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Feature Article

Hydrogels in drug delivery: Progress and challenges☆

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Abstract

There has been considerable progress in recent years in addressing the clinical and pharmacological limitations of hydrogels for drug delivery applications but substantial challenges remain. Here we discuss recent progress in overcoming these challenges, particularly with regards to effectively delivering hydrogels inside the body without implantation, prolonging the release kinetics of drugs from hydrogels, and expanding the nature of drugs which can be delivered using hydrogel-based approaches.

Keywords: Hydrogels; Drug delivery; Polymer science

1. Introduction

Hydrogels are three-dimensional, cross-linked networks of water-soluble polymers. Hydrogels can be made from virtually any water-soluble polymer, encompassing a wide range of chemical compositions and bulk physical properties. Furthermore, hydrogels can be formulated in a variety of physical forms, including slabs, microparticles, nanoparticles, coatings, and films. As a result, hydrogels are commonly used in clinical practice and experimental medicine for a wide range of applications, including tissue engineering and regenerative medicine [1], diagnostics [2], cellular immobilization [3], separation of biomolecules or cells [4], and barrier materials to regulate biological adhesions [5].

The unique physical properties of hydrogels have sparked particular interest in their use in drug delivery applications. Their highly porous structure can easily be tuned by controlling the density of cross-links in the gel matrix and the affinity of the hydrogels for the aqueous environment in which they are swollen. Their porosity also permits loading of drugs into the gel matrix and subsequent drug release at a rate dependent on the diffusion coefficient of the small molecule or macromolecule through the gel network. Indeed, the benefits of hydrogels for drug delivery may be largely pharmacokinetic – specifically that a depot formulation is created from which drugs slowly elute, maintaining a high local concentration of drug in the surrounding tissues over an extended period, although they can also be used for systemic delivery. Hydrogels are also generally highly biocompatible, as reflected in their successful use in the peritoneum [6] and other sites *in vivo*. Biocompatibility is promoted by the high water content of hydrogels and the physiochemical similarity of hydrogels to the native extracellular matrix, both compositionally (particularly in the case of carbohydrate-based hydrogels) and mechanically. Biodegradability or dissolution may be designed into hydrogels via enzymatic, hydrolytic, or environmental (e.g. pH,

Abbreviations: PEG, poly(ethylene glycol); PEO, poly(ethylene oxide); PPO, poly(propylene oxide); PDMAEMA, poly(dimethylaminoethyl methacrylate); PLGA, poly(lactide-*co*-glycolic acid); PNIPAM, poly(*N*-isopropylacrylamide); PPF, poly(propylene fumarate); PCL, poly(caprolactone); PU, poly(urethane); POP, poly(organophosphazene); PHB, poly(*R*-3-hydroxybutyrate); FITC, fluorescein isothiocyanate; NSAID, non-steroidal anti-inflammatory drug; IPN, interpenetrating polymer network; BAM, *N*-*tert*-butylacrylamide.

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temperature, or electric field) pathways; however, degradation is not always desirable depending on the time scale and location of the drug delivery device. Hydrogels are also relatively deformable and can conform to the shape of the surface to which they are applied. In the latter context, the muco- or bioadhesive properties of some hydrogels can be advantageous in immobilizing them at the site of application or in applying them on surfaces that are not horizontal.

Despite these many advantageous properties, hydrogels also have several limitations. The low tensile strength of many hydrogels limits their use in load-bearing applications and can result in the premature dissolution or flow away of the hydrogel from a targeted local site. This limitation may not be important in many typical drug delivery applications (e.g. subcutaneous injection). More important, perhaps, are problems relating to the drug delivery properties of hydrogels. The quantity and homogeneity of drug loading into hydrogels may be limited, particularly in the case of hydrophobic drugs. The high water content and large pore sizes of most hydrogels often result in relatively rapid drug release, over a few hours to a few days. Ease of application can also be problematic; although some hydrogels are sufficiently deformable to be injectable, many are not, necessitating surgical implantation. Each of these issues significantly restricts the practical use of hydrogel-based drug delivery therapies in the clinic.

In this review, we focus on recent developments addressing three key clinically relevant issues regarding the use of hydrogels for drug delivery: facilitating the *in vivo* application of drug-eluting hydrogels, extending their duration of drug release, and broadening the range of drugs which they effectively deliver.

2. Improving the delivery of hydrogels

Hydrogels used in drug delivery are usually formed outside of the body and impregnated with drugs before placement of the hydrogel–drug complex in the body. A wide range of cross-linking strategies can be used, including UV photopolymerization and various chemical cross-linking techniques. Such cross-linking methods are useful only if toxic reagents can be completely removed prior to hydrogel implantation, which may be difficult to achieve without also leaching loaded drug out of the hydrogel. The main disadvantage of such approaches is that the preformed material must be implanted, since bulk hydrogels have a defined dimensionality and often high elasticity which generally excludes their extrusion through a needle. The latter problem can sometimes be circumvented by making the preformed gel into micro- or nanoparticles. In some applications, the hydrogels can also be formed *in situ* (i.e. *in vivo*), although one then has to consider the potential risks of exposure to UV irradiation (and the need for additional equipment) or to cross-linking chemicals.

As an alternative, non-cross-linked linear polymers can be used as the drug delivery vehicle. In general, the rate of drug release from a linear polymer matrix is inversely proportional to its viscosity [7]. However, it may be difficult or impossible to dissolve the polymer(s) of interest to a high enough concentration to control the rate of drug release to the extent desired. Even if that were possible, the yield stress of the resulting material may be so high that injection is impossible, or the viscosity may be so high that resistance to flow in a narrow and/or long extrusion device (needle, laparoscope) is prohibitive, as described by Poiseuille's equation. Furthermore, unless the water-soluble polymer chains are somehow cross-linked, they swell and subsequently dissolve in the aqueous *in vivo* environment, sometimes within a few hours for highly hydrophilic polymers. Because of these considerations, there has been considerable interest in formulations which exhibit the properties of linear polymer solutions outside of the body (allowing easy injection) but gel *in situ* within the body, providing prolonged drug release profiles. Both physical and chemical cross-linking strategies have been pursued to achieve *in situ* gelation.

2.1. Physically cross-linked hydrogels

Physical cross-linking of polymer chains can be achieved using a variety of environmental triggers (pH, temperature, ionic strength) and a variety of physicochemical interactions (hydrophobic interactions, charge condensation, hydrogen bonding, stereocomplexation, or supramolecular chemistry).

2.1.1. Hydrophobic interactions

Polymers with hydrophobic domains can cross-link in aqueous environments via reverse thermal gelation, also known as 'sol–gel' chemistry. Polymers (or oligomers) with such gelation properties are referred to as gelators and are typically moderately hydrophobic. Hydrophobicity-driven gelation often occurs via the mechanism shown in Fig. 1. A gelator (the hydrophobic segment) is coupled to a hydrophilic polymer segment by post-polymerization grafting or by directly synthesizing a block copolymer to create a polymer amphiphile. Such amphiphiles are water soluble at low temperature. However, as the temperature is increased, hydrophobic domains aggregate to minimize the hydrophobic surface area contacting the bulk water, reducing the amount of structured water surrounding the hydrophobic domains and maximizing the solvent entropy. The temperature at which gelation occurs depends on the concentration of the polymer, the length of the hydrophobic block, and the chemical structure of the polymer: the more hydrophobic the segment, the larger the entropic cost of water structuring, the larger the

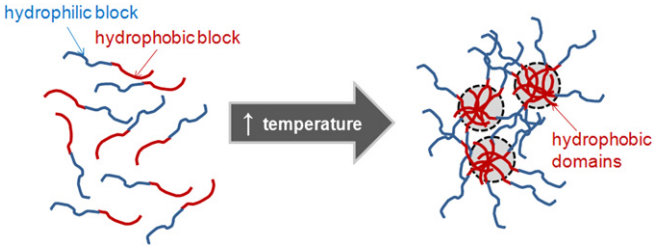

Fig. 1. Mechanism of *in situ* physical gelation driven by hydrophobic interactions.

driving force for hydrophobic aggregation, and the lower the gelation temperature.

The chemical structures of some common hydrophobic blocks which can undergo reverse thermal gelation at or near physiological temperature are shown in Fig. 2. Triblock copolymers of poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) (PEO–PPO–PEO, the poloxamers/Pluronics) are the most widely used reverse thermal gelation polymers [8]. At a concentration of 25% (w/v), an aqueous solution of poloxamer 407, a PEO–PPO–PEO triblock copolymer containing ~101 repeat units in each of the PEO blocks and ~56 repeat units in the PPO block, is a viscous liquid at room temperature or below but forms a hydrogel at body temperature (37 °C) which is sufficiently gel-like to hold its shape in an inverted test-tube. Poloxamer 407 has been used to extend the duration of lidocaine release [9,10]. The drug was formulated in the polymer solution at a cool temperature and then injected at the sciatic nerve in rats, where body temperature caused gelation, resulting in a marked prolongation of nerve blockade. However, it is instructive to compare the several hours duration of drug release/nerve blockade achieved with poloxamer to the days- to weeks-long duration nerve blockade that can be achieved with some microparticle-based systems [11]. In addition to the relatively rapid diffusion of drugs out of the hydrophilic gel matrix [9], the maximum duration of drug release is limited by the influx of water which dilutes the polymer below its critical gelation concentration such that the matrix loses gel-like properties. We have seen this happen within a small number of hours after intraperitoneal injection of concentrated solutions of poloxamer 407.

The rapid dissolution or dissipation of such copolymers *in vivo* can be overcome by covalent-cross-linking. For example, in ethoxysilane-capped PEO–PPO–PEO triblocks, the ethoxysilane groups hydrolyze over time to form silanol groups which covalently cross-link, preventing the rapid dilution of the polymer with water *in vivo* [12]. Alternately, an amine-terminated poloxamer can be grafted with carbohydrates such as hyaluronic acid to form self-assembled carbohydrate-rich networks which slow down release of small-molecule drugs such as ciprofloxacin [13] and biomolecular drugs such as human growth hormone [14]. Carbohydrate grafting to poloxamers reduces the critical gelation concentration and the dissolution rate of the networks *in vivo* because of the high viscosity of the hyaluronic acid grafts. Poloxamers can also be modified by adding an additional polymer block at each chain terminus, forming an ABCBA pentablock copolymer with improved properties for drug delivery. For example, pentablock PDMAEMA–PEO–PPO–PEO–PDMAEMA forms free-flowing liquids at room temperature but forms elastic hydrogels at concentrations above 12% when heated, facilitating the near zero-order release of sparingly soluble drugs [15].

Other types of multi-block amphiphiles (i.e. polymers with both hydrophilic and hydrophobic domains) have been synthesized using a wide range of polymers. Triblock (ABA) copolymers containing biodegradable poly(L-lactic acid), poly(L-glycolic acid), or copolymers thereof are the most common alternative to poloxamer-based copolymers. The hydrophobic block may be contained as the center (B) block (e.g. PEG–PLGA–PEG [16]) or in the arm (A) blocks (e.g. PLGA–PEG–PLGA [17,18]). PL(G)A-based gelators typically exhibit better biodegradability, higher gelation temperatures (permitting easier handling pre-injection), and longer periods of sustained drug release compared to poloxamer systems [19]. Release of hydrophilic compounds from PLGA–PEG–PLGA copolymers was found to be diffusion-controlled, while release of hydrophobic compounds showed an initial diffusion-controlled stage followed by a prolonged polymer degradation-controlled stage [19]. Asymmetric ABC

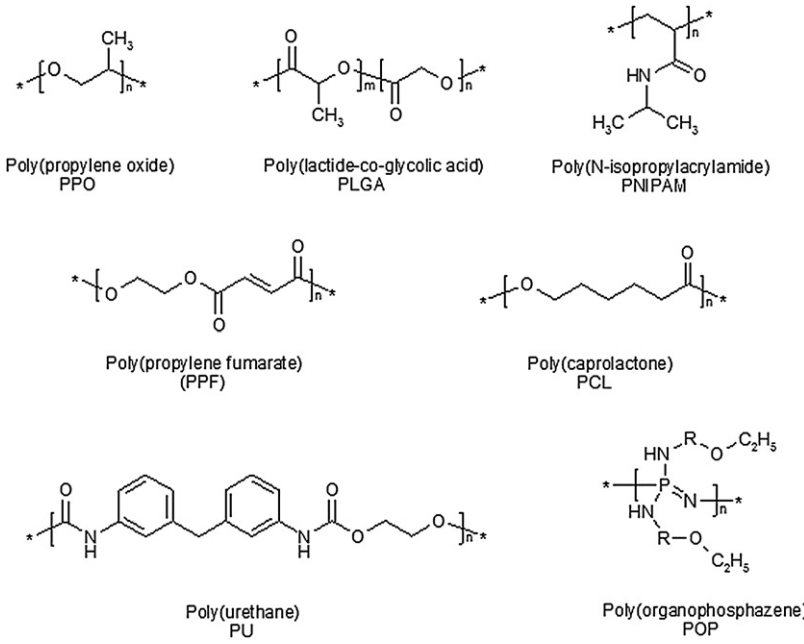

Fig. 2. Chemical structures and abbreviations of common thermogelling hydrophobic blocks; R = any thermogelling polymer.

triblock copolymers may also be used to achieve specific functionalities within the thermally induced gel. For example, triblock copolymers of PEG, PLA, and poly(L-glutamic acid) have been synthesized which can permit selective modification of the L-glutamic acid block with specific targeting groups such as the cell-adhesive RGD peptide [20].

A range of other synthetic thermally gelling polymers have also been investigated to further prolong drug release or reduce the concentration at which gelation occurs. Poly(*N*-isopropylacrylamide) (PNIPAM) is one of the most widely studied thermoresponsive polymers. PNIPAM–poly(phosphorylcholine)–PNIPAM triblock copolymers have been reported which form gels at 6–7 wt% when the phase transition temperature of the PNIPAM arms (~32 °C) is exceeded [21]. Grafting PNIPAM linear chains onto natural polymers can also convert those polymers into physically cross-linkable hydrogels. For example, PNIPAM-grafted hyaluronic acid formed a gel *in vivo* which showed a burst release of riboflavin for 12 h and sustained release thereafter [22]; NIPAM-grafted chitosan has also been used to control the release of 5-fluorouracil [23]. Polycaprolactone (PCL) homopolymers or copolymers with glycolic acid [24] have also been combined with poly(ethylene glycol) in both triblock [25] and diblock [26] forms to facilitate prolonged release. Diblock PEG–PCL polymers facilitated the release of FITC-labeled bovine serum albumin over a period of 30 days owing to the lower water content and longer network stabilities of PEG–PCL copolymers compared to poloxamers and other common physical gelators [26].

Other types of synthetic thermally gelling polymers have been used, increasing the range of chemical functionalities which can be incorporated into the hydrophobic block. Poly(organophosphazenes) can produce mechanically strong gels at concentrations below 15 wt% polymer and permit the introduction of various hydrophobic, hydrophilic, or other functional substituents into the polymer backbone to modify the mechanical properties of the hydrogel, the gel degradation rate, and the polymer–drug affinity [27]. Doxorubicin was released over a period of 1 month from a poly(organophosphazene) containing structured hydrophobic, hydrophilic, and biodegradable domains [28]. Polyurethanes [29] or poly(ether ester urethanes) [30] can also be used to impart a wide range of functionalities into the polymer backbone. The double bond in the polymer backbone of poly(propylene fumarate) (PPF) can be used to subsequently polymerize the physically cross-linked gels formed from block copolymers of PPF and/or copolymerize other types of vinyl monomers into the gel to further modify the gel properties. Block copolymers of PPF with methoxy poly(ethylene glycol) undergo reverse thermal gelation at temperatures between 30 and 75 °C at concentrations as low as 5 wt% [31].

Some natural polymers also undergo reverse thermal gelation. Chitosan solutions containing glycerol-2-phosphate gel at a temperature close to 37 °C [32], and a solution of chitosan grafted with 40 wt% PEG gels at 37 °C, releasing bovine serum albumin over 70 h after an initial burst release [33]. Similar thermally triggered transitions have also been demonstrated with hydroxypropylcellulose [34,35] and methylcellulose [36].

Changes in the morphology of the gelator can also tune the physical and pharmacokinetic properties of physically cross-linked gels. For example, star diblock copolymers can be produced from multi-functional controlled radical polymerization initiators to form highly efficient thermally gelling polymers. Star diblocks are typically prepared by first polymerizing a water-soluble polymer in the center of the star (e.g. phosphorylcholines) followed by a thermosensitive (e.g. poly(propylene oxide) methacrylate) or pH-sensitive (e.g. 2-diisopropylaminoethyl methacrylate) gelator in the outer arms [37]. The advantage of such polymer architectures is that lower polymer concentrations are required to achieve strongly gelled systems. Formulating thermogelling polymers as particles can also significantly lower the polymer fraction required to form gels due to long-range electrostatic double layer interactions between the surfaces of the particles. For example, biocompatible interpenetrating polymer network microgels comprising poly(*N*-isopropylacrylamide) and polyacrylic acid undergo reversible gelation to form particle assemblies at 33 °C at weight concentrations above 2.5 wt% and can control the release of loaded dextran markers [38]. This critical concentration is approximately one order of magnitude lower than that observed for conventional poloxamer systems.

Several other types of low molecular weight gelators have been investigated, many of which may be suitable for drug delivery applications [39]. Different gelators can be used to achieve gelation at different concentrations or time scales, to tune the mechanical strength of the injectable hydrogels, and/or to control the release kinetics by optimizing interactions between the hydrogel and a target drug. The mechanical strength required from a drug-releasing hydrogel depends on the specific location and use of the hydrogel in the body, for example, whether or not the hydrogel is intended for a high-stress field (such as at a weight-bearing joint). The correlation between drug release properties and mechanical strength remains somewhat unclear.

2.1.2. Charge interactions

Charge interactions have been widely investigated for cross-linking *in situ* gelling polymers. One advantage of this approach is that biodegradation can occur as ionic species in extracellular fluid bind competitively with the gel components, breaking down the cross-linked network. Cross-linking (or de-cross-linking) can also be triggered by pH changes which ionize or protonate the ionic functional groups that cause gelation, in some cases enabling the delivery of the liquid-like gel precursors in a single syringe.

Charge interactions may occur between a polymer and a small molecule or between two polymers of opposite charge to form a hydrogel, as illustrated in Fig. 3. As an example of small-molecule cross-linking, elastin-like polypeptides have been cross-linked via electrostatic interactions between their cationic lysine residues and anionic organophosphorus cross-linkers under physiological conditions [40]. As examples of polymer–polymer cross-linking, ionic-complementary

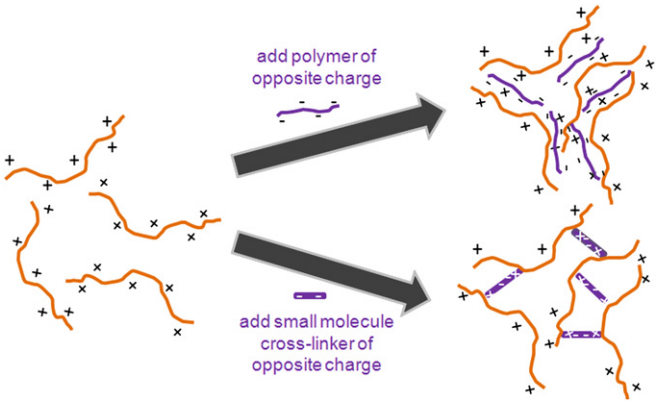

Fig. 3. Mechanisms of *in situ* physical gelation based on charge interactions with an oppositely-charged polymer or an oppositely-charged small molecule cross-linker.

peptides with alternating positive and negative charge domains can self-assemble to form hydrogels *in situ* [41], and a mixture of quaternized chitosan and glycerophosphate forms an optically clear, ionically cross-linked gel at physiological temperature which can release doxorubicin hydrochloride as a function of pH [42]. Charge interactions can also be used to cross-link microparticle or nanoparticle gels to create three-dimensional particle assemblies with favorable drug delivery properties. For example, dextran microspheres coated with anionic and cationic polymers exhibit spontaneous gelation upon mixing due to ionic complex formation between the oppositely charged microparticles [43].

2.1.3. Hydrogen bonding interactions

Hydrogen bonding interactions can be used to produce hydrogels *in vitro* by freeze-thawing, e.g. in the formulation of poly(vinyl alcohol)-based hydrogels [44]. Hydrogen bonding can also be used to formulate injectable hydrogels. Mixtures of two or more natural polymers can display rheological synergism, meaning that the viscoelastic properties of the polymer blends are more gel-like than those of the constituent polymers measured individually [45]. This synergism is typically a result of hydrogen bonding interactions between the polymer chains facilitated by the compatible geometries of the interacting polymers, as illustrated in Fig. 4. Shearing the mixture (i.e. forcing the blend through a needle) can disrupt these relatively weak hydrogen bonds, facilitating injection. Blends of natural polymers such as gelatin–agar [46], starch–carboxymethyl cellulose [47], and hyaluronic acid–methylcellulose [48] form physically cross-linked gel-like structures which are injectable. Such blends generally exhibit excellent biocompatibility due to the absence of chemical cross-linkers and because the formulations are typically based on or resemble extracellular matrix polymers. However, hydrogen-bonded networks can dilute and disperse over a few hours *in vivo* due to influx of water, restricting their use to relatively short-acting drug release systems unless some other form of cross-linking is also used.

2.1.4. Stereocomplexation

Stereocomplexation refers to synergistic interactions which can occur between polymer chains or small molecules of the same chemical composition but different stereochemistry. Of particular relevance, *in situ* forming hydrogels with high storage moduli (up to 14 kPa) can be prepared by exploiting the strong interaction between polylactide blocks with L- and D-stereochemistry [49], as illustrated schematically in Fig. 5. Multi-arm PEG–PLA dendrimers or star diblock copolymers can be cross-linked using this stereospecific interaction to form hydrogels with transition temperatures ranging from 10 to 70 °C depending on the polymer concentration and PLA block length [50]. Natural polymers can also be cross-linked via stereocomplexing grafts. Grafting L-lactide and D-lactide oligomers to dextran precursors induces spontaneous gelation in water [51–53], resulting in excellent biocompatibility and biodegradability [53] without requiring the use of harsh/denaturing conditions such as organic solvents, chemical cross-linkers, or the formation of hydrophobic domains which may denature embedded proteins. One significant limitation of stereocomplexation is the relatively restricted range of polymer

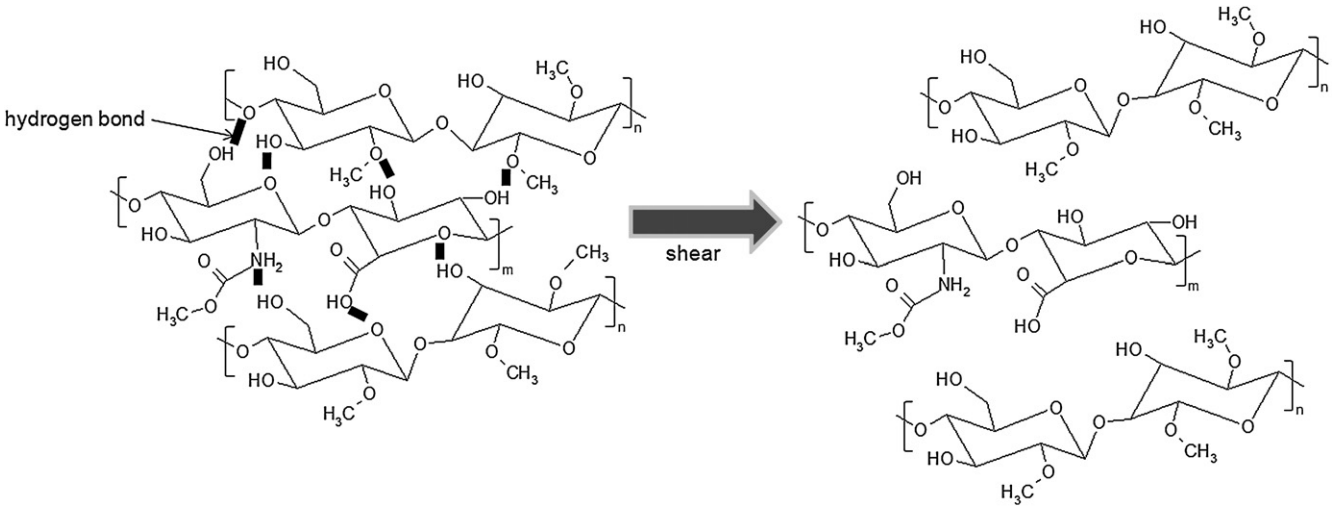

Fig. 4. *In situ* physical gelation via hydrogen bonding interactions between geometrically-compatible biopolymers (methylcellulose and hyaluronic acid); the hydrogen bonds break under shear.

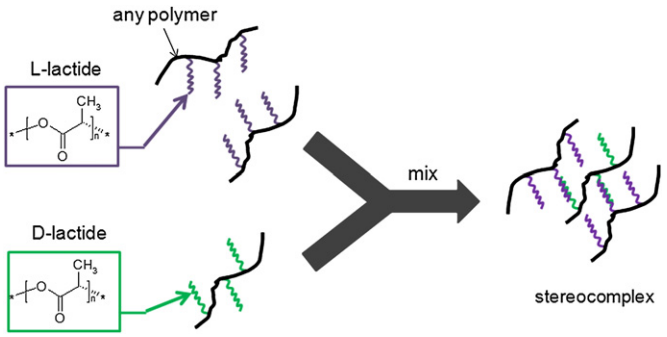

Fig. 5. Mechanism of *in situ* physical gelation via stereocomplexation between L- and D- lactide polymer chains.

compositions which can be used; even small changes in the stoichiometry or otherwise changing the composition of matter within the lactate gelators can significantly weaken or altogether eliminate the stereochemical interaction.

2.1.5. Supramolecular chemistry

A newer approach to form hydrogels *in situ* involves using specific molecular recognition motifs and/or supramolecular chemistry (i.e. the ordered arrangement of molecules into defined structures). The most common type of cross-linking interaction in this category is the formation of inclusion complexes between poly(alkylene oxide) polymers and cyclodextrins [54], as illustrated in Fig. 6. Cyclodextrins are molecules which have hydrophilic surfaces but hydrophobic pockets which are geometrically compatible with poly(alkylene oxide)-based polymers such as PEO or PPO. For example, poly(ethylene oxide)-based hydrogels can be cross-linked using alpha-cyclodextrin to form a reversible hydrogel which can be injected through a needle [55,56]. Similarly, beta-cyclodextrin can be used to gel poly(propylene oxide)-grafted dextran into a hydrogel [57]. Self-assembled systems have also been reported that apply both hydrophobic interactions and supermolecular chemistry to facilitate the formation of denser and/or more stable hydrogel networks. PEO–poly(*R*-3-hydroxybutyrate) (PHB)–PEO triblock copolymers were complexed with alpha-cyclodextrin to form strong hydrogel networks cross-linked both by the thermal gelation of the hydrophobic PHB segments and by the inclusion complexes formed between the PEO segments and cyclodextrin; this system can release FITC–dextran for up to 1 month [58].

Recognition between naturally occurring macromolecules can also be used to assemble hydrogels *in situ*. For example, interactions between glycosaminoglycans (e.g. heparin) and polymer-grafted peptide sequences extracted from heparin-binding proteins can be used to rapidly form hydrogels which exhibit drug release kinetics and degradation profiles related to the affinity between heparin and the heparin-binding peptide [59]. Thermally associating synthetic polypeptides can similarly cross-link via hydrophobic domain interactions to yield hydrogels with high mechanical strength. In this case, assembly is controlled not only by the amphiphilic amino acid sequences but also by the chain conformations of the assembling polypeptides [60], with polypeptides containing helical coiled–coil structures giving particularly strong gels [61,62]. Polypeptide-based systems are of interest given their compositional flexibility, enabling precise tuning of the gelation time, mechanical properties, and degradation time as desired to control drug release [63].

2.2. Covalently cross-linked hydrogels

While physically cross-linked hydrogels have the general advantage of forming gels without the need for chemical modification or the addition of cross-linking entities *in vivo*, they have limitations. Because the strength of a physically cross-linked hydrogel is directly related to the chemical properties of the constituent gelators, it is difficult to decouple variables such as gelation time, network pore size, chemical functionalization, and degradation time, restricting the design flexibility of such hydrogels. In addition, the tissue dwell time of physically bonded hydrogels is often poor due to dilution followed by dissipation. In contrast, covalent cross-linking prevents both dilution of the hydrogel matrix and diffusion of the polymer away from the site of injection.

Many chemistries have been explored for *in situ* cross-linking hydrogels, the most common of which are summarized in

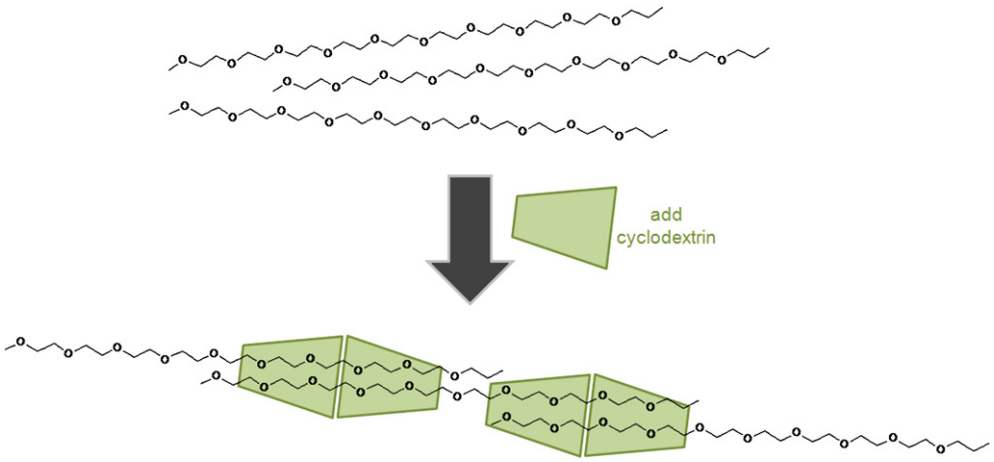

Fig. 6. Mechanism of *in situ* physical gelation via the formation of a supramolecular complex between poly(ethylene oxide) (PEO) and cyclodextrin.

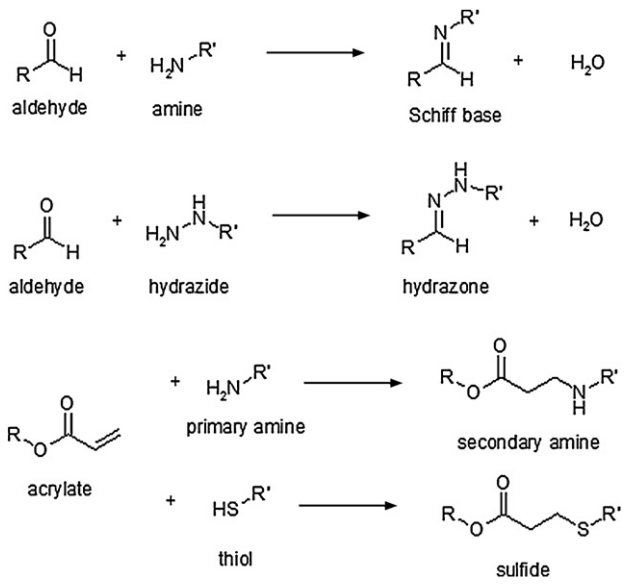

Fig. 7. Typical *in situ*-cross-linking chemistries: (a) reaction of an aldehyde and an amine to form a Schiff base; (b) reaction of an aldehyde and hydrazide to form a hydrazone; (c) Michael reaction of an acrylate and either a primary amine or a thiol to form a secondary amine or a sulfide.

Fig. 7 and are discussed below. The cross-linking groups can be added to reactive pre-polymers as small molecules or conjugated directly to them.

2.2.1. Small-molecule cross-linking

Small-molecule cross-linkers can be used to produce *in situ* cross-linked hydrogels, as illustrated by several recent examples. Dextran–tyramine [64] and hyaluronic acid–tyramine [65] hydrogels have been prepared using horseradish peroxidase and hydrogen peroxide as cross-linkers, with controllable gelation times ranging from 5 s to 9 min according to the reactant concentrations used. Human serum albumin was cross-linked with the active ester form of tartaric acid to create a highly tissue adhesive hydrogel capable of controlling doxorubicin release [66]. Periodate-oxidized sodium alginate can be rapidly cross-linked with proteins such as gelatin in the presence of low concentrations of sodium tetraborate (borax) to generate hydrogels which are suitable for delivery of primaquine and encapsulation of hepatocytes with minimal cytotoxicity [67]. Genipin (a naturally derived chemical from gardenia fruit) has also been found to efficiently cross-link amino-functionalized pre-polymers into hydrogels while exhibiting minimal toxicity to native tissues. Hydrogels based on amino-terminated PEG, *N*,*O*-carboxymethyl chitosan [68], gelatin [69], and bovine serum albumin [69] have been prepared using genipin cross-linking, with dissolution rates tailorable from 3 min to more than 100 days. The drug itself may also in some cases be used as the cross-linker. For example, primaquine (a di-amino drug) has been used to cross-link periodate-oxidized gum arabic into a hydrogel via the rapid formation of Schiff bases between the drug-bound amine groups and the aldehyde groups in the polymer [70]. This approach is restricted to cases in which the drug has two reactive functional groups available for functional group chemistry. A general disadvantage of each of these small-molecule cross-linking methods is the potential toxicity of residual unreacted small-molecule cross-linkers. For example, glutaraldehyde is often used to form carbohydrate-based hydrogels [71] but is also a tissue fixative.

2.2.2. Polymer–polymer cross-linking

Polymers pre-functionalized with reactive functional groups avoid the use of potentially toxic small-molecule cross-linking agents. The main limitation of this approach is that significant polymer modification chemistry may be required to prepare the functionalized pre-polymers. In addition, the pre-gel polymers are often themselves somewhat cytotoxic, even when prepared from highly biocompatible polymer precursors. While this problem is largely mitigated during gel formation due to the rapidity of cross-linking and the multiple functional groups attached to each polymer precursor (reducing the probability of unreacted residual polymers), such toxicity could become problematic as the polymer degrades to form potentially tissue-reactive oligomers.

Several types of linkages can be made depending on the desired speed of cross-linking and biodegradability of the resulting conjugates. The formation of a hydrazone bond – an asymmetric Schiff base – via the reaction of an aldehyde and a hydrazide facilitates rapid cross-linking of gel precursors [72]. We have used hyaluronic acid cross-linked by hydrazone bonds to provide prolonged-duration local anesthesia [73] and to control the release of tissue plasminogen activator [74] and budesonide [74] to the peritoneum. Similar approaches have been used to design hydrogels based on dextran [75], poly(vinyl alcohol) [76] and poly(aldehyde guluronate; an oxidized alginic acid derivative) [77]. The latter has been used as an injectable matrix for the effective delivery of osteoblasts and growth factors [77].

Michael addition between a nucleophile (i.e. an amine or a thiol) and a vinyl group is another widely investigated *in situ* cross-linking chemistry which is particularly useful for *in situ* cross-linking hydrogels due to its rapid reaction time, its flexibility in forming multiple types of bonds, and the relative biological inertness of the polymeric precursors. Michael addition has been used to cross-link vinyl sulfone-functionalized dextrans with thiolated poly(ethylene glycol), with gel formation occurring over 0.5–7.5 min according to the properties of the functionalized polymers [78]. A PEG diacrylate can be used to cross-link dithiolated PEG [79] or thiolated natural polymers including hyaluronic acid, chondroitin sulfate, and gelatin [80] with gelation times ranging from 2 to 6 min [80]. As an example, a mixture of thiol-modified heparin and thiol-modified hyaluronic acid can be gelled with PEG diacrylate to form a hydrogel which can prolong the release of basic fibroblast growth factor *in vivo* [81]. A thiolated peptide has also been used to cross-link methacrylated hyaluronic acid using the same chemistry, although reported gelation times exceeded 30 min [82]. Efficient design of Michael addition cross-linked hydrogels is further facilitated by the development of kinetic modeling approaches for predicting the rates of hydrogel formation and degradation [83] and/or the release

kinetics of model proteins entrapped or covalently bonded to the hydrogel network [84]. Such model approaches have considerable potential for the bottom-up design of future drug delivery vehicles.

Other types of injectable hydrogel delivery strategies have been reviewed comprehensively elsewhere [85–87]. Many have yet to be evaluated for drug delivery and may offer additional advantages compared to current chemistries. The simpler the process in terms of chemistry and the need for accessory equipment, the better.

Although the preceding discussion focused on the potential toxicity of various cross-linking approaches, both local and systemic toxicity can also arise from the rapid release of the drug payload itself. For example, local tissue injury from cross-linked hyaluronic acid hydrogels containing the local anesthetic bupivacaine was entirely due to the drug [88]. This could also be an issue with the release of macromolecules such as proteins. However, drug toxicity is neither specific to, nor acutely more problematic in, hydrogel-based systems compared to other drug delivery approaches.

2.3. Optimization of in situ gelling hydrogels

Successful optimization of injectable hydrogels must consider several factors. The concentration of the polymers used to prepare the gel influences both the diffusion-based drug release kinetics and the degradation time of the hydrogel. However, the concentration of polymers or their functionalized derivatives is often limited by the aqueous solubility of the gel precursors or the resulting high viscosity of the solutions, although the concentration can be increased when lower molecular weight gel precursors are used. The rate of *in situ* cross-linking is determined by the underlying chemical kinetics of the cross-linking reaction, the ease of diffusion of the polymer precursors through the partially viscous pre-gel solution, and the concentration of polymers used to prepare the hydrogel. Different rates of gelation may be desirable in different applications. Fast-gelling formulations may be advantageous in surgical settings and may entrap drugs more effectively to delay release; slower-gelling formulations may give the mucoadhesive pre-polymers time to penetrate the surrounding tissues and enhance bioadhesion. The cross-linking density in the hydrogels can be controlled by the amount of small-molecule cross-linker added and/or the density of reactive functional groups on the gel precursors. Higher cross-linking densities result in hydrogels with smaller mesh sizes, thereby reducing the release rate of entrapped drugs; however, the high degree of chemical modification required to form gels with high cross-link densities can significantly alter the physical properties of the base hydrogel, particularly in terms of the drug–hydrogel affinity or mechanical strength of the gel. Thus, trade-offs must be made in the hydrogel design according to the targeted application of the drug-eluting hydrogel.

Applying *in situ* gelling hydrogels can be awkward clinically. The interacting or reactive gel precursors may have to be kept separate prior to injection by use of a double-barreled syringe or some other device. Depending on the gelation time, injection may have to be done in haste as the needle may become clogged as the polymers heat up or react. This may prevent injection of part of or all of the gel, a major problem particularly if the placement of the needle itself was difficult. Triggered release of the cross-linker *in vivo* may help to address this problem. For example, liposomes are designed to rupture at physiological temperature and release calcium ions effectively cross-linked aqueous sodium alginate via ionic interactions and fibrinogen via the *in situ* activation of a calcium-dependent transglutaminase enzyme [89].

3. Extending the effectiveness of hydrogels for drug delivery

The high water content of most hydrogels typically results in relatively rapid release of drugs from the gel matrix over the period of hours or days, particularly in the case of hydrophilic drugs for which hydrogel delivery is typically applied. This release profile is much shorter than those which can be achieved using microspheres or macroscopic devices based on more hydrophobic polymers (for example, PLGA). In response, a range of strategies have been explored to reduce the release rate of drug from hydrogels. These strategies can be categorized by whether they enhance the interactions between the drug and the hydrogel matrix and/or increase the diffusive barrier to drug release from the hydrogel.

3.1. Drug–hydrogel interactions

Both physical and chemical strategies can be employed to enhance the binding between a loaded drug and the hydrogel matrix to extend the duration of drug release, as illustrated schematically in Fig. 8.

3.1.1. Physical interactions

Charge interactions between ionic polymers and charged drugs have frequently been employed to increase the strength

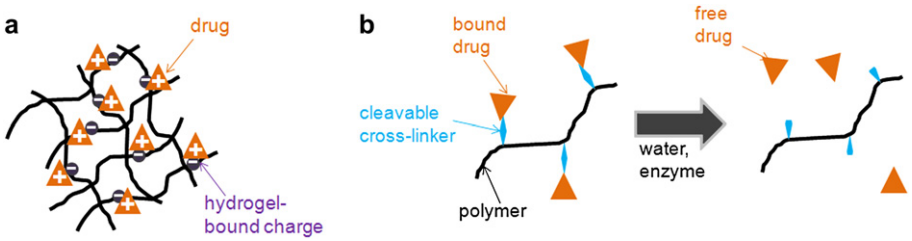

Fig. 8. Physical (a) and chemical (b) strategies for enhancing the interaction between a loaded drug and a polymeric gel to slow drug release.

of the interactions between the gel and a target drug to delay drug release. Phosphate-functionalized polymers are effective because of their multivalent anionic charge. Phosphate-containing soft contact lenses can bind the cationic drug naphazoline in quantities directly proportional to the phosphate content [90]. Similarly, the uptake of cationic lysozyme into *N*-isopropylacrylamide-based hydrogels functionalized with polyoxyethyl phosphate-containing comonomer is significantly enhanced compared to non-functionalized PNIPAM hydrogels [91]. Amino functional groups can similarly be applied to delay the release of anionic drugs. For example, copolymerization of 4-vinylpyridine or *N*-(3-aminopropyl)methacrylamide increased the loading of NSAIDs into a poly(hydroxyethyl methacrylate) hydrogel by more than one order of magnitude and prolonged drug release up to 1 week without changing the mechanical properties of the network [92].

Both anionic and cationic functional groups typically found in carbohydrate-based polymers can have significant effects on prolonging the release of a drug of opposite charge [93]. Amino acid-modified gelatin hydrogels slow down the release of lysozyme and trypsin inhibitor protein to an extent directly proportional to the strength of the charge interactions between the amino acid chain and the entrapped proteins [94]. Charge interaction has also been cited as one of the reasons for using hyaluronic acid as a delivery vehicle for local anesthetics, the others being viscosity and biocompatibility [95]. Hyaluronic acid is anionic, while most local anesthetics are cationic in aqueous solution. However, the literature regarding the use of hyaluronic acid with local anesthetics shows a range of results, from marked [96] or modest [95] prolongation of effect to none [97]. This variability is likely due to differences in formulation (concentration, molecular weight, viscosity) and animal model which may affect the effectiveness of charge–charge interactions for prolonging drug release.

As an alternative, monomers or polymers with specific non-ionic affinities to particular drugs can be copolymerized into hydrogels to delay or enhance the release of drugs. The antifungal drug amphotericin B has a strong interaction with photocross-linked dextran-based hydrogels, allowing contact killing of fungi for 2 months [98]. Amphotericin B did not bind to PEG-derived hydrogels of the same chain density. The exact molecular binding mechanism remains unclear.

3.1.2. Covalent bonding

Drugs can also be covalently conjugated to the hydrogel matrix such that their release is primarily controlled by the rate of chemical or enzymatic cleavage of the polymer–drug bond. For example, dexamethasone has been conjugated to a photoreactive mono-acrylated PEG through a degradable lactide bond to facilitate osteogenic differentiation of human mesenchymal stem cells [99], and daunomycin cross-linked to poly(aldehyde guluronate) was released over periods ranging from 2 days to 6 weeks according to the hydrolysis rate of the drug–polymer covalent linkage [100]. Alternately, drug release may be regulated via the hydrolysis of the polymer backbone, possibly inducing the release of a partially modified drug analogue. For example, methacrylic-functionalized non-steroidal anti-inflammatory drugs have been conjugated to methacrylic-functionalized dextrans via UV irradiation; a chemically modified drug analogue is released as the dextran hydrogel degrades [101]. The cross-linker can be engineered to give specific durations of release. For example, by changing the length of a sulfide-based cross-linker from three to four carbons, the time required to release bound paclitaxel from a hydrogel was increased from approximately 4 days to 2 weeks [102].

3.2. Gel network engineering

Several approaches have been explored to control the diffusion of drugs out of hydrogel matrices by modifying the microstructure of the hydrogel, either throughout the full gel network or locally at the hydrogel surface. A simple method of performing such modifications is to increase the percentage of cross-linking monomer incorporated into the gel. However, highly cross-linked gels exhibit very slow responses to environmental stimuli and may possess undesirable mechanical properties. As a result, more sophisticated strategies may be required.

3.2.1. Interpenetrating polymer networks (IPNs)

An interpenetrating polymer network is formed when a second hydrogel network is polymerized within a pre-polymerized hydrogel. This is typically done by immersing a pre-polymerized hydrogel into a solution of monomers and a polymerization initiator. IPNs can be formed either in the presence of a cross-linker to produce a fully interpenetrating polymer network (full IPN) or in the absence of a cross-linking mechanism to generate a network of embedded linear polymers entrapped within the original hydrogel (semi-IPN), as illustrated in Fig. 9. The main advantages of IPNs are that relatively dense hydrogel matrices can be produced which feature stiffer and tougher mechanical properties, more widely controllable physical properties, and (frequently) more efficient drug loading compared to conventional hydrogels. Drug loading is often performed in conjunction with the polymerization of the interpenetrating hydrogel phase [103].

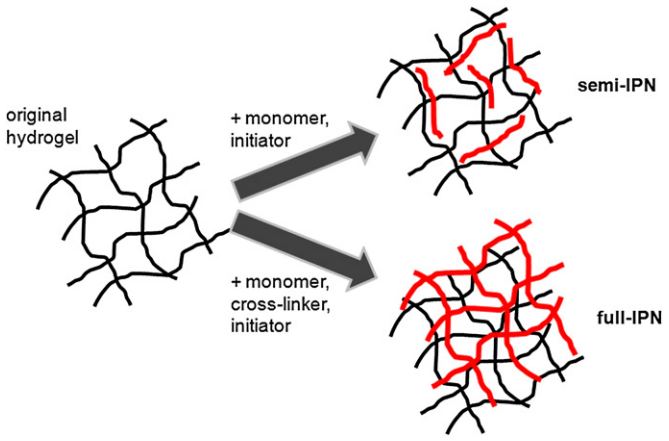

Fig. 9. Formation and structure of semi- and full interpenetrating polymer networks (IPN).

IPN pore sizes and surface chemistries can also be controlled to tune the drug release kinetics, the interactions between the hydrogel and the tissues, and the mechanical properties of the gel [104]. Interpenetrating phases with different degradation profiles and/or different swelling responses to physiological conditions can be used to provide multiple controls over the swelling responses of hydrogels and thus the potential drug release kinetics [105]. IPNs can also moderate the effect of environmental changes on hydrogel responses and burst drug release because of their ability to restrict the equilibrium swelling of either or both of the interpenetrating phases according to the elasticity (i.e. cross-linking density) of either or both gel phases. For example, a highly cross-linked interpenetrating network of a pH-sensitive hydrogel and a hydrolysable hydrogel restricts the typically rapid swelling response of a pH-swelling hydrogel to facilitate linear swelling profiles following an abrupt pH change from pH 7.4 to 2 [106]. Such responsivity is particularly suitable for minimizing burst release of drugs in oral drug delivery applications. As another example, a lightly cross-linked chitosan–PNIPAM interpenetrating network significantly increased the loading capacity of diclofenac compared to a pure PNIPAM hydrogel while maintaining the sharp thermosensitivity of the PNIPAM phase to regulate the release kinetics [107].

Semi-IPNs can more effectively preserve rapid kinetic response rates to pH or temperature (due to the absence of a restricting interpenetrating elastic network) while still providing most of the benefits of IPNs in drug delivery (e.g. modifying pore size, slowing drug release, etc.). For example, entrapping linear cationic polyallylammonium chloride in an acrylamide/acrylic acid copolymer hydrogel imparted both higher mechanical strength and fully reversible pH switching of theophylline release [108].

3.2.2. Surface diffusion control

As an alternative to changing the bulk structure of a hydrogel, surface-specific modifications can be performed to generate a reduced-permeability "film" layer at the hydrogel surface, often in conjunction with a thermosensitive switch for on–off drug release. Drug diffusion control via this mechanism is illustrated in Fig. 10. By this mechanism, thermosensitive PNIPAM polymers can be grafted onto the surface of hydrogels to provide temperature-dependent surface permeability and thus release kinetics [109]. Drug release is rapid at low temperatures but is significantly slowed at higher temperatures as the thermosensitive polymer undergoes a phase transition and collapses onto the hydrogel surface. Alternately, a drug-loaded hydrogel can be coated with a dense polyelectrolyte multilayer film [110], limiting drug diffusion out of the bulk hydrogel. The rate of diffusion can be designed to be dependent on the pH of the medium, the degradation rate of the film, or the environmentally controlled swelling state of the coated hydrogel, which can exert mechanical pressure on the coating to cause film rupture and thus burst drug release at a targeted condition [111].

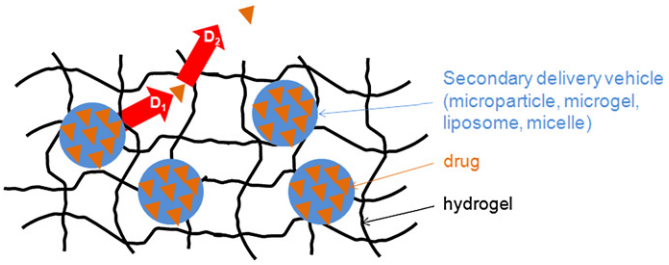

Fig. 11. "Plum pudding", composite hydrogels containing drug encapsulated in a secondary controlled release vehicle (e.g. microparticles, nanoparticles, microgels, liposomes, micelles). D_1 and D_2 represent the diffusion coefficients of drug out of the hydrogel (D_1 = release from secondary release vehicle; D_2 = diffusion through hydrogel).

3.2.3. Composite hydrogels

Microspheres, liposomes, and other types of particle-based drug delivery vehicles have proven capacity for long-term release. As a result, growing interest has focused on overcoming the inherent pharmacological limitations of hydrogels by co-formulating particulate systems into the hydrogel matrix to form composite or "plum pudding" hydrogel networks, as illustrated in Fig. 11.

The formation of composite hydrogel drug release vehicles may increase the biocompatibility of the particulate vehicle by "hiding" the microparticles within the hydrogel while also preventing microparticle migration away from their targeted site *in vivo*. Poly(lactic-*co*-glycolic acid) nanoparticles can be incorporated within a cross-linkable hyaluronan-based hydrogel matrix without compromising the biocompatibility or anti-adhesion properties of the hyaluronic acid carrier [112], facilitating the incorporation of a wider array of anti-adhesion drugs within the matrix. The hydrogel phase may also improve the kinetic release profile of microspheres by providing an additional diffusion barrier to drug release, moderating or eliminating the burst release typically observed with microspheres and extending release of drugs [9,73].

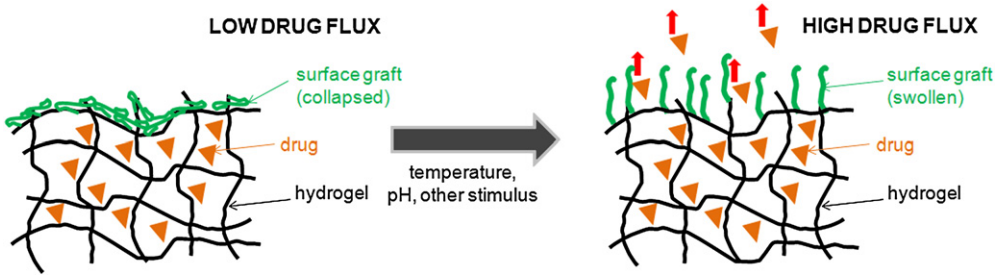

Fig. 10. Drug diffusion control by surface-modifying a hydrogel with an environmentally-responsive polymer graft.

Physically cross-linked hydrogels are commonly used as the particle entrapment matrix. For example, PLGA microparticles entrapped in a reverse thermally gelled PNIPAM-*g*-chitosan matrix released 5-fluorouracil with minimal burst and near zero-order release kinetics [23], poloxamer 407 has been used to extend the duration of nerve blockade from lidocaine-containing microparticles by a few hours [9], and PLGA particles entrapped in a poly(vinyl alcohol) hydrogel achieved approximately zero-order release of dexamethasone over a period of 1 month [113].

Liposomes can also be entrapped in hydrogels. Liposomes entrapped in carbopol and hydroxyethylcellulose-based hydrogels can control the release of calcein and griseofulvin according to the rigidity of the liposomal membrane [114], while liposomes entrapped in poly(hydroxyethyl methacrylate) hydrogels mimicking contact lenses can control the release of anti-glaucoma drugs for up to 8 days [115]. *In situ* gelling, physically cross-linked hydrogels can also be prepared to entrap liposomes. When a poly(*N*-isopropylacrylamide) solution is mixed with liposomes surface-functionalized with a copolymer of NIPAM and octadecylacrylate, a physically cross-linked gel can be formed at temperatures in excess of 30 °C which exhibits increasing drug release with increasing temperature [116].

The microparticles entrapped within the hydrogel can themselves be gel-based (microgels). For example, gelatin microparticles entrained in a thermal-gelling poly(ethylene glycol fumarate) matrix delivered TGF-beta 1 for cartilage tissue repair [117]. As with other particle types, multiple types of gel microparticles can be entrapped in the same hydrogel matrix to deliver multiple drug payloads; for example, an *N*-isopropylacrylamide–*N*-*tert*-butylacrylamide (NIPAM–BAM) microgel can deliver pyrene while a NIPAM–BAM–acrylic acid copolymer microgel can deliver rhodamine B at controllable rates [118]. Microgels can also be cross-linked directly, without an encapsulating bulk hydrogel phase, to form a hierarchal gel network which permits dual tuning of drug release and degradation according to the structure and composition of the individual microgel particles and the density and cross-linking chemistry of the macroscopic nanoparticle network [35].

Surfactant-stabilized microemulsion droplets [119], surfactant micelles [93], and polymeric micelles [120] can similarly be entrapped in hydrogel networks to provide prolonged drug release. Polymeric micelles based on block copolymers have particular promise due to their lower toxicity given the absence of small-molecule surfactants or organic solvents. For example, poly(*N*-isopropylacrylamide)-*block*-poly(methyl methacrylate) micelles entrapped inside a poly(*N*-isopropylacrylamide) hydrogel can release prednisone acetate in a controlled manner according to the temperature of the thermosensitive hydrogel network [121].

4. Expanding the range of drugs amenable to hydrogel-based delivery

Classically, hydrogels have been used to deliver hydrophilic, small-molecule drugs which have high solubilities in both the hydrophilic hydrogel matrix and the aqueous solvent swelling the hydrogel. In this case, it is relatively simple to load a high quantity of drug into a swollen hydrogel by simple partitioning from a concentrated aqueous drug solution and subsequently release the hydrophilic drug payload into an aqueous environment. However, this process is relatively inefficient in the case of large macromolecular drugs (e.g. proteins, nucleic acids, etc.) which have diffusive limitations to their partitioning into a hydrogel phase or hydrophobic drugs which are sparingly soluble in both the aqueous and the hydrogel phases. Both of these classes of drugs, however, are becoming increasingly important clinically as a result of improved understanding of the molecular basis of disease and the more frequent application of molecular design approaches for small-molecule drug design. Macromolecular drug uptake is typically restricted by the diffusion of the macromolecular drug payload through the hydrogel network and thus can be addressed at least partially by engineering the pore size of hydrogels, as described in Section 3.2. Hydrogel-based hydrophobic drug delivery is in many respects a more difficult problem given the inherent incompatibility of the hydrophilic hydrogel network and the hydrophobic drug. Thus, the problem of hydrophobic drug delivery is two-fold: how to load the hydrophobic drug into the gel matrix and, once present, how to effectively release the drug into the aqueous gel environment.

A variety of strategies have been used to improve hydrophobic drug loading into hydrogels. One simple approach is to form a solid molecular dispersion of a poorly soluble drug, exploiting the enhanced solubility of many hydrophobic compounds in the amorphous state rather than the crystalline state [122]. By this strategy, drugs are loaded into hydrogels in an appropriate solvent and bind strongly to the polymer chains in the hydrogel via hydrogen bonding interactions, preventing drug re-crystallization when the hydrogels are exposed to water and enhancing release of the hydrophobic drug. However, drug re-crystallization typically occurs over time, limiting the commercial use of solid molecular dispersions. Any of the composite hydrogel strategies outlined in Section 3.2.3 could be useful for hydrophobic drug delivery. However, such systems can be complex to fabricate and deliver. Instead, a variety of strategies for introducing hydrophobic domains directly into otherwise hydrophilic hydrogel networks have permitted significant improvements in the loading of hydrophobic drugs. These basic strategies are illustrated schematically in Fig. 12 and are reviewed below.

4.1. Incorporation of hydrophobic sites

The most common approach for generating hydrophobic domains within hydrogels is the copolymerization with hydrophobic comonomers, introducing statistically distributed hydrophobic sites within the networks. This strategy introduces binding sites for hydrophobic drugs and condenses the bulk dimensions of the gel, reducing the average pore size and slowing diffusion-limited release. In one approach, *n*-(meth)-acrylate esters of varying chain lengths are copolymerized

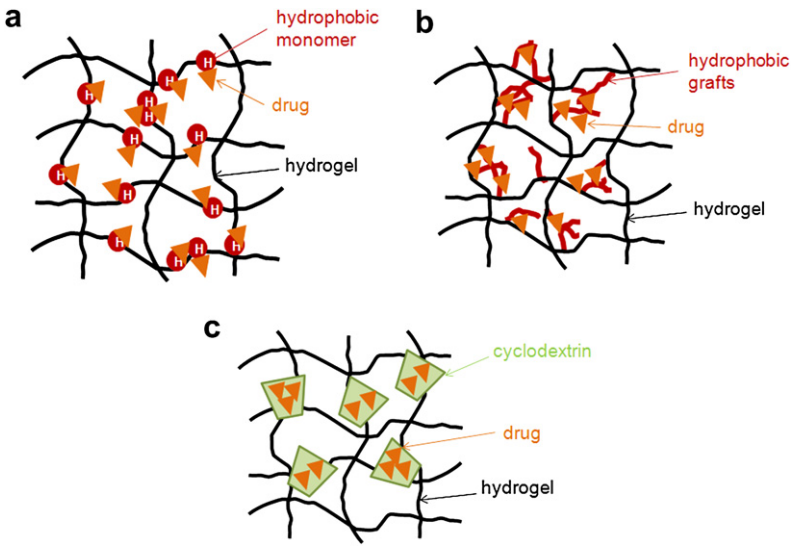

Fig. 12. Strategies for hydrophobic drug delivery via hydrogels (a) random copolymerization of a hydrophobic monomer; (b) grafting of hydrophobic side-chains; (c) incorporation of cyclodextrin.

with vinyl comonomers, often in conjunction with degradable cross-linkers (e.g. azobenzenes [123]), to achieve the hydrophobic modification. For example, copolymerization of acrylic acid-2-ethylhexyl ester in a methacrylic acid-based hydrogel improves the loading of *p*-hydroxyanisole and extends its release from the hydrogel independent of pH [124]. Fluorine-containing polymers can also be applied as the hydrophobic modifier. For example, a copolymer gel of *N*,*N*-dimethacrylamide and 2-(*n*-ethyl-perfluorooctanesulfonamido) ethyl acrylate prolongs the release of the ocular antihistamine pheniramine maleate [125]. Hydrophobic macromonomers can also be incorporated into hydrogels. For example, a copolymer of allyl-functionalized dextran and poly(lactide) diacrylate macromonomer increased indomethacin loading and could control the release rate of indomethacin according to the rate of poly(lactide) degradation [126].

More recently, molecular design approaches have been applied to maximize the affinity of a polymer-bound hydrophobic domain for a particular drug target while minimizing the non-specific binding of other hydrophobic compounds in the gel environment. Bulk screening of a range of different small molecules with hydrophobic binding properties can identify those which bind most strongly to a given drug. For example, paclitaxel loading can be improved 700-fold over its aqueous solubility when a self-assembled hydrogel of linear polymers based on picolylnicotinamide (identified as an optimum paclitaxel binder via a bulk screening process) was used as the drug-eluting hydrogel [127].

Alternately, hydrogel networks can be modified to generate hydrophobic domains with more localized and controllable distributions. Hydrophobic side chains can be grafted onto the polymer precursors which can self-assemble to form hydrophobic domains within the bulk hydrogel network and bind hydrophobic drugs; this approach has been demonstrated with octyl-modified carboxymethylpullulan [128]. Semi-interpenetrating networks can also be prepared by entrapping a partially hydrophobic hydrogel phase (i.e. PEG–PCL diacrylate macromer) within a hydrophilic precursor hydrogel (hydroxypropyl guar gum), improving the mechanical properties of the hydrogel while prolonging the release of bovine serum albumin [129]. Similarly, the entrapment of poly(ethyl acrylate) in a functionalized poly(*N*-isopropylacrylamide) matrix slowed the release of daidzein and significantly moderated the burst release of drug typically observed from PNIPAM matrices [130].

4.2. Cyclodextrins

The main problems with rendering the hydrogel hydrophobic via grafting, copolymerization, or IPN-based approaches are the significant hydrogel deswelling and delocalized surface and bulk hydrophobicity which are introduced into the gel network, potentially reducing the biocompatibility and/or the low protein binding properties of hydrogels. Cyclodextrins are of interest in this context given their hydrophilic exterior, which is useful for maintaining the bulk hydrophilicity and swelling state of the hydrogel, and their hydrophobic interior, which can facilitate the entrapment and controlled release of hydrophobic drugs. Cyclodextrin-containing hydrogels can be prepared in many ways. Most simply, preformed cyclodextrin–drug complexes can be loaded into the hydrogel after [131] or during [132] gel cross-linking. However, this strategy may result in the diffusion of the drug–cyclodextrin inclusion complex out of the hydrogels, leading to non-optimal control over release kinetics. Grafting cyclodextrin to the hydrogel provides improved control over drug release kinetics. Copolymerization of a vinyl monomer (acrylic acid [133], *N*-isopropylacrylamide [134], or 2-hydroxyethyl acrylate [135]) with an acrylamidomethyl- or acryloyl-functionalized cyclodextrin can facilitate the loading and release of triamcinolone acetonide [133], ibuprofen [134], or melatonin [135]. Alternately, cyclodextrins can be cross-linked directly using digylcidyl-ethers to form a hydrogel. This strategy improved the loading

of estradiol approximately 500-fold compared to that achieved by simple aqueous partitioning into hydrogels of similar composition and water contents and resulted in release of a therapeutic level of drug for up to a week [136].

5. Conclusion and future perspective

Significant progress has been made in improving the properties of hydrogels used for drug delivery and expanding the range of drugs and kinetics which can be achieved using a hydrogel-based delivery vehicle. However, several challenges remain to improve the clinical applicability of hydrogels for drug delivery.

One set of major challenges relates to improving the ease of clinical usage. Designing physical gelators which gel at lower polymer concentrations and at more precise gelation temperatures would reduce the risk of premature gelation inside the needle upon injection. Similarly, for covalently cross-linked hydrogels, the further development of strategies to release cross-linker in a triggered manner inside the body would minimize the risk of syringe clogging, improve the localization of cross-linker release to minimize *in vivo* toxicity, and enable mixing of the chemically reactive gel precursors in a single syringe, eliminating the need for double-barreled syringes. Improvements in this domain could also be achieved by developing better applicator systems for the hydrogels. The application of new physicochemical strategies (or combinations of existing cross-linking techniques) to simultaneously control not only the gelation process but also the interactions between the gel and the native tissues would further expand the utility of injectable hydrogels for both drug delivery and tissue engineering-based applications.

There are also persistent challenges in expanding the types of kinetic release profiles which can be achieved using hydrogels. Extending the duration of release would be useful in many applications and could allow hydrogels to supplant hydrophobic systems for long-term release applications. This would be beneficial because of the better biocompatibility of hydrogels. The development of hydrogel-based systems where the rate of drug delivery could be easily modulated on–off over time could also be of benefit for applications requiring varying doses of a drug over time (e.g. delivery of insulin or analgesics). Hydrogels with different degradation profiles and/or environmentally responsive segments may help to address these kinetic issues.

There is a need for continued improvement in the delivery of not only hydrophobic molecules, but also the delivery of more sensitive molecules such as proteins, antibodies, or nucleic acids which can readily be deactivated or unfolded by interactions with the hydrogel delivery vehicle. This is a particular issue with *in situ* cross-linking hydrogels, in which the hydrophobic domains formed in thermal, physically gelling polymers or the functional group chemistry used to form covalently gelling hydrogels can significantly affect the biological activity of the entrapped biomolecule. Pre-encapsulation or complexation of biomolecules prior to *in situ*-hydrogel formation may help to address this issue.

Progress on any or all of these challenges would greatly expand the potential of hydrogel-based drug delivery to successfully deliver the next generation of designed drugs at the desired rate and location in the body. In addition, there are many broad and niche applications not covered in this review where there is ample room for progress. As in many branches of drug delivery, it is likely that "convergence" [137] – the merging of once disparate fields of science – will guide the future development of drug-eluting hydrogel design.

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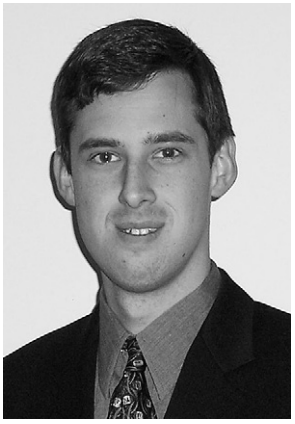

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