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Review Article

# Hydrogels in ophthalmic applications

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ABSTRACT

More and more people worldwide are affected by severe eye diseases eventually leading to visual impairment or blindness. In most cases, the treatment involves the application of ophthalmic dosage forms such as eye drops, suspensions or ointments. Unfortunately, some of the therapeutic approaches have major shortcomings, especially in the treatment of the posterior segment of the eye, where many vision-threatening diseases originate. Therefore, research focuses on the development of new materials (*e.g.*, for vitreous substitution) and more advanced drug delivery systems. Hydrogels are an extremely versatile class of materials with many potential applications in ophthalmology. They found widespread application as soft contact lenses, foldable intraocular lenses, *in situ* gelling formulations for ophthalmic drug delivery and ocular adhesives for wound repair; their use as vitreous substitutes and intravitreal drug delivery systems is currently under investigation. In this article, we review the different applications of hydrogels in ophthalmology with special emphasis placed on the used polymers and their suitability as ocular drug delivery systems.



## 1. Introduction

More and more people worldwide are affected by severe eye diseases, such as glaucoma, proliferative diabetic retinopathy (PDR) and age-related macular degeneration (AMD) [1–4]. Without adequate treatment, these diseases will eventually lead to severe visual impairment or blindness. Today, two major strategies for the treatment and management of ocular disorders can be identified: (1) the attempt to specifically deliver drug molecules to diseased ophthalmic tissues and (2) surgical procedures to repair or replace damaged tissues, such as the lens or the vitreous body [5–7]. Unfortunately, most currently available therapeutic approaches have major shortcomings, especially in the treatment of the posterior segment of the eye, where most vision-threatening diseases originate. The main challenges are as follows: (1) poor adherence of patients to the currently available therapeutic regimens, (2) maintaining effective drug levels over extended time periods and extending the required dosing intervals, (3) the delivery of drug molecules to the posterior segment of the eye, (4) the administration of therapeutic proteins and nucleic acids, and (5) the repair or substitution of dysfunctional cells or tissues. For example, over 50% of 500 surveyed glaucoma patients were found to be either non-adherent to their therapeutic regimens or demonstrated improper administration techniques [8]. While patients can be educated on the importance of adherence and instructed on proper eye drop administration, the inherent shortcomings of eye drops, such as low ocular bioavailability of the applied drug, are less easy to overcome. For example, it has been shown that less than 5% of the administered dose reaches the target tissue due to drainage and limited corneal permeability [9–11]. Moreover, only the anterior segment of the eye can be treated by eye drop installation, whereas different application routes (*e.g.*, intravitreal injections) and/or more complex drug delivery systems (*e.g.*, intraocular implants) may be required to reach the posterior segment [12–15]. For example, the development of anti-vascular endothelial growth factor (VEGF) drugs, such as monoclonal antibodies or antibody fragments, revolutionized the therapy of neovascular AMD and other vision-threatening diseases [16–18]. However, the required intravitreal injections are associated with

*Abbreviations:* ADH, adipic dihydrazide; AMD, age-related macular degeneration; $c_{max}$, maximum plasma concentration; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; EGF, epidermal growth factor; ESHU, poly(ethylene glycol)-poly-(serinol hexamethylene urethane); HA, hyaluronic acid; MC, methyl cellulose; HEMA, 2-hydroxyethyl methacrylate; HPMC, (hydroxypropyl)methyl cellulose; IOL, intraocular lenses; IOP, intraocular pressure; PAA, poly(acrylic acid); PCO, posterior capsule opacification; PDMS, poly(dimethylsiloxane); PDR, proliferative diabetic retinopathy; PEG, poly(ethylene glycol); pHEMA, poly(2-hydroxyethyl methacrylate); PNIPAAm, poly(*N*-isopropylacrylamide); PVA, poly(vinyl alcohol); PVP, poly(vinyl pyrrolidone); RPC, retinal progenitor cells; RSPC, retinal stem-progenitor cells; SCL, soft contact lenses; STMP, trisodium trimetaphosphate; VEGF, vascular endothelial growth factor.

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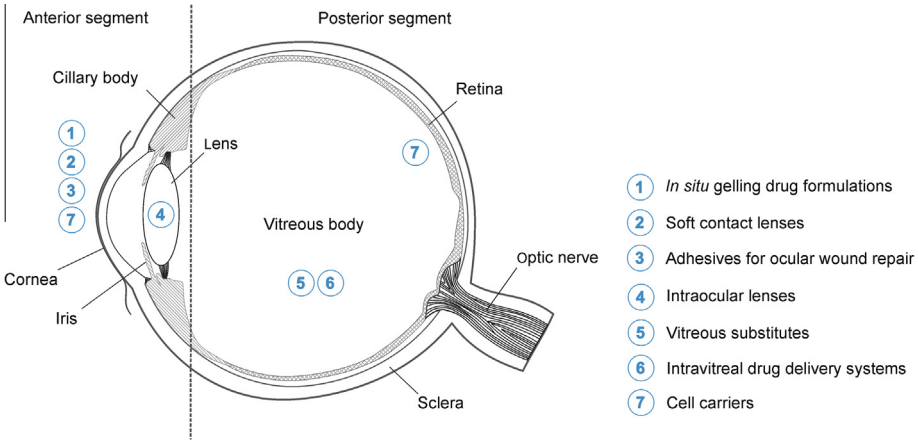


**Fig. 1.** Application sites of hydrogels in ophthalmology.

significant discomfort and complications including endophthalmitis, retinal tears or detachment, and cataract [19]. It is obvious that sustained delivery systems for anti-VEGF drugs would make the current therapeutic regimens more patient-friendly and cost-effective.

The given examples illustrate the need for new developments in the field of ophthalmic drug delivery, and indicate the great market potential of those drug delivery systems. Compared to the different materials and dosage forms that have been developed for ophthalmic applications, such as colloidal drug delivery systems [20–22] or polymeric implants [23], hydrogels may offer several advantages. For example, the mild preparation conditions and high water content of hydrogels are beneficial in preserving the activity of biopharmaceuticals such as peptides, proteins or nucleic acids [24–26]. Moreover, many hydrogels, such as temperature-responsive or *in situ* chemically cross-linked systems, can be administered by minimally invasive methods [24–27]. Hydrogels have already been approved for several ophthalmic applications, with many more currently being under investigation. For instance, they are successfully marketed as corrective soft contact lenses (SCL) [28], foldable intraocular lenses (IOL) [29,30], or *in situ* gelling vehicles for ophthalmic drug delivery [31,32]. Most research efforts currently aim at improving existing formulations for antibiotics, anti-inflammatory drugs or β-blockers, or at developing sustained release formulations for therapeutic proteins and nucleic acids. Furthermore, hydrogels are investigated as adhesives for ocular wound repair [33] or potential vitreous substitutes [6,7]. A graphical overview on possible ophthalmic applications of hydrogels is given in Fig. 1.

In most of these applications, hydrogels are used because of their favorable physicochemical properties (*e.g.*, transparency, high water content, and mechanical flexibility) or in combination with active pharmaceutical ingredients. In this review article, we present a general overview on ophthalmic applications of hydrogels with special emphasis on drug delivery systems for the posterior segment of the eye. We particularly focus on the different gel-forming polymers, the physicochemical properties of the resulting hydrogels, and the challenges associated with the preparation of hydrogel-based drug delivery systems. Recent developments in the field of ophthalmic drug delivery are presented and critically reviewed regarding the potential therapeutic benefits.

## 2. Methods of hydrogel preparation and properties of hydrogels

Before discussing the diverse applications of hydrogels in ophthalmology, a short review on the different methods of hydrogel preparation will be presented along with an overview on the characteristic properties of hydrogels. According to the definition by the International Union of Pure and Applied Chemistry, a hydrogel is a polymer network that is expanded throughout its whole volume by water [34]. A wide range of natural, semisynthetic and synthetic polymers can be used as starting materials for hydrogels. Typical examples for polymers of natural origin include alginate, collagen, and hyaluronic acid (HA) (Fig. 2). Poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA), polymers based on acrylate monomers, and siloxanes are important examples for synthetic gel-forming materials (Fig. 3) [24,26,35–37].

Polymers of natural origin usually have the advantage of being non-toxic and biodegradable. Furthermore, natural polymers often interact with proteins and cells through non-specific or specific binding, which can be desired in hydrogel-based sustained release systems or cell carriers. However, hydrogels made from natural polymers may suffer from weak mechanical strength, high batch-to-batch variability, and immunogenicity. Synthetic polymers, on the other hand, allow for the preparation of hydrogels with well-defined network architecture, tunable mechanical properties, and prolonged stability. However, many synthetic polymers, such as PEG or PVA, do not inherently interact with proteins or cells; furthermore, biocompatibility and biodegradability must be carefully evaluated.

Hydrogels can be further classified into physical and chemical gels, depending on how the polymer networks are formed [24,26,35–37]. In physical or reversible hydrogels, the networks are formed by physical aggregation of polymer chains, caused by molecular entanglements, hydrogen bonds, hydrophobic interactions, ionic bonding, or complexation. All of these interactions

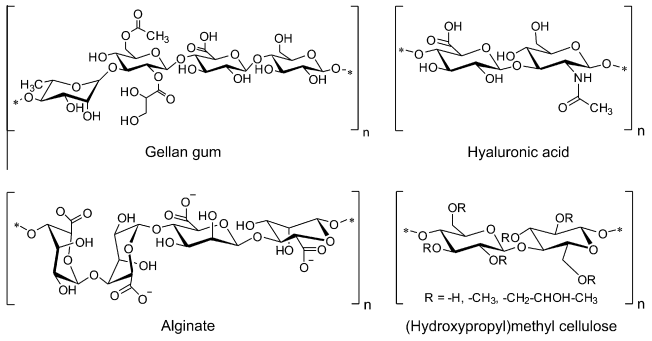


**Fig. 2.** Chemical structures of selected polymers from natural sources commonly used for the preparation of hydrogels.