A Comprehensive Review on the Polymers used for the Ocular Drug Delivery System

Tarannum Shamshad, Shashank Soni*

Department of Pharmaceutics, Amity Institute of Pharmacy, Amity University Uttar Pradesh Lucknow Campus, Lucknow, India

Abstract

This review identifies and examines the types of polymers used in ocular drug delivery systems, as well as their key roles such as solubility, penetration enhancers, and so on. Maintaining an effective concentration of the medicine in the target area for an extended period is a difficult issue in ocular drug delivery. The development of effective strategies for drug administration to the eye employing current developments in material sciences and innovative drug delivery approaches is urgently needed. As a result, there is a need to create new and improved drug delivery techniques for the eye. This could be accomplished by adding new polymers into existing formulations or developing novel medication delivery methods. The limits of traditional ocular therapy are discussed in this article, as well as recent developments in materials science and drug delivery techniques that have been employed to improve ocular bioavailability. This study outlines the key components of ocular drug delivery as well as the factors that influence drug absorption in the eye, including the use of encapsulating polymers (alginate, hyaluronic acid, and poloxamer) to modify drug delivery. Polymers and their maximum potency amounts used in FDA-approved ophthalmic formulations are also listed in this review.

Keywords: FDA-approved polymers, Ophthalmic polymers, Cyclodextrins, Polymers, Bioadhesives

Introduction

The physiological and anatomical obstacles found in the eye have traditionally made drug delivery to the eye a difficulty for researchers. The delicate nature of the eye, as well as medication/excipient toxicity, have added to the difficulty of ocular drug administration. Traditional drug delivery to the eye has several drawbacks, including low bioavailability due to quick lacrimal clearance, reduced contact time, worse patient acceptance, and drug burst release. As a result, there has been much research in recent years aimed at designing innovative ocular delivery systems with the main goal of achieving an optimal drug concentration at the desired site with a sustained drug release profile that is free of toxicity. Nanoparticles, liposomes, and other novel medication delivery technologies have been explored from past few years to overcome these difficulties. Polymers are essential components of both traditional and new medication delivery systems. They are an essential component of drug delivery systems, serving a variety of purposes ranging from inert diluents to drug release rate control. Polymers used in ocular medication delivery systems are listed and discussed in this chapter. The chapter also focuses on a list of polymers used in FDA-approved ophthalmic formulations [1].

Polymer Classification for Ocular Drug Delivery Systems

Polymer in ocular drug delivery systems are classified based on their role and function. In drug delivery systems, various polymers are used to prepare/modify the formulation or to build specific drug delivery systems. Inserts or liposomes are examples of such systems. Figure 1 shows a variety of drug administration methods for the ophthalmic drug delivery system. These methods for drug delivery are based on the following principles: Polymers and the specific processes for the preparation and evaluation must be consistent. Each excipient is unique. It was assessed based on the benefits it provides in a certain drug delivery method. However, certain excipient qualities are sought from these polymers, so that they can be used to administer ophthalmic drugs [2].

Figure 1: Types of formulations used in ocular drug delivery system

Polymers with the desired physicochemical qualities for the ophthalmic drug delivery system[3]

- No side effects, both local and systemic.
- Extend the contact time that the ocusert implanted in the ocular tissues stays in the ocular tissues.
- Act as drug reservoirs to extend the active molecule's residence period.
- Reduce the frequency of delivery by controlling medication release
- Polymers should be inexpensive, simple to handle, and consistent.
- Compatibility with medicines used in ocular drug delivery systems.
- Biocompatible and biodegradable.

Figure 2: Polymers/additives used in Ocular drug delivery system

Polymers and their Use in Ophthalmic Drug Delivery Systems

1. Solubility Enhancers

In the ocular drug delivery system, a drug formulation formulated as a solution is usually employed. It's critical to dissolve the medicine thoroughly enough to generate a solution that can pass past the membrane. Many powerful lipophilic medicines have proven pharmacological benefits in a variety of eye disorders; however, solubility is a problem. These medications are solubilized using a variety of cyclodextrins (CDs) and polymers before being prepared for ocular delivery [4].

2. Penetration Enhancers

These polymers permeate the cornea, lowering barrier resistance. By doing so, these polymers temporarily improve the permeability of the ocular tissues, allowing medications to flow through. Surfactants can change the physical properties of cell membranes and act as penetration enhancers because they diminish surface tension. They function by eliminating phospholipids from the ocular membranes and solubilizing them [5].

3. Viscosity enhancers

Increased viscosity can increase drug residence time in the eyes, resulting in increased diffusion through the cornea. Due to their high viscosity, gels are widely employed for ophthalmic preparation. Traditional premade gels with viscosity-enhancing polymers can be administered directly to the eyes, while additional gelling polymers can be employed for in situ gel production. Polymers, primarily polymers, are used in in-situ gel production to create viscous liquids that go through sol-gel phase transitions. To generate in situ gels, they are normally exposed to specific physiological parameters such as temperature, pH, and so on. The use of viscous formulations has the disadvantage of causing obscured vision during application [6].

4. Polymers that are used in the *in-situ* gelation process

In situ gelling is performed by modifying temperature, ion concentration, or pH to solve issues associated with viscous ophthalmic drug delivery systems. There are various polymers that have these characteristics. Polymers such as poloxamers, which convert from solution to gel at the temperature of the eye, can be used to achieve sustained medication administration in the eye. These thermally gelling solutions, on the other hand, have several drawbacks, such as the possibility of gelling prior to administration due to an increase in ambient temperature during packing or storage, for example. Other polymers have been used to provide osmotic-induced gelation for ocular administration, such as gellan gum [7].

5. Mucoadhesive / Bioadhesives-

Polymers that adhere to biological membranes, such as epithelial tissues or the mucous coat, can improve formulation contact time. As bioadhesives, hydrophilic polymers are often employed. Polymers derived from cellulose, such as HPMC, poly-acrylics, such as carbomer, polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), sodium hyaluronate, sodium alginate, and others are among the bioadhesives. Patient compliance is a key drawback of utilizing bio adhesives/mucoadhesive because of the stickiness of the formulation including adhesive to the eye[8].

6. Polymers for Drug Release Control-

To maintain optimal drug concentrations in the targeted areas of the eyes, the drug release rate must be managed. To manage the release of medicine from the formulations, a matrix containing diverse polymers is used[9].

7. Solvents-

Solvents are employed in the formulation of medications and, in some cases, polymers. They make up most drug delivery systems in certain circumstances, such as ophthalmic solutions and suspensions. Despite the fact that they are not categorized as polymers, they play a significant part in the formulations. It's critical to investigate the stability of pharmaceuticals and polymers in ophthalmic drug delivery solvent systems[10].

8. Preservatives-

Preservatives are used to stop the growth of microorganisms or to prevent unwanted physical or chemical reactions. Because the eyes are so delicate, it's critical to include preservatives in ophthalmic formulations. In ocular formulations, polymers like benzalkonium chloride are widely employed as preservatives.[11]

9. Agents that act as buffers-

A buffering agent is a mild acid or base used in ophthalmic formulations to keep the pH stable. Buffering polymers avoid a sudden shift in pH, which could cause the medicine to degrade or cause serious ocular adverse effects[11].

10. Polymers to Improve Physical and Chemical Stability-

Various polymers are utilized to improve the chemical and physical stability of ophthalmic formulations [12].

Various types of polymers used in Ocular Drug Delivery Systems –

1. Cyclodextrins

Cyclodextrins (CD s) are commonly employed in ocular formulations to solubilize and stabilise medicines. CDs are cyclic oligosaccharides that form complexes with lipophilic medicines to boost their solubility. CD interactions with biological membranes have also been discovered to influence CD solubility enhancing efficacy. The number of CDs used for solubility improvement is quite important. Large amounts can reduce absorption by keeping the medication in tears . Chloramphenicol (Clorocil ®: Edol), diclofenac (Voltaren Ophthalmic ®: Novartis), and indomethacin (Indocid ®: Merck Sharp & Dohme-Chibret) are all eyedrops that contain CDs that are registered in Europe [13].

2. Carbopol

Carbopol, carbomer, and acrylic acid polymers are acrylic acid polymers with allyl sucrose or allyl ethers of pentaerythritol that are synthesised at high molecular weight. Each can be employed in ophthalmic formulations as a bioadhesive material, controlled release agent, emulsifying agent, emulsion stabiliser, rheology modifier, or stabilising agent. The -blockers timolol, betaxolol, carteolol, and metipranolol were combined with carbopol to create a formulation that was demonstrated to be particularly successful in lowering intraocular pressure. In comparison to other polymers, carbopol-containing hydrogels were shown to contain extra medicines such as pilocarpine, timolol, antibiotics, betaxolol, ribozymes, and topical steroids[14].

3. Poloxamers

Poloxamers are non-ionic tri-block copolymers made up of a core polypropylene oxide hydrophobic chain bordered by two polyethylene oxide hydrophilic chains. Miller and Donovan looked at a temperature-sensitive poloxamer solution for pilocarpine administration. When compared to the drug's aqueous solution, the formulation containing Pluronic F127 showed an increase in meiosis[15].

4. Xyloglucan

Tamarind seeds contain a polysaccharide called xyloglucan. In dilute aqueous solution, it is partially destroyed by -galactosidase and exhibits thermally reversible gelation. Xyloglucan formulations were utilised to administer pilocarpine hydrochloride in a sustained release vehicle; relatively low quantities of xyloglucan were observed to improve the miotic response, similar to high concentrations of poloxamer 407 gel[16].

5. Methylcellulose

Methylcellulose (MC) is a water-soluble cellulose derivative that gels at roughly 40–50 degrees Celsius due to hydrophobic interactions. MC gels are thermo-reversible, meaning they gel when heated and liquefy when cooled. Salts, such as NaCl, lower the transition temperature to 32–34 °C[17].

6. Hydroxypropyl Methylcellulose (HPMC)

Between 75 and 90 degrees Celsius, it demonstrates sol–gel transitions. To bring this transition temperature down to acceptable levels, chemical or physical alterations are used[18].

7. Ethyl (Hydroxyethyl) Cellulose (EHEC)

EHEC also exhibits thermo-sensitive behaviour in aqueous solutions. At room temperature (20–25 °C), EHEC is liquid, while at 30–40 °C, it gels[19].

8. Pseudolatexes

Artificial latexes are made by distributing polymers in an aqueous solution. Ocular formulations of pilocarpine based on pseudolatex have shown promise for regulated ocular administration[20].

9. Cellulose Acetate Phthalate (CAP)

The cellulose polymer known as CAP is a kind of cellulose. When the pH of the solution is elevated to 7.4 due to the presence of tears, it begins to coagulate[21].

10. Gum Gellan

It's a natural polymer derived from Pseudomonas elodea cells. Gellan gum generates a transparent solution when monovalent and divalent cations are present. In the tear fluid, the aqueous solution of gellan gum generates high viscosity hydrogels. Several studies have demonstrated that gellan gum is superior to other ophthalmic formulations in ocular formulations[22].

11. Alginate

Alginate is a block copolymer of -D mannuronic acid and -guluronic acid that occurs naturally. Calcium ions combine with guluronic acid monomers to produce ionotropic hydrogels . Alginate has been employed in ocular formulations with great effectiveness, including control release formulations[23].

12. Carrageenans

Carrageenans are a type of sulfated galactan that is isolated from red seaweed and is water-soluble. In the presence of tears, they will also gel. Lang et al. used carrageenans to create a topical for the treatment of the dry eye[24].

13. Hyaluronic Acid (HA)

Hydrogels based on HA are increasingly being utilised to treat the dry eye condition. HA is a linear polysaccharide polymer with a high molecular weight. It creates hydrogels and has been utilised in a variety of ocular formulations, including dry eye treatments. HA has desirable features such as a high water binding capacity, mucus-like rheological qualities, and is relatively safe. Johnson et al. discovered that using sodium salts of hyaluronate at concentrations of 0.1 percent and 0.3 percent considerably lowers ocular irritation sensations. It was discovered that antibiotic gentamicin compounded with 0.25 percent HA increased precorneal drug residence duration[25].

Use of auxiliary polymers

For the manufacture and improvement of ocular formulations, polymers can be employed in combination to take advantage of their pharmacological properties. To boost drug availability at the lipophilic ocular surface, traditional penetration enhancers such as benzalkonium chloride (BAC), solubility enhancers, and CDs can be utilised. CDs can be coupled with hydrophilic polymers in the same way. Ito et al. recently investigated the effects of hydroxypropyl-beta-cyclodextrins (HP—CD) and hydroxypropyl methylcellulose (HPMC) on disulfiram formulation in rabbits with experimentally induced ocular hypertension. They discovered that combining HP—CD and HPMC increased disulfiram solubility and improved pharmacological effects. When viscosity enhancers and in situ gelling properties of polymers are combined, the concentrations of polymers can be greatly reduced without compromising their gelling properties. In vivo tests with timolol maleate, for example, indicated that combining Pluronic with methylcellulose increased ocular bioavailability by approximately 2.5 times when compared to timolol maleate solutions.

Various researchers have successfully improved the efficacy of many ophthalmic formulations by combining polymers. When used alone, most of these polymers do not provide an appropriate platform for ophthalmic administration. Combining these polymers, on the other hand, was found to increase formulation properties, patient compliance, and therapeutic efficacy significantly[26].

Polymers that have been approved by the FDA

As previously stated, traditional ophthalmic formulations fall into various categories, including solutions, suspensions, emulsions, gels, and ointments. The objective of this section is to present a full list of FDA-approved ophthalmic medication products, as well as substantial information about those products, as multiple prior chapters have covered several features of these dosage forms. Table.1 shows a selection of commercially available ophthalmic formulations, together with the medication name, chemical structure, therapeutic indication, and polymers utilised. Regulatory organisations around the world have established stringent rules and guidelines for the development and approval of pharmaceutical goods [27].

Table 1: FDA approved marketed formulations [28]

Drug product	MoA/indication	API	Polymers
Apraclonidine ophthalmic solution	Selective alpha-2-adrenergic agonist/ indicated for the reduction of elevated intraocular pressure (IOP)	Apraclonidine – 0.5 %	Benzalkonium chloride – 0.01 %; Sodium acetate, Sodium chloride
Atropine sulfate ophthalmic solution	Antimuscarinic agent/indicated for cycloplegia, mydriasis, penalization of the healthy eye in the treatment of amblyopia	Atropine sulfate – 1 %	Benzalkonium chloride – 0.01 %; Edetate disodium, Hypromellose
Azelastine hydrochloride solution	Selective histamine H1 antagonist/ treatment of itching of the eye associated with allergic conjunctivitis	Azelastine hydrochloride – 0.5 mg/ml	Benzalkonium chloride – 0.125 mg/ml; Disodium edetate dihydrate , Hydroxypropyl methylcellulose, Sorbitol solution
Azithromycin ophthalmic solution	Macrolide antibiotic/treatment of bacterial conjunctivitis	Azithromycin – 1 %	Mannitol, Citric acid monohydrate, Sodium citrate, Poloxamer 407 Polycarbophil, Sodium chloride, Edetate disodium Benzalkonium chloride – 0.003
Bacitracin zinc and polymyxin B sulfate ophthalmic ointment	Antibacterial/infections of the external eye and its adnexa caused by susceptible bacteria	Bacitracin zinc – 500 units in 1 g ,Polymyxin B sulfate – 10,000 units in 1 g	Petrolatum, Mineral oil
Bepotastine besilate solution	Histamine H1 receptor antagonist/ indicated for the treatment of itching	Bepotastine besilate – 15 mg/ml	Benzalkonium chloride – 0.05 mg/ml ,Sodium phosphate monobasic

	associated with signs and symptoms of allergic conjunctivitis		,Dihydrate sodium chloride .
Besifloxacin ophthalmic suspension	Anti-infective	Besifloxacin – 0.6 %	Benzalkonium chloride – 0.01 %, Polycarbophil, Mannitol, Poloxamer 407, Sodium chloride Edetate disodium dihydrate
Brimonidine tartrate ophthalmic solution	Selective alpha-2 adrenergic receptor agonist/indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension	Brimonidine tartrate – 0.1 % or 0.15 %	Boric acid Calcium chloride, Magnesium chloride, Potassium chloride, Sodium borate Carboxymethylcellulose sodium, sodium chloride
Brinzolamide suspension	Carbonic anhydrase inhibitor/ treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma	Brinzolamide – 10 mg/ml	Benzalkonium chloride – 0.1 mg/ml, Mannitol, Carbomer 974P, Tyloxapol, Edetate disodium
Dexamethasone sodium phosphate ophthalmic solution	Anti-inflammatory	Dexamethasone sodium phosphate, [equivalent to 0.1 % of dexamethasone phosphate]	Sodium citrate Sodium borate Creatinine Polysorbate 80 Edetate disodium dihydrate Sodium bisulfite – 0.1 % Phenylethyl alcohol – 0.25 % Benzalkonium chloride – 0.02 %
Difluprednate ophthalmic emulsion	Corticosteroids/treatment of inflammation and pain associated with ocular surgery	Difluprednate – 0.05 %	Boric acid, Castor oil Glycerin, Polysorbate 80, Sodium acetate Sodium, EDTA, Sorbic acid – 0.1 %
Dorzolamide hydrochloride ophthalmic solution	Carbonic anhydrase/treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma	Dorzolamide – 2 %	Hydroxyethylcellulose (2000cps) – 1 % Mannitol Sodium citrate dihydrate Benzalkonium chloride – 0.0075 %
Emedastine difumarate ophthalmic solution	Histamine H1 antagonist/temporary relief of the signs and symptoms of allergic conjunctivitis	Emedastine difumarate equivalent to 0.5 mg/ml emedastine	Benzalkonium chloride – 0.01 % Tromethamine Sodium chloride Hypromellose
Fluorometholone ophthalmic suspension	Corticosteroids	Fluorometholone – 0.1 %	Benzalkonium chloride – 0.004 %, Edetate

			disodium, Polysorbate 80, Polyvinyl alcohol – 1.4 %, Sodium chloride
Ganciclovir ophthalmic gel	Inhibits DNA replication by Herpes simplex viruses/treatment of acute herpetic keratitis	Ganciclovir – 0.15 %	Carbopol, Mannitol Benzalkonium chloride – 0.075 mg/ml
Hypromellose 2910 (4000 MPAs) solution	For use as a lubricant to prevent further irritation or to relieve dryness of the eye	Hypromellose 2910 (4000 MPAs)	Boric acid, Edetate disodium Sodium borate, Benzalkonium chloride
Ketorolac tromethamine ophthalmic solution	Nonsteroidal anti-inflammatory/relief of ocular itching due to seasonal allergic conjunctivitis	Ketorolac tromethamine – 0.5 %	Benzalkonium chloride – 0.01 % ,Edetate disodium – 0.1 % Octoxynol 40 ,Sodium chloride
Levobunolol hydrochloride ophthalmic solution	Non-cardio selective beta-adrenoceptor blocking agent/lowering intraocular pressure and may be used in patients with chronic open-angle glaucoma or ocular hypertension	Levobunolol HCl – 0.5 %	Benzalkonium chloride – 0.004 % Polyvinyl alcohol – 1.4 % Edetate disodium Sodium metabisulfite Sodium phosphate, dibasic potassium phosphate, monobasic Sodium chloride
Medrysone ophthalmic suspension	Anti-inflammatory agent/treatment of allergic conjunctivitis, vernal conjunctivitis, episcleritis, and epinephrine sensitivity	Medrysone – 1 %	Edetate disodium Hypromellose Polyvinyl alcohol – 1.4 % Potassium chloride Sodium chloride, Sodium phosphate, dibasic Sodium phosphate, monobasic
Nedocromil sodium ophthalmic solution	Mast cell stabilizer/treatment of itching associated with allergic conjunctivitis	Nedocromil sodium – 2 %	Edetate disodium – 0.05 % Sodium chloride – 0.50 % Benzalkonium chloride – 0.01 %
Olopatadine hydrochloride ophthalmic solution	Mast cell stabilizer and a histamine H1 antagonist/treatment of ocular itching associated with allergic conjunctivitis	Olopatadine hydrochloride equal to 2 mg/ml of olopatadine	Povidone Dibasic sodium phosphate Sodium chloride Edentate disodium Benzalkonium chloride – 0.01 %
Pemirolast potassium ophthalmic solution	Mast cell stabilizer/prevention of itching of the eye due to allergic conjunctivitis	Pemirolast potassium – 0.1 %	Benzododecinium chloride – 0.005 %, Glycerin – 1.8 %
Retapamulin ointment	Antibacterial agent/topical treatment of impetigo	Retapamulin – 10 mg/g of white petrolatum	White petrolatum

Suprofen solution	Analgesic, antipyretic, and anti-inflammatory	Suprofen – 1.0 %	Thimerosal – 0.005 % Caffeine – 2 % Edetate disodium Dibasic sodium phosphate Monobasic sodium phosphate Sodium chloride
Tafluprost solution	Selective FP prostanoid receptor agonist/indicated to elevate intraocular pressure	Tafluprost – 0.015 mg/ml	Glycerol, Sodium dihydrogen phosphate dihydrate, Disodium edetate , Polysorbate 80
Tetracaine hydrochloride ophthalmic solution	Local anesthetic	Tetracaine hydrochloride – 0.5 %	Chlorobutanol, Boric acid, Edetate disodium, Potassium chloride

Conclusions

Due to the intricacy of the ocular tissues and the obstacles present in the eye, ocular medication delivery is a genuinely challenging field. However, significant progress has been done in the past few years of delivery systems to improve the therapy options available. Hyaluronic acid, poloxamers, and gelatin are just a few of the intriguing polymers that could potentially overcome the major limits in ocular medication delivery that have yet to be addressed.

List of abbreviations

FDA	Food drug and administration
CDs	Cyclodextrins
PVP	Polyvinylpyrrolidone
PVA	Polyvinyl alcohol
MC	Methylcellulose
HPMC	Hydroxypropyl Methylcellulose
EHEC	Ethyl (Hydroxyethyl) Cellulose
CAP	Cellulose Acetate Phthalate

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