequestrants, and the chemical strucutre of representative polymer drugs is shown in Figure 6.

Insoluble hydrogel particles are not expected to be digested or systemically absorbed. Polymer particles greater than 1 μm have been shown to be not absorbed via transcellular or paracellular routes in the GI and are not detected in blood or organs.[19]

Crosslinked hydrogels with tailored functionality have found particular application in aiding patients with chronic kidney disease (CKD) by indirectly reducing the levels of toxic species in the blood, as described below. CKD is an area of particular relevance for the development of polymer binders to facilitate clearance, as the loss of kidney function removes one of the bodies primary mechanisms to eliminate toxins and control the balance of physiological species through selective excretion.

First Generation Polymer Binders

Polystyrene sulfonate and sevelamer are examples of insoluble binding agents for which consideration of physical properties and salt form illustrate the potential to obtain polymer drugs with enhanced performance or tolerability, as described below.

Sodium polystyrene sulfonate (Kayexalate®, SPS) was amongst the first synthetic polymers to be widely used as a clinical sequestrant.[20] As the salt of a polymeric acid, SPS is

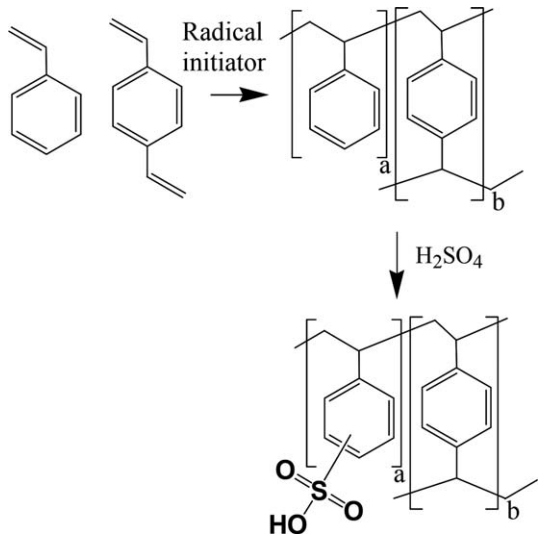

FIGURE 3 Synthesis of Crosslinked Polystyrene Sulfonate.

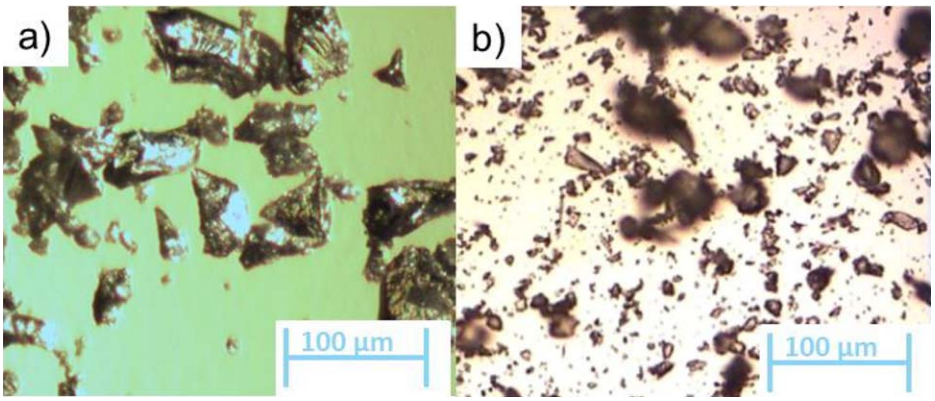

FIGURE 4 Ground polymer morphology of a) Sevelamer; b) Kayexalate by optical microscopy. [Color figure can be viewed at wileyonlinelibrary.com]

able to reversibly bind a range of cations, including potassium. Since potassium is the most abundant ion in the colon, and is reversibly absorbed in the lower GI tract,[21] a GI-restricted polymeric agent with capability to bind potassium may provide an effective means to reduce serum potassium. Elevated serum potassium (hyperkalemia) is a significant concern for patients with CKD or cardiovascular conditions and can result in arrhythmia and sudden death. SPS was approved by the FDA for the treatment of hyperkalemia in 1958.[20] SPS may be produced by the polymerization of styrene in the presence of crosslinking agent divinylbenzene, followed by functionalization to the sulfonic acid (Fig. 3)[22] and subsequent conversion to the sodium salt. Kayexalate® is produced as a ground gel, with a range of particle sizes (Fig. 3).[23]

Sevelamer hydrochloride (Renagel®) was the first polymeric phosphate sequestrant to be approved for clinical use.[24] The control and removal of excess phosphate is of benefit to patients with CKD where dialysis is unable to maintain safe phosphorus levels. Sevelamer limits the absorption of dietary phosphorus by binding phosphate in the intestine through ionic interaction with the polyamine polymer. Sevelamer is a crosslinked form of poly(allylamine) containing primary and secondary aliphatic amine residues and was approved for the treatment of hyperphosphatemia by the FDA in 1998.[25]

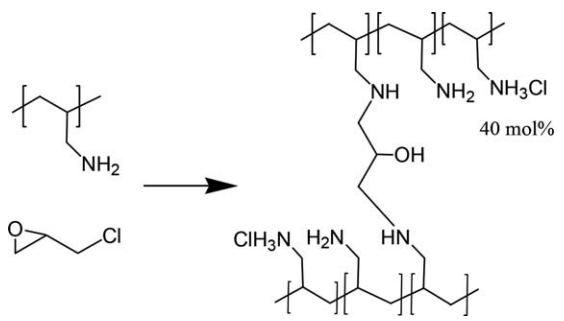

FIGURE 5 Synthesis of Sevelamer Hydrochloride. Approximately 40% of the amine moieties are in the HCl form. Crosslinking degree is 10%.[25]

The sevelamer polymer may be produced by a process whereby initial polymerization is conducted to provide a linear poly(allylamine) followed by a second crosslinking reaction (Fig. 5).[26] Subsequently the polymer gel may be ground to a fine powder and formulated into a tablet for administration to the patient. Although the ground polymer may be sieved to remove both larger and finer particles; particle size control is limited (Fig. 4).[27]

Sequestrants have been successfully used to bind and enable excretion of bile acids in the GI. Bile acids are an array of large amphiphilic molecules (MW ~400 Da) which form micelles and solubilize lipids in the GI. Elimination of bile acids lowers cholesterol systemically. This application of polymer sequestrants demonstrates the binding of a more complex target in comparison to other drugs which bind small inorganic ions (i.e., K^+, PO_4^{2-}).

Several bile acid sequestrant (BAS) polymers have been commercially marketed and have been previously reviewed including colestipol, cholestyramine, and colesevelam.[28] The structure of colesevelam uses poly(allylamine) crosslinked with epichlorohydrin as a backbone modified with pendant decane and hexane trimethylammonium chloride groups (Fig. 6).[28] The hydrophobic motifs in combination with quaternary amine functional groups are key to efficiently binding the amphiphilic bile acids.

Understanding of the role of bile acids in the body and the impact of scavenging them provide opportunities of the ongoing development of bile acid sequestrants. In addition to treatment of dyslipidemia, colesevelam is approved for treatment of type 2 diabetes[29] and is under development for bile acid diarrhea[30] which is a form of irritable bowel syndrome (IBS). Proof of principal of colonic delivery of cholestyramine for IBS has been demonstrated in a successful Phase 2 trial.[31]

Side Effects of Polymer Binders

In certain cases, polymer drug sequestrants have been reported to be associated with undesirable side effects. Some reports suggest that these side effects may be linked to

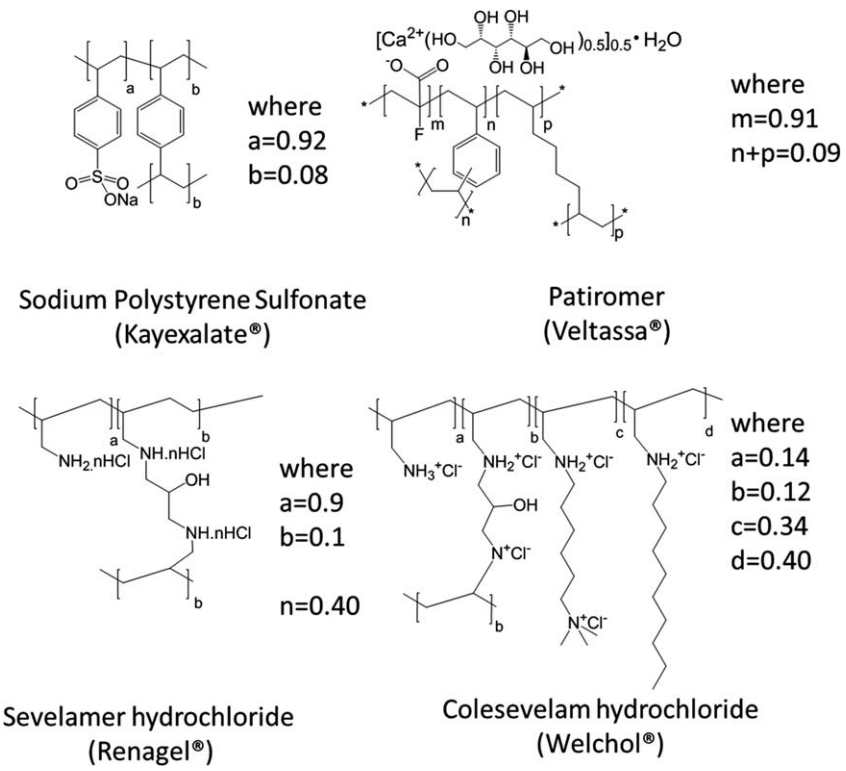

FIGURE 6 Structure of commercially available polymer sequestrant drugs.

specific properties of the polymer, such as the particular salt form of the administered drug, its swelling properties, and physical form. Specific examples are described below.

Ionic polymers are typically administered to patients in a salt form designed so that the counterion is exchanged for a target ion in vivo, resulting in the excretion of the target ion. For example, it has been suggested that lower serum bicarbonate levels associated with use of sevelamer hydrochloride may, at least in part, be due to an increased dietary acid load from ingestion of the drug.[32] A different salt form of the same polymer, sevelamer carbonate (Renvela®),[33] was subsequently developed that has not been associated with reduction in serum bicarbonate.[34] The bile acid-binding agent cholestyramine, a crosslinked polymer containing aromatic quaternary amine groups, which is also administered as the hydrochloride salt, has been similarly associated with hyperchloremic acidosis in a number of reported cases.[35]

SPS is the sodium salt form of poly(styrene sulfonate). The package insert for Kayexalate® states that, since the resin is a source of sodium, caution is advised when the drug is administered to patients who cannot tolerate even a small increase in sodium loads and for whom an increase in sodium load may be detrimental.[36] A calcium salt form of polystyrene sulfonate has also been developed and marketed in several countries (e.g., Resonium® calcium or Kalimate®).[37]

Use of SPS has been associated with colonic necrosis and other serious GI adverse events.[38] While the mechanism of the injury has yet to be firmly established (and may be multifactorial), in some reported cases colonic damage has been associated with the presence of angular particles embedded in colonic tissue, which are identified as granules of SPS.[39] This effect was also noted for treatment with the calcium form of polystyrene sulfonate.[37] The potential role of sorbitol, which is frequently dosed with SPS as a laxative, has been noted, and in 2009, the FDA issued a warning advising against the use of SPS mixed with sorbitol.[20] However comparison of effects in patients treated with SPS with and without sorbitol suggest that the polymer itself may be pathogenic.[38] These effects have called into question the risk-benefit profile of SPS,[20] noting that the drug was approved by the US FDA before modern standards for drug approval based on controlled clinical studies were in place. A recent report details an electronic alert system implemented at a tertiary care academic medical center to decrease SPS ordering for hyperkalemia based on safety concerns.[40]

Reports have also associated sevelamer hydrochloride and sevelamer carbonate with intestinal perforation in a small number of cases.[41] The presence of sevelamer "crystals" was identified within the affected tissue in each reported case. The observation of gastrointestinal symptoms associated with sevelamer hydrochloride was suggested in one report to be due to swelling of the polymer in the GI tract.[42] Swelling of a polymer sequestrant drug may reflect effective permeation with the GI media, allowing ion exchange to the desired bound species. Sevelamer has a swelling ratio of 8 g of water per g of gel.[43]

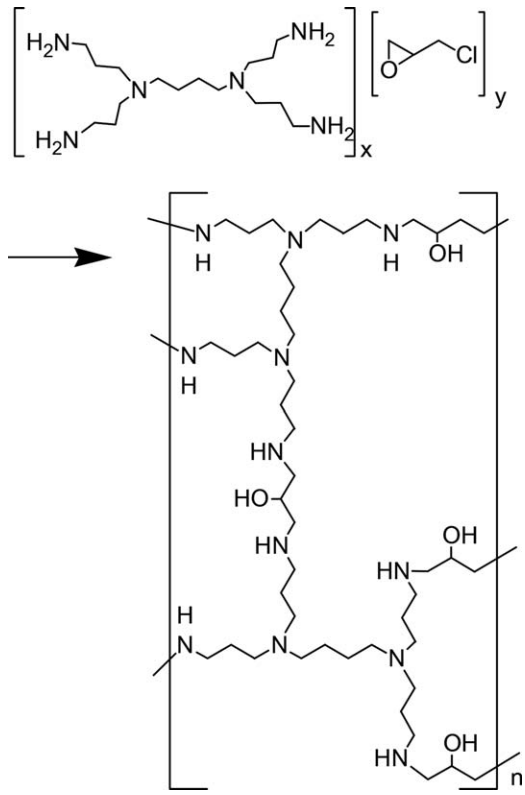

FIGURE 7 Synthesis of Bixalomer.

Although the physical form of SPS and sevelamer in the above examples has not been shown to be directly causative of these GI side effects, it has been reported and suggested as a matter for further research.

Next Generation Polymer Binders

Recent work in polymer sequestrant development has sought to extend the application of polymeric drugs to achieve more defined physical properties for the administered drug, in part through the use of polymerization techniques.

Bixalomer, a phosphate binding polymer formed from crosslinked N,N,N′,N′-tetrakis(3-aminopropyl)butane-1,4-diamine, was developed in Japan for the treatment of hyperphosphatemia.[44] Noting the low swelling of this product (2 g water/g polymer), a recent report suggested that the drug may be useful in treating hyperphosphatemia with fewer gastrointestinal side effects compared to sevelamer.[44] The reduced swelling of bixalomer was achieved by using a branched amine starting material that was highly crosslinked with epichlorohydrin, resulting in a hyperbranched, high amine-content functional material (Fig. 7). The polymer may be synthesized using suspension conditions (discussed later) as a spherical beaded hydrogel. Bixalomer has high selectivity for phosphate in the presence of other anions, which is suggested to be associated with the decreased mesh size as a result of high crosslinking.[45] Furthermore the polymer is one of the first examples of sequestration of the full target species. As Bixalomer is administered in the neutral amine form, this allows sequestration of both the phosphate anion and proton, by acid/base reaction rather than ion exchange, and thus proposed to avoid risk of metabolic acidosis.[45,46]

Patiromer is a non-absorbed, potassium-sequestering polymer which is a crosslinked form of poly(fluoroacrylic acid).[47] The fluorine substituent lowers the pKa of the acid group in patiromer compared to acrylic acid such that a higher proportion of acid groups are available for ion binding under

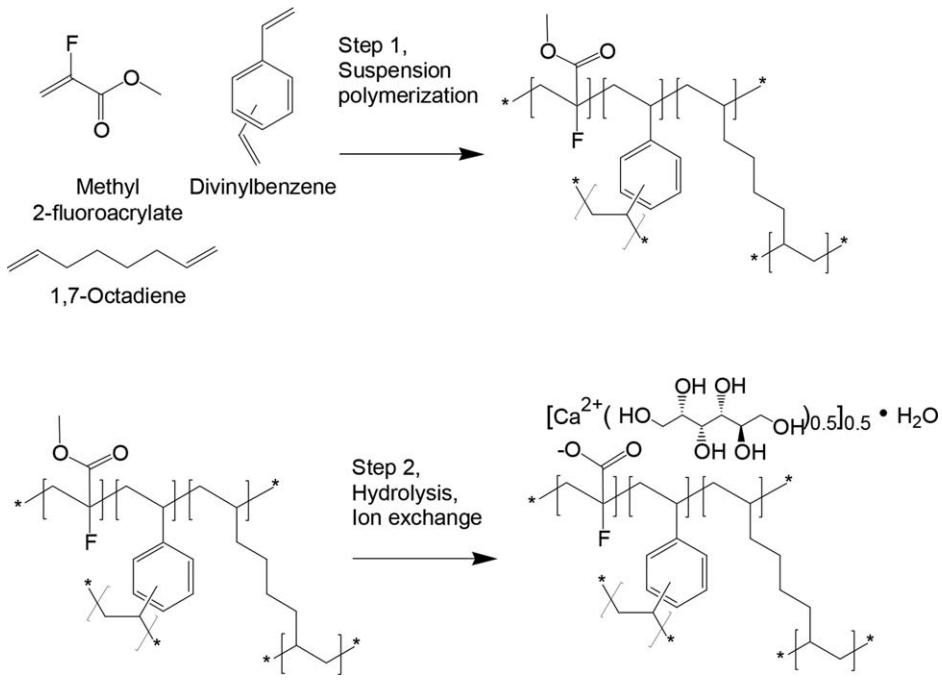

FIGURE 8 Synthesis of Patiromer.

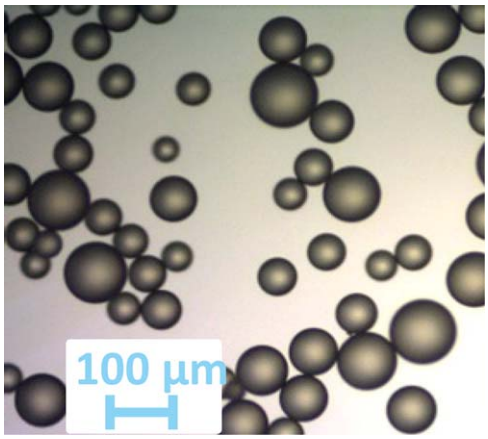

FIGURE 9 Patiromer beads by optical microscopy. [Color figure can be viewed at wileyonlinelibrary.com]

the conditions of the GI tract. Patiromer may be produced by suspension polymerization techniques to obtain a crosslinked hydrogel using two crosslinking agents, namely divinylbenzene and 1,7-octadiene (Fig. 8). The polymer is formed from copolymerization of methyl 2-fluoroacrylate, 1,7-octadiene, and divinylbenzene and has a total degree of crosslinking of 9%. Hydrolysis and salt exchange provide the calcium/sorbitol complex.

Suspension polymerization during patiromer manufacture allows for the generation of monodisperse uniform polymer particles, with spherical shape, controlled size distribution, and low swelling.[47] The bead particles have a median diameter of around 100 μm (Fig. 9). Patiromer was approved by the FDA for the treatment of hyperkalemia in 2015 based on clinical studies showing effective potassium lowering and acceptable safety profile in clinical studies of up to 52 weeks duration.[48]

The drug substance comprising patiromer and a calcium-sorbitol counterion was found to be more stable than the drug substance comprising the polymer anion and calcium counterion, and was used for the majority of clinical investigations.[47] Clinical studies showed that administration of patiromer resulted in a small increase in urinary calcium excretion and a decrease in urinary phosphate excretion.[49] This suggests that only a small fraction of the calcium in patiromer is available for absorption and that some of the released calcium is binding to intestinal phosphate.[49]

Other recent reports indicate the use of material engineering and salt form considerations in the design of polymer sequestrants. A bead-based presentation of polystyrene sulfonate in the calcium salt form has been reported in the patent literature including a description of experiments performed to define crosslinking density and particle size to evaluate potassium binding and texture properties ("grittiness" and "tackiness") to improve palatability of the polymer.[50] A product of this type is currently under clinical development for the treatment of hyperkalemia.[51]

The patent literature also discloses the use of polymer sequestrants for the treatment of metabolic acidosis, by the purported removal of protons and/or chloride ions from the GI tract to control pH homeostasis.[52] The non-absorbed, orally administered polymer is designed to treat chronic metabolic acidosis associated with CKD as measured by an increase of serum bicarbonate levels, and recent clinical results of a polymer treatment for CKD patients have been reported.[52,53]

Suspension Polymerization

For several of the recent insoluble polymer sequestrants described above, the use of suspension polymerization

TABLE 1 Soluble polymer drugs in late stage development or commercially available

Drug name (Brand name)	Disease	Polymer class	Development milestone	Reference
Hydroxyethyl starch 130/0.4 (Voluven®)	Hypovolemia (blood loss)	Nonionic starch derivative	Approved drug (box warning)	57
Glatiramer (Copaxone®)	Relapsing multiple sclerosis	Synthetic polypeptide	Approved drug	65
Vepoloxamer	Sickle cell disease	Poly(ethylene oxide) poly(propylene oxide) copolymer	Phase 3 trial was unsuccessful	59
Tolevamer	Clostridium difficile associated diarrhea	Poly(styrene sulfonate)	Phase 3 trial was unsuccessful	71
SPL7013 (Vivagel®)	Bacterial vaginosis	1-Naphthyleneyl-3,6-disulphonic acid functionalized dendrimer	Phase 3 trial ongoing	72
Oligo-G	Cystic fibrosis	Alginate oligosaccaride	Phase 2a trial completed	62
BL-7010	Celiac disease	Poly(styrene sulfonate)-*co*-(hydroxyethyl methacrylate)	Phase 1/2 trial completed	75

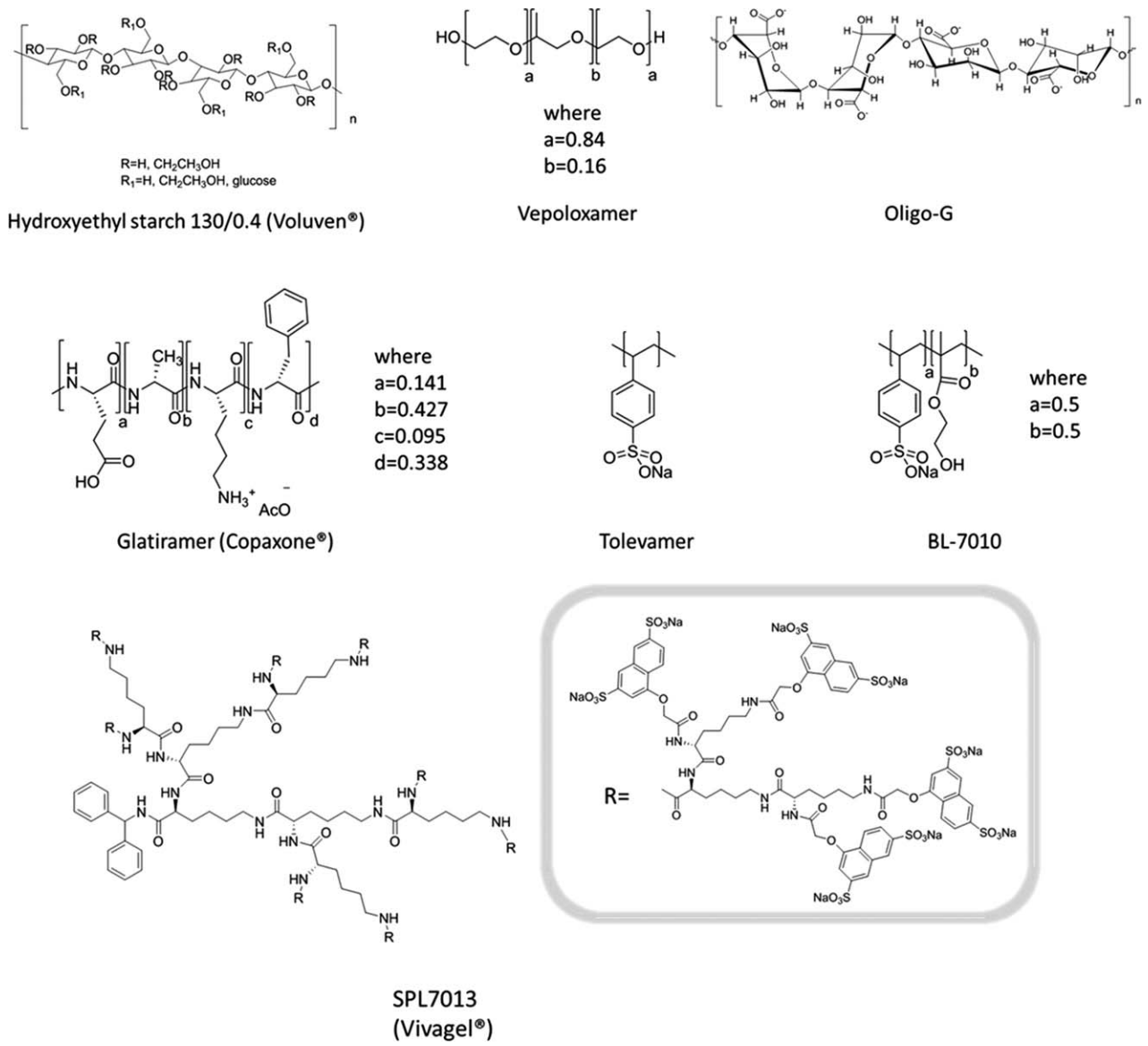

FIGURE 10 Structure of soluble polymer drugs in late stage development or commercially available.

techniques to prepare polymer particles has been described. This approach has benefits for polymer manufacturing, since the polymer suspension is a mobile, quasi-homogenous fluid, for which scaling behavior may readily be assessed to meet product needs, using stirred batch reactors which are commonplace in pharmaceutical manufacturing at a range of sizes.[54] In contrast, bulk gel formation may present challenges of adequate mixing and temperature control with increasing scale. Batch reactors which are equipped with monitoring probes (e.g., temperature, near-IR and particle size probes) support enhanced process control and understanding with benefits in production and regulatory consideration.[55] Particle size can be controlled with the appropriate choice of surfactant and stir rate. The isolation and purification of a spherical bead-based hydrogel is also advantageous as they present a free-flowing, homogeneous material which is expected to offer consistent permeation of aqueous media for washing out reagents and byproducts.

Suspension polymerization has also allowed crosslinking techniques that control the pore size of the hydrogel, which has been reported to provide additional ion-binding selectivity based on the hydrated radius of the species targeted for removal from the GI.[35,46] Polymers exhibiting this behavior also typically reported low swelling in aqueous media which may be advantageous for in vivo use as described above.

Soluble Polymer Drugs

A large number of soluble polymer agents have also been considered for therapeutic purposes, although only a very limited number have been approved for commercial application. This article will review those soluble polymer drugs that have been approved, or reached late stage clinical development. Information about the polymer drugs including the disease indication, polymer description, and development

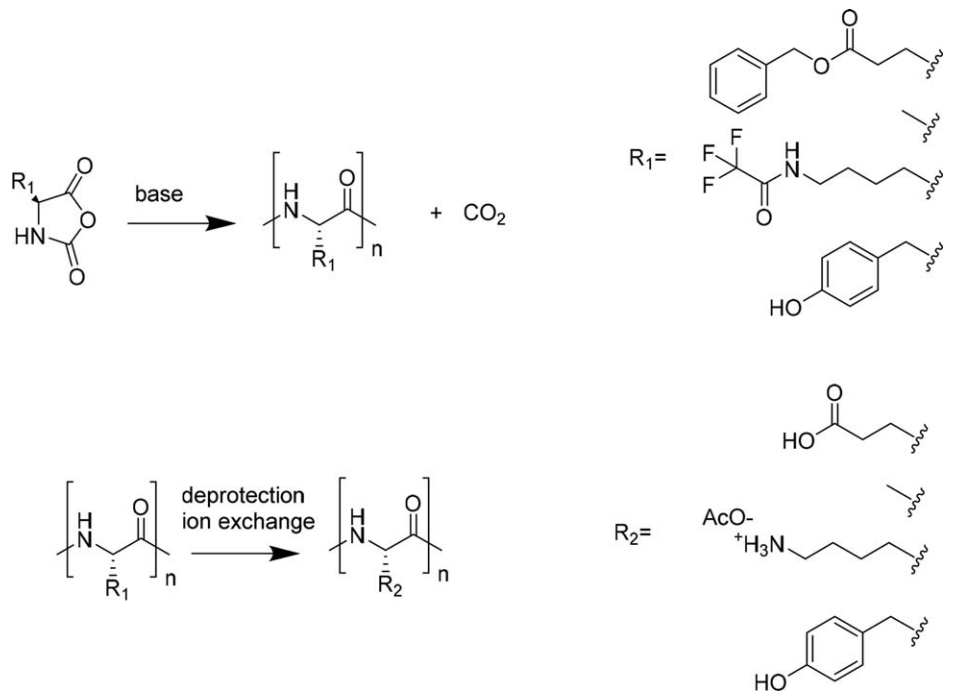

FIGURE 11 Synthesis of Glatiramer.

stage is presented in Table 1, and the structure of each polymer reviewed is shown in Figure 10.

Synthetic polymers drugs have used to mimic the physical effects of serum proteins such as albumin. Water soluble polysaccharides are used as plasma volume expanders to treat significant blood loss as an alternative to blood transfusion. The soluble polymer increases the osmotic pressure in the blood vessel resulting in migration of water from the surrounding tissue. Molecular weight control is important for synthetic polymers used as plasma expanders, as high molecular weight fractions can cause anaphylactic shock and low molecular weight polymers are cleared from the body via the kidneys.[56] Voluven® is a marketed hydroxyethyl starch based product approved for treatment of hypovolemia. However, the product label contains warnings of risks of renal injury and liver failure for at-risk patients.[57]

Another example of a polymer drug under development to mimic a biological entity is the use of non-ionic block copolymers for the treatment of sickle cell disease. Vepoloxamer is purified poloxamer 188, a poly(ethylene oxide)-*block*-poly(propylene oxide)-*block*-poly(ethylene oxide) (PEO-PPO-PEO) copolymer with a molecular weight of 8400 Da. Poloxamers are widely used, non-ionic surfactant excipients, but in the case of Vepoloxamer the surfactant properties are directly applied to achieve the desired therapeutic effect. The polymer is proposed to enhance the cell wall of the misshaped sickle cell, thereby reducing adhesion and aggregation of abnormal red blood cells and reduce blood viscosity.[58] However, a recent Phase 3 trial did not show reduction of duration in episodes associated with sickle cell disease.[59] Additional applications for the treatment of impaired microvascular blood flow (e.g., stroke) are under development.[60]

The modification of physical properties of a biological system by a polymer is exemplified by the development of alginate oligosaccharide (Oligo-G) for the treatment of cystic fibrosis (CF). The polymer modifies the viscosity of mucus in the lungs of a CF patient and has the potential to allow more effective treatment of infections with antibiotics.[61] The drug has been shown to be well tolerated in a recent Phase 2a trial.[62]

A more complex application of a soluble polymer therapeutic is observed for the most successful example of this class of drugs, glatiramer for the treatment of relapsing multiple sclerosis (MS).[63] Glatiramer acetate is a random copolymer of 4 amino acids, formed through the amine-initiated, ring-opening polymerization of the N-carboxyanhydride amino acid derivatives (Fig. 11), with an average molecular weight of 5000–9000 Da.[64,65] Glatiromer acetate is the only approved drug in drug class and is the first line of treatment for MS. The specific interaction of peptide sequence is not understood for this drug however the polypeptide is thought to modulate the immune response reducing detrimental inflammation which occurs during MS.[66]

Soluble polymers have seen significant investigation as antimicrobial agents, due to potential high-avidity interactions between repeating polymer units and multivalent surface features on a bacteria or virus. This effect may bind and prevent virulent factors from engaging their targets in the body. Several examples in clinical development are described below.

The anti-infective activity of soluble anionic polymers has been determined for viruses,[67] bacteria,[68] and microbial toxins.[69] Binding interactions of polyanions with microbes are can be considered nonspecific and based on electrostatic interactions. Thus these treatments have the potential to

have broad antimicrobial effects. Another advantage of using polymers as drugs is the opportunity for polyvalent interactions between the polymer side chains and the biological target. This was demonstrated in the development of polymers with carbohydrate based ligands to scavenge Shiga-like toxins. Precise placement of multiple ligands connected to a polymer backbone showed superior in vitro inhibitory activity in comparison to monomeric and dimeric inhibitors.[70]

Tolevamer, a soluble anionic poly(styrene sulfonate), was developed for the treatment of Clostridium difficile associated diarrhea. The polymer binds to toxin A and B which is produced by the bacteria. Preclinical studies showed a correlation between molecular weight and binding affinity, supporting a proposed mechanism based on binding avidity, and suggesting that multiple binding interactions were necessary to effectively sequester the toxin.[18] Tolevamer did not meet the clinical endpoint for Phase III as it was inferior to antibiotics metronidazole and vancomyin, although it was observed that the reoccurrence of infection was lower for patients who responded to treatment with tolevamer than for other treatments.[71]

A soluble dendrimeric polymer drug, Vivagel®, with highly defined molecular weight and branched architecture has been approved in the EU for acute treatment of bacterial vaginosis and is undertaking Phase 3 trials for chronic use.[72] The dendrimer has a benzhydrylamine amide core with four L-lysine based layers, functionalized with 1-naphthylenyl-3,6-disulphonic acid.[73]

An example of a polymeric binder to sequester proteins is under development for the treatment of celiac disease. Celiac disease is thought to arise, in part, from exposure to gliadin-containing proteins in the GI tract of gluten-sensitive patients. Gliadin is a proline-rich peptide which is not readily proteolyzed, and may act as a sensitizer in the bowel. BL-7010 is a random copolymer of poly(styrene sulfonate)-*co*-(hydroxyethyl methacrylate) with a molecular weight of $>$20,000 Da. The proposed mechanism of action is that the polymer binds gliadin in the GI and protects it from enzymatic degradation limiting the formation of immunogenic peptides which trigger an immune response causing intestinal damage.[74] A Phase 1/2 study has been completed demonstrating safety and tolerability and the polymer has been demonstrated to be non-absorbed.[75]

Further development in this field is likely to focus on increasing specificity of polymer therapeutics for target molecules bringing together knowledge of specific motifs from small molecule therapeutics and the potential for polyvalency intrinsic in polymer drugs.

REGULATORY CONSIDERATIONS

Polymer drugs require particular consideration of regulatory strategy as they typically do not fit in either of the two main molecular categories of drugs, namely small molecules and biologics. In particular, the applicability of analytical methods to molecular characterization becomes relevant. In general terms, small molecules are well characterized by typical chemical analytical methods, whereas biologics such as proteins are more challenging to completely characterize through chemical methodologies, since attributes such as higher order structure or post-translational modifications are process-dependent and may not be identified by many analytical methods. The relatively recent accessibility of regulatory pathways for "biosimilar" drugs reflects these aspects, in contrast to the more well-established availability of generic small molecule drugs.

Polymer drugs share some similarities with each of the major classes of drugs. Like most small molecules, they are prepared from well-characterized chemical starting materials by an entirely chemical process. However, like biologics, they are complex species which may be difficult to fully characterize by typical analytical chemical methods.

The concept of Non-Biological Complex Drugs has been proposed to include polymeric drugs, as well as related materials such as liposomes and other complex species. Definitions and concepts associated with this area have been presented[76] and two recent papers from the European Medicines Agency reflect data requirements for characterizing liposomal products[77] and iron-based colloids.[78] Additional recent examples may illustrate expectations for characterization in the field of polymer drugs. Authors from the US FDA published an approach to characterize the phosphate-binding ability of sevelamer in the hydrochloride and carbonate salt forms, with the stated purpose of avoiding requirement for in vivo testing through extensive in vitro binding analysis.[79] Similarly, a thorough chemical and biological analysis of glatiramer acetate was reported[64] including detailed analysis of starting materials and process chemistry, structural analysis of the polymeric materials, equivalence of physicochemical, biological, and immunological properties. Full characterization of this product was reported to entail the application of more than 60 methods on up to 50 batches of the test drug. A generic version of glatiramer was approved by the US FDA in 2014.

Another area that has been of regulatory interest for polymer drugs is the potential for drug-drug interaction (DDI). In the GI tract, polymer sequestrants may encounter other orally administered drugs, and it is possible the absorption of such drugs may be affected by the polymer. A study of the potential for DDI with colesevelam hydrochloride was reported,[80] in which in vitro and in vivo results were used to build a predictive model to identify potential binders to the polymer drug. Perhaps unsurprisingly for a cholesterol binder, lipophilicity (logD) was identified as the most important physicochemical parameter for predicting binding. The potassium-binding drug patiromer also reported an extensive set of data from clinical studies designed to evaluate the potential for DDI with potentially co-administered drugs.[81] Of 12 drugs that were tested, three showed a change in pharmacokinetic properties when coadministered with patiromer. Separation from dosing other oral drugs of 3 h is currently recommended for patiromer.[82]

CONCLUSIONS

Polymer drugs are a unique class of therapeutics with a wide range of current and potential clinical applications. Recent polymer drugs which have been introduced to the market or are in clinical development show that the field continues to evolve as polymerization techniques are developed and deployed. Additional research and development is anticipated to provide further understanding of the importance of the physical characteristics of polymer drugs, and the impact that polymer science can play in shaping future therapeutics.

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