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Review Article

A Review on Hydrogels and Its Use in *In Situ* Ocular Drug Delivery

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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.

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, cellular immobilization, separation of biomolecules or cells, and barrier materials to regulate biological adhesions [2].

Hydrogels show minimal tendency to adsorb proteins from body fluids because of their low interfacial tension. Further, the ability of molecules of different sizes to diffuse into (drug loading) and out of (drug release) hydrogels allows the possible use of dry or swollen polymeric networks as drug delivery systems for oral, nasal, buccal, rectal, vaginal, ocular and parenteral routes of administration. Several terms have been coined for hydrogels, such as 'intelligent gels' or 'smart hydrogels' [3]. The smartness of any material is the key to its ability to receive, transmit or process a stimulus, and respond by producing a useful effect [4]. Once acted on, stimuli can result in changes in phases, shapes, optics, mechanics, electric fields, surface energies, recognition, reaction rates and permeation rates. Hydrogels are 'smart' or 'intelligent' in the sense that they can perceive the prevailing stimuli and respond by exhibiting changes in their physical or chemical behavior, resulting in the release of entrapped drug in a controlled manner [5].

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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 e 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, 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 the current niche of drug delivery technologies, hydrogels have made an irreplaceable space because of their unique characteristics. This review presents a brief introduction to hydrogels, their application for controlled drug delivery and ophthalmic drug delivery

Gels versus hydrogels

Technically, gels are semi-solid systems comprising small amounts of solid, dispersed in relatively large amounts of liquid, yet possessing more solid-like than liquid-like character [8]. Sometimes, hydrogels are also described as aqueous gels because of the prefix 'hydro'. Although the term 'hydrogel' implies material already swollen in water, in a A common misinterpretation in polymer science is the use of the terms 'gel' and 'hydrogel' synonymously. As polymeric networks, both gels and hydrogels might be similar chemically, but they are physically distinct. Dorothy Jordan Lloyd aptly described gels as; true sense hydrogels are a cross-linked network of hydrophilic polymers. They possess the ability to absorb large amounts of water and swell, while maintaining their three-dimensional (3D) structure [7]. This definition differentiates hydrogels from gels, which are polymeric networks already swollen to equilibrium, and the further addition of fluids results only in dilution of the polymeric network (Fig. 1). Although some of the gels are rigid enough to maintain their structure under a small stress, after exceeding the yield-value, gel fluidity is observed with loss of polymer structure. A hydrogel exhibits swelling in aqueous media for the same reasons that an analogous linear polymer dissolves in water to form an ordinary polymer solution. Thus, the feature central to the functioning of a hydrogel is its inherent cross-linking. Conventional gels can also develop small levels of cross-links as a result of a gain in energy under the influence of shear forces, but this is reversible because of the involvement of weak physical forces. Because polymeric systems are analogous to each other, several misrepresentations exist in their nomenclature, which can be prevented by a thorough understanding of their physical, chemical, mechanical and behavioural characteristics.

HYDOGELS FOR OCULAR DELIVERY

One of the main problems encountered in ophthalmic drug delivery is the rapid and extensive elimination of conventional eye drops from the eye. This process results in extensive drug loss. Consequently, only a small amount (1 - 6%) actually penetrates the cornea and reaches the intra ocular tissues. [9, 10]

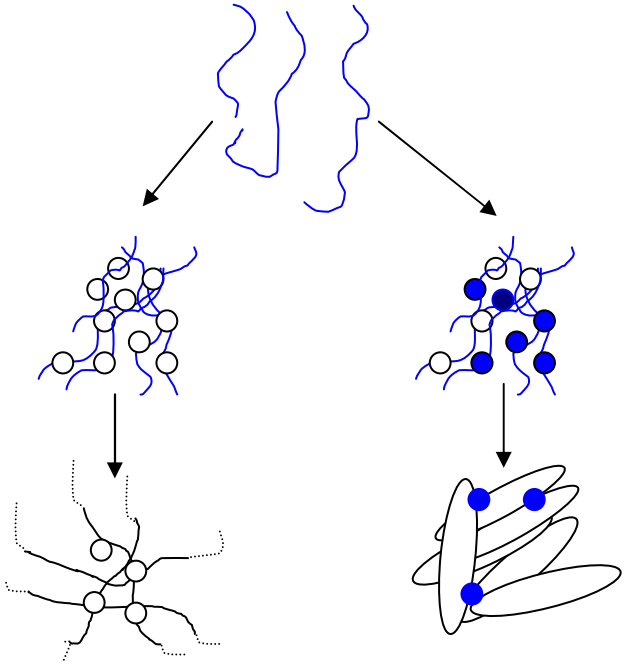

Figure 1: Polymer strands forming a gel and a hydrogel, showing different behaviour in an aqueous environment. Solid circles represent covalent cross-links and hollow circles represent virtual cross-links formed by entanglements.

The reason for this inefficient drug delivery includes rapid tear turnover, lachrymal drainage and drug dilution by tears. [11] The higher drainage rate is due to tendency of the eye to maintain its residence volume at 7-10 µl permanently, whereas volumes of topically instilled range from 20-50µl. It has been demonstrated *in vivo* that 90% of the dose was cleared within 2 min. for an instilled volume of 50µl [12]. Consequently, the ocular residence time of conventional solution is limited to few minutes, and the overall absorption of a topically applied drug is limited to 1-10% [13]. Consequently, most drugs get systemically absorbed via the nose or gut after draining from eye.

This excessive systemic absorption not only reduces the ocular bioavailability but also may lead to unwanted side effects and toxicity.

The following characteristics are required to optimize ocular drug delivery systems. [14]

- A good corneal penetration.
- A prolonged contact time with corneal tissue.
- Simplicity of installation for the patient.
- A non-irritative and comfortable form (the viscous solution should not provoke lachrymation and reflex blinking).
- Appropriate rheological properties and concentration of viscolyzer.

Some common methods to prolong pre-corneal residence time include use of Hydrogels, Liposomes, Inserts, Micro and Nano-carrier systems. In comparison with traditional formulation, theses systems have the following advantages:

- Increase contact time
- Prolonged drug release

- Reduced systemic side effects
- Reduced number of applications
- Better patient compliance

Over the last three decades greater attention has been focused on development of controlled and sustained drug delivery systems. The goal in designing these systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, decreasing the dose required or providing uniform drug delivery. Polymers have historically been the keys to the great majority in drug delivery systems.

The most common way to improve drug retention on the corneal surface is undoubtedly by using polymers to increase solution viscosity. Previous studies on rabbits by Robinson et al [15] established that the rate of drainage from the eye of an instilled solution is markedly reduced as the viscosity of the solution is increased. More recently, the approach to improve pre-corneal retention is based on the use of mucoadhesive polymers that are able to interact with the mucin-coating layer present at the eye surface. [16]

Hydrogels can be defined as polymers endowed with the ability to swell in water or aqueous solvents and induce a sol-gel transition and are stimuli responsive (Fig. 2). However, in ophthalmology the limit between actual hydrogels and highly viscous solution is not clearly established. According to plazonnet et al, [17] aqueous gels are at the upper limit of viscous preparations, and they are formed when high molecular weight polymers or high polymer concentrations are incorporated in the formulations.

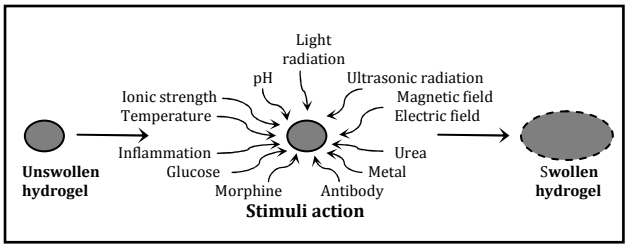

Figure 2: Stimuli responsive swelling of hydrogels

Currently, two groups of hydrogels are distinguished, namely preformed and *in situ* forming gels. Preformed hydrogels can be defined as simple viscous solutions, which do not undergo any modifications after administration, while *in situ* forming gels are formulations, applied as a solution, which undergoes gelation after instillation due to physico-chemical changes inherent to the eye.

The polymers chosen to prepare ophthalmic hydrogels should meet some specific rheological characteristics (Table 1). It is generally well accepted that the instillation of a formulation should influence tear behavior as little as possible [18]. Because tears have a pseudoplastic behavior, pseudoplastic vehicles would be more suitable as compared to the Newtonian formulations, which have a constant viscosity independent of the shear rate. Pseudoplastic solutions exhibit decreased viscosity with increasing shear rate thereby offering lowered viscosity during blinking and stability of the tear film during fixation.

Table 1: Characteristics of polymers used to prepare preformed Hydrogels for Ophthalmic applications

Polymer	Origin	Characteristics
Sodium hyaluronate	Skin, Connective tissues, muscles, tendons, Aqueous humor, Vitreous humor	Biocompatible, Mucoadhesive Pseudoplastic behavior
Cellulose derivatives	Semi-synthetic	Good tolerance, Optical clarity Newtonian Behavior
Poly vinyl alcohol	Synthetic	Wetting agent, Newtonian behavior
Carbomer	Synthetic	Good tolerance, Bioadhesion Pseudoplastic behavior

pH-sensitive hydrogels

Gelling of the solution is triggered by a change in the pH. Cellulose acetate phthalate (CAP) latex, cross linked acrylic, and derivatives such as Carbomer are used. [19] Cellulose acetate derivatives are the only polymer known to have a buffer capacity that is low enough to gel effectively in the cul-de-sac of the eye. The pH change of about 2.8 units after instillation of the native formulation (pH 4.4) into the tear film leads to an almost instantaneous transformation of the highly fluid latex into viscous gel. [20, 21, 22]

The gamma scintigraphy technique was used to monitor the ocular residence time of an ophthalmic preparation based on Cellulose acetate phthalate (CAP) dispersion. The gelled system constitutes a micro-reservoir of high viscosity [23, 24] First preliminary investigations of pH-sensitive latexes for ophthalmic administration began in early 1980s and have been extensively studied by Boye [25] He proposed the preparation of latexes containing Pilocarpine with Cellulose acetate phthalate (CAP).

Cellulose acetate phthalate latex is a polymer with potentially useful properties for sustained drug delivery to the eye because latex is a free-running solution at a pH of 4.4, which undergoes coagulation when the pH is raised by the tear fluid to pH 7.4. The use of pH-sensitive latex nanoparticles has been described by Gurny. [26] But the low pH of the preparation can elicit discomfort in some patients. [27] The poly acrylic acid and its lightly cross-linked commercial forms (Polycarbophil and Carbopol) exhibit the strongest mucoadhesion. In the pioneering paper, Hui and Robinson demonstrated that the use of acrylates for ocular delivery of progesterone was based not only on viscosifying but also on bioadhesion properties.[28] Carbomer (Carbopol) a cross-linked acrylic acid polymer (PAA) also shows pH induced phase transition as the pH is raised above its pKa of about 5.5. [29] Different grades of Carbopol are available. The manufacturer states that Carbopol 934 gel has the lowest cross-linking density, while Carbopol 981 intermediate and Carbopol 940 have the highest.

However, the amount of PAA required to form stiff gel upon instillation in the eye is not easily neutralized by the buffering action of tear fluid. Combination PAA with a suitable viscosity-enhancing polymer e.g. Hydroxy propyl methyl cellulose [30] or Methyl Cellulose [31] allows a reduction in the PAA concentration without comprising

the *in situ* gelling properties. The formulation containing Carbopol ® 940 and Methocel E50LV (HPMC) afforded sustained release of ofloxacin over an 8-h period.

Polycarbophil-based *in situ* gelling systems were developed by Robinson and Miynek. [32] Polycarbophil is insoluble in water, but its high swelling capacity in a neutral medium permits the entanglement of the polymer chains with the mucus layer. The non-ionized carboxylic acid group binds to the mucin by means of hydrogen bonds [33, 34]

The proposed theory behind pH induced sol-gel phase transition

All the pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH [35] The polymers with a large number of ionizable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. The most of anionic pH-sensitive polymers are based on PAA (Carbopol®, carbomer) or its derivatives [36]. Likewise polyvinylacetaldiethylaminoacetate (AEA) solutions with a low viscosity at pH 4 form hydrogel at neutral pH condition [37].

Ion-sensitive hydrogels

Ion-sensitive polymers belong to the mainly used *in situ* gelling materials for ocular drug delivery. Gelling of the instilled solution is also triggered by change in ionic strength. It is assumed that the rate at which electrolytes from the tear fluid is adsorbed by the polymer will depend on the osmotic gradient across the surface of the gel. It is therefore likely that the osmolality of the solution might have an influence on the rate of the sol-gel transition occurring in the eye. One example is Gelrite, an anionic extra cellular polysaccharide, low acetyl Gellan gum secreted by pseudomonas elodea. Gelrite formulations in aqueous solutions form a clear gel in the presence of the mono or divalent cations typically found in the tear fluids. The electrolyte of the tear fluid and especially Na^{+}, Ca^{++} and Mg^{++} cations are particularly suited to initiate gelation of the polymer when instilled as a liquid solution in to the cul-de-sac. Gelrite has been the most widely studied and seems to be preferred compared to the pH sensitive or temperature setting systems. The polymeric concentration is much lower compared to previously described systems. [38]

Slightly viscous gellan gum solutions in low concentrations (<1%) show markedly increase in apparent viscosity, when introduced into presence of a physiological level of cations, without requiring more ions than 10–25% of those in tear fluid [39]. The precorneal contact times for drugs can thus be extended up to 20-h [40]. Gellan containing formulations of pilocarpine HCl allowed reduction of drug concentration from 2% to 0.5% obtaining the same bioavailability [41].

Rozier et al [42] found an improvement in the ocular absorption of timolol in albino rabbits when absorption of timolol in albino rabbits when administered in Gelrite when compared with an equiviscous solution of hydroxyl-ethyl cellulose.

Sanzgiri et al [43] compared various systems of Methyl prednisolone (MP); esters of MP with Gelrite eye drops, Gellan-MP film, and Gellan film with dispersed MP. Gellan eye drops provided better performance because they afforded the advantage of faster gelation over a high surface area in eye, whereas the results obtained with the Gellan-MP film seemed to indicate that the gelation at the surface of the film occurred very slowly, and the surface of release was not controlled.

Mourice and srinivas [44] measured a two fold increase in the permeation of the fluorescein in humans when using Gellan gum compared to isotonic buffer solution.

The ability of gel formation at physiological Ca^{2+} levels was used in case of alginic acid as well. Presence of this polymer significantly extended the duration of the pressure reducing effect of pilocarpine to 10-h [45] and carteolol to 8-h [46] allowing only once a day administration in case of carteolol.

Cohen et al demonstrated that an aqueous solution of sodium alginate could gel in the eye, without addition of external calcium ions or other bivalent/polyvalent cations.

The extent of alginate gelation and consequently the release of Pilocarpine were found to be dependent upon the percentage of Glucuronic Acid residues in the polymer backbone. Alginates with G content more than 65%, such as Manugel DMB [45], instantaneously formed gels upon their addition to STF. In vitro release studies indicated the slow release of Pilocarpine over a period of 24 hours. Recently, some other natural polymers believed to be able to form in situ gels by interacting with the lachrymal fluid have been evaluated as potential adjuvant in ophthalmic formulation.

This includes carageenans, xyloglucans and some alginates that are rich in guluronic acid residues. K-carrageenan forms rigid, brittle gels in reply of small amount of K^{+}, I-carrageenan forms elastic gels mainly in the presence of Ca^{2+}. Gelation of the low-methoxy pectins can be caused by divalent cations, especially Ca^{2+}. Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations e.g. Ca^{2+} due to the interaction with guluronic acid blocks in alginate chains. Sodium alginate consists chiefly of the sodium salt of alginic acid, a linear glycuronan polymer consisting of a mixture of β- (1, 4)-D-mannosyluronic acid and α- (1, 4)-L-Gulosyluronic acid residues.

Silver et al compared the commercial product Timoptic XE 0.5% with a timolol mealeate gel-forming solution with xanthan gum as the gelling polymer (Timolol GFS 0.5% Alcon Research). The xanthan gum preparation was developed for once-daily dosing. The reported data indicated equivalent efficacy in the reduction intraocular pressure (a maintained reduction during long term use) and consequently therapeutic equivalence. [47]

Table 2: Hydrogel-based products on the market

Product	Product Manufactured by/ marketed by	Hydrogel Composition	Indication	Remarks	Reference
SQZ Gel oral release system	Macromed (Sandy, UT, USA)	Chitosan and polyethylene glycol	Hypertension	pH-Sensitive, once a-day tablet of dilteazem hydrochloride	http://www. macromed.com
Hycore-V™ and Hycore- R™	™ CeNeS Drug Delivery (Irvine, UK)	-	Vaginal and rectal infections, respectively	Localized delivery of metronidazole	http://www. cenes.com
Cervidil® vaginal (PGE2)	Controlled Therapeutics, UK; marketed by insert Forest Pharmaceuticals St Louis, MO, USA)	Poly(ethylene oxide) and urethane	Initiation and/or continuation of cervical ripening (at or near term	Product contains 10 mg dinoprostone and exhibits *in vivo* release rate of ~0.3 mg h–1	htt://www btgplc.com
Smart c HydrogeL	MedLogi Global™ (Plymouth, UK)	liquid Poly(acrylic acid) (oxypropylene-, co-oxyethylene) glycol.	Used for development of ophthalmic, buccal, nasal, vaginal and transdermal.	Mucoadhesive composition that undergoes sol–gel transformation at body temperature,	http://www medlogic.com.
Aquamere™	Hydromer (Somerville, NJ, USA)	Interpolymers of PVPand PVP-grafted copolymers with urethane	Skincare, topical and oral drug delivery	–	http://www. hydromer.com

Keipert reported that the increase in therapeutic effects (i.e., miosis) in rabbits could be due to a permeation enhancing effect of gellan gum comparable to EDTA. Apart from its *in situ* gelling property, Gellan gum diminishes drainage after instillation.

The commercial product Timoptol XE preparation containing Gelrite remains for a longer period at the eye surface when compared to conventional timolol maleate eye drops. This resulted in an enhanced drug transfer sufficient enough to obtain an intro ocular pressure reduction after a once-daily topical instillation. [48-50]

Divalent ions were found superior to monovalent in promoting the gelation of the polysaccharides. However, the conc. of sodium in tears (2.6 g/L) is quite sufficient to induce gelation. Because the presence of lachrymal fluid is necessary to induce gel formation, accidental gelation during storage does not occur as with thermo reversible gels. The characteristics of polymers used to prepare smart hydrogel for ocular drug delivery is shown in Table 1.

CONCLUSIONS

Drug delivery has undergone a revolutionary advancement in the past few years. With the advent of novel delivery systems, various drug molecules have been revived of their therapeutic and commercial benefits. The introduction of stimuli-responsive systems has further strengthened the link between therapeutic need and drug delivery. A lot of research is ongoing in various laboratories to explore stimuli- responsive hydrogels as drug delivery systems for better patient care. The success of hydrogels as delivery systems can be judged by several marketed preparations (Table 2). In the present scenario, the major considerations during the formulation of hydrogel-based drug products are their mechanical strength and response-time in a physiological environment. Fast-responding hydrogels releasing maximal drug in less time while maintaining the structural integrity in a biological system will be the more appreciated delivery systems. Moreover, a high level of *in vitro–in vivo* correlation in their performance will determine their future success. The exploitation of these polymeric networks for improved therapeutic efficacy will open newer arenas in drug delivery.

Drug delivery as it pertains to the eye is a generic term, which is defined broadly as representing an approach to controlling and ultimately optimizing delivery of the drug to its target tissue in the eye thus it is easier to treat ocular diseases and complicated at the same time because the eye has specific characteristics, which make the development of ocular drug delivery systems extremely difficult. The most widely developed drug delivery system is represented by the polymeric hydrogels. Hydrogels generally offer a moderate improvement of ocular drug bioavailability despite their favorable bioadhesive properties. One of the disadvantages is that hydrogel may result in blurred vision as well as foreign body sensation to patients. *In situ* activated gel-forming systems seem to be preferred as they can be administered in drop form and create significantly less problems with vision. Moreover, they provide good sustained release properties. Over the last decades, an impressive number of novel temperature,

pH, and ion induced *in situ* forming solutions have been described in the literature. Each system has its own advantages and drawbacks. The choice of a particular hydrogel depends on its intrinsic properties and envisaged therapeutic use. Thus, the *in situ* gelling system seems promising because as with non-viscous eye drops, accurate and precise sustained release properties with little or no eye irritation is possible.

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