Available online on 15.06.2021 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Review Article

In-Situ Forming Polymeric Drug Delivery Systems for Ophthalmic Use: An Overview

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Article Info:

Article History:

Received 18 April 2021
Review Completed 23 May 2021
Accepted 28 May 2021
Available online 15 June 2021

Cite this article as:

Chhetri P, Chakraborty P, Das D, Afnan T, *In-Situ* Forming Polymeric Drug Delivery Systems for Ophthalmic Use: An Overview, Journal of Drug Delivery and Therapeutics. 2021; 11(3-S):98-103 DOI: http://dx.doi.org/10.22270/jddt.v11i3-S.4874

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Abstract

Delivery of drug into the ocular region is hindered by the protective layers that encapsulate the eyes, it has always been a major problem to get an effective bioavailability of the active drug in the ocular region due to the low precorneal resident time of most of the ocular delivery systems specifically convention once such as ointment, solution and suspension, as a result, most of the delivery systems are not capable of effectively treating ocular diseases. Several works have and are being carried out to overcome this problem one of which is using *in-situ* forming polymeric systems. Ocular *In-situ* gelling systems are a novel class of ocular drug delivery systems that are initially in a solution form but instantaneously gets converted into a viscous gel upon introduction or installation in the ocular cavity from which the active drugs get released in a sustained manner. This sol-to-gel phase transition depends upon various factors like change in pH, ion presence and change in temperature. Gel formed after the transformation has preferred viscosity along with bio-adhesive property, which increases the gel's resident time in the ocular area and also releases the drug in a prolonged and sustained manner unlike conventional eye drops and ointments. This review emphasizes various ocular *in-situ* systems namely, pH triggered, Ion activated, and Temperature triggered systems which have prolonged residence time in the cul-de-sac area of the eye, hence increasing the ocular bioavailability.

Keywords: *In-situ* gel, Ocular Drug delivery, Ocular Bioavailability, Polymer

INTRODUCTION

Drug delivery into the ocular region by using conventional delivery systems like drops and ointment requires frequent dosing the reason being that when they are introduced in the precorneal region they are quickly washed away due to the lachrymal nasal drainage and tear flow. Further, the efficacy of the administered drug is hindered by the barrier system of the eye making it nearly impossible for drugs to easily penetrate the eye[1].A very small fraction of drug gets access to the active site i.e., approximately less than 1%of total drug instilled, this is why ocular delivery of the drug is a major challenging endeavour faced by the pharmaceutical scientist today[2].

Over the last decade's number of novel works has been carried out to develop a newer and novel ocular delivery system to provide effective and easy to use systems by patients, in addition, to reduce the side effects and increasing the bioavailability as well, which could overcome the problems related to conventional once. One of the discoveries is a breakthrough which is *in-situ* gelling systems having significantly unique characteristics. A highly impressive number of these novel systems such as pH triggered ocular *in-situ* systems, ion activated systems and temperature triggered systems have been described in the literature which can be used as a perfectly efficacious alternative to conventional systems[3].

Ocular *in-situ* gelling systems are delivery systems that are designed in such a way that they instantaneously change into gel form when dropping conventionally as a solution or suspension in the eye cavity. As these gels are viscous and have some bioadhesive property the residence time of the systems is likely higher than the conventional systems like eye drops, ultimately resulting in maximum ocular bioavailability[3,4]. The increase in the precorneal residence time leads to increased bioavailability consequently, increasing patient compliance. These *in-situ* gelling systems are highly acceptable and preferably convenient to be used by the patients and the features this system holds i.e., residence time up to several hours make it most impressive and convenient[4]. These attractive features of this novel ocular systems are due to the use of polymers that have an ability to transform from a sol-to-gel form in the presence or due to the change in various physiochemical environment as disused already, that are; pH, ions and temperature of the cul-de-sac area of the eye[4,5].

Some examples of the polymers used in the different *in-situ* systems are as follows; pH triggered system using Carbopol, ion activated systems using alginates such as sodium alginate and temperature triggered systems using xyloglucan[5]. Ideally, an ocular *in-situ* forming polymeric systems in solution form must have minimum viscosity and must be free-flowing for easy installation but after installation when it gets converted to a gel form it must have a slightly higher viscosity and must not be free-flowing and must be capable

of resisting the shear force that it will experience in the cul-de-sac area of the eye[6].

ANATOMY OF THE EYE AND OCULAR DRUG PENETRATION

The human eye is broadly divided into two distinct segments namely, the anterior and the posterior segments. The anterior segment consists of the conjunctiva, pupil, anterior chamber, lens, cornea iris, culinary body, aqueous humor, and trabecular meshwork. The posterior segment consists of the sclera, choroid, optical nerve, virtuous humor, retina, and macula. The cornea forms the outermost layer of the eye. It is found directly on the front side of the iris and pupil; it is an avascular and transparent part of the eye. It is further divided into five layers[7]. The corneal epithelium, which is the outermost layer of the cornea, Bowman's layer which is very thin, the corneal stroma, Descemet's membrane and the last innermost layer i.e., the corneal endothelium. The permeability of the drugs by the cornea is the most important factor that decides the aqueous humor drug concentrating. For the hydrophilic drugs, it is difficult for them to penetrate due to the epithelium layer thus epithelium acts as a rate-limiting layer or barrier for hydrophilic drugs. And for a lipophilic drug the rate-limiting layer is the corneal stroma due to the presence of hydrophilic collagen which is highly organized[8].

The Conjunctiva, a thin and clear membrane, covers parts of the front surface of the eye and the inner surface of the eyelids. It consists of goblet cells and non-keratinized epithelium cells. Its main function is to protect the eyes as it has goblet cells it secrets mucus, preventing the entry of microbes in the eye and lubricates the eye[8,9]. Conjunctiva in the human eyes covers 17-times the surface that is covered by the cornea, and drugs permeate more from the conjunctiva than from the cornea facilitating higher drug absorption from the conjunctiva. But drug absorbed from the conjunctiva is not that significant as a large number of lymphatics and blood capillaries are present in the conjunctiva resulting in the loss of a considerable amount of drug into the blood and ultimately resulting in the low ocular bioavailability[9].

Now talking about the aqueous humor it simply includes a clear watery fluid inside the front of the eye. It is non-vascular and transparent which allow the light to get through it. Aqueous humor works to provide nutrients to the eye and maintains the eye's normal shape and pressure. It has an excessive amount of ascorbate about 15-fold the amount present in plasma, the pH of the aqueous humor is usually 7.2[10].

The eye consists of a white portion known as sclera, it has good elastic property, is opaque and full of collagen fibres. The drug which is hydrophilic in nature generally penetrate through the sclera without much hindrance as compared to cornea and conjunctiva, this is due to the presence of proteoglycans in between the collagen mess which is aqueous in nature and through which the hydrophilic substance can easily diffuse through which is a wisher alternative than crossing via cell membrane[10,11]. The functions of the sclera include its serves as a protective layer of the eye and maintain intraocular pressure. The sclera receives or has a very low blood supply, some of the blood vessels run across the sclera but sclera itself is considered avascular. The retina where the process of vision formation begins when the light is converted into signals by the specialized cell known as photoreceptor cells present in the retina which are further interpreted inside the brain to create a vision. Due to its thick layer of cells substances with higher molecular weight finds it difficult to get through[11].

CHALLENGES IN DEVELOPING AN OPHTHALMIC DRUG DELIVERY SYSTEM

1. Anatomy and physiology of the eye

A lot of impressive reviews are present in the books of literature from where we can get a clear view on anatomy and physiology of the eye with relation to ocular drug delivery. The anatomical and physiological features of the eye considerably interfere with the absorption and transport of administered active drug. Firstly, the primary features of the eye that is tear secretion, blinking of the eye and nasolacrimal drainage along with reflex action of the eye affects the precorneal residence time of the delivery system containing the active drug[12].

Tears are almost every time secreted in the eye cavity for moistening the outer surface of the eye. These tears generally wash away the drug substance permanently after administration in a very short period, along with that it has an anti-infectious property due to the presence of immunoglobulins and the lysozyme, causing increased tear secretion after administration as a protective response. Then comes another problem that is nasolacrimal drainage, which is a process of drainage of lachrymal fluids through the nasolacrimal pathway that reaches pharynx and eventually oesophagus[13].

2. Delivery of drug to the internal regions of the eye

Ocular Penetration of drugs administered systemically: Various barriers are present in the eye to prevent the transport of various unwanted substances into the eye, one of which is the blood-eye barrier. Aqueous humor;a clear aqueous liquid that is needed to maintain the intraocular pressure is formed through the ciliary process by ciliary epithelium. The ciliary epithelium is considered as an ultra-filter due to its preventive nature as it guards the passage or transport of substance with higher molecular weight including antibiotics and proteins. During the formation of aqueous humor some substances can be secreted in it, preferably those molecules which are having low molecular weight. Another barrier i.e. the blood-aqueous humor barrier gets disrupted when some inflammation occurs in the eye due to some ocular disease or infection. At this disrupted stage some of the drugs can get access to the aqueous humor and eventually reaches the anterior parts of the eye. Another highly viscous barrier present in the eye is the blood-vitreous humor barrier. Due to its high viscosity, it is extremely difficult for a drug molecule to diffuse through it. Drug delivery to the posterior part of the eye is considered highly difficult and an extremely challenging endeavour[13,14].

Ocular penetration of locally administered drugs: Active Drug substance which is intended to work or show its effects inside the eye and not in the outer surface has to pass through the protective barriers and layers of the eye to enter inside. A general agreement exists that says, the trans corneal route is the most essential one for the transport of drugs into the eye, however, another route i.e. non-corneal is also having some significant importance in contributing to the absorption of some drug in the ocular region, for example, timolol. Additionally, many blocking agents used in ocular diseases shows high permeability to the sclera. A tear that is secreted has a primary function to keep the cornea clear, healthy, and moist which is evenly spread with the help of eyelids as a result of blinking, this blinking can change or modify the pattern and rate of trans corneal absorption[15].

OCULAR *IN-SITU* GELLING SYSTEMS

Ocular *In-situ* gelling system is ocular drug delivery systems which can undergo phase transition upon some physiochemical change from a solution or suspension to a gel form which is having some viscoelastic and sometimes bioadhesive property. The so formed gel results in the increased bioavailability along with it shows a prolonged and a sustained drug release pattern[16].

Pharmaceutical industries with the help of their formulation development departments have made a significant amount of progress in this polymer technology which has an impressive feature of transforming instantaneously to a viscous gel from a free-flowing clear liquid. As already been discussed before; these formulations before installation are free-flowing liquid but undergo phase transition after installation in the ocular region in a very short period. Three methods namely, pH triggered, ion activated, and temperature triggered have been till now used to formulate an ocular *in-situ* gelling system[17].

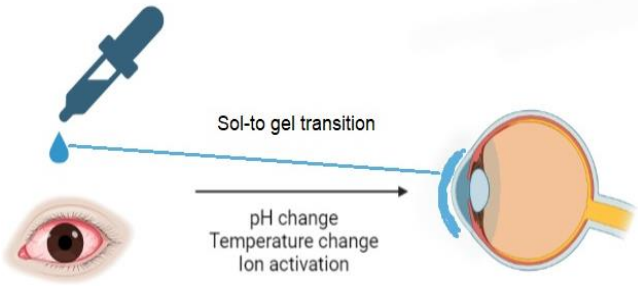

Figure 1: Mechanism of *in-situ* gel formation in the ocular region.

1. Ion activated systems

Ion activated systems as the name itself describe that phase transition is activated by some ion presence. The free-flowing liquid is converted to a viscous gel after installing it to the ocular region due to the change in ionic strength. For example, sodium alginate forms a viscoelastic gel which is clear in the presence of divalent cations such as calcium which is found in the tear fluid[18].

Polymers used in ion activated systems:

Alginate/ Alginic acid: Alginic acid also known as algin or alginate is an anionic polysaccharide that is found abundantly in the cell walls of brown algae which is a sea weed and is also found in some types of bacteria. It is hydrophilic in nature and forms a viscous gel when it comes in contact with water. Structurally it is a copolymer having a linear shape with homopolymeric blocks of (1→4)-linked β-D-mannuronate (M) and α-L-guluronate(G) residues, respectively, covalently linked together in different blocks or sequences. The most widely used alginate in *in-situ* gel technology is the sodium salt of alginic acid i.e., sodium alginate. Its phase transition from sol-to-gel is due to its interaction with the divalent action i.e., calcium ion (Ca2+) found in the tear fluid[19].

Pectin: Pectins belongs to the family of heteropolysaccharides, which is found abundantly in the primary and middle lamella and cell walls of terrestrial plants. Pectin is produced commercially from citrus fruits as is usually used as a gelling agent in the food industry. Structurally they are rich in α-(1,4)-d-galacturonic acid, various other distinct polysaccharide is identified within the pectin. It is soluble in water which is the most advantageous feature of the pectin that allows the avoidance of other solvents like organic solvents to be used in the delivery system[19,20].

Gellan gum: Gellan gum is another water-soluble anionic polysaccharide that is employed to produce ion-activated hydrogels. It is a having a linear heteropolysaccharide having a repeating unit of tetrasaccharide, which consist of D-glucose and one of each residue of L-rhamnose and D-glucuronic acid. Gellan gum is categorized into two groups; low acyl and high acyl depending upon the number of acetate groups attached to the polymer. Electrolytes like Ca^{2+}, Na^{+} and Mg^{2+} present in the lachrymal fluid is responsible for inducing gel formation upon administration of the formulation as a free-flowing liquid solution into the precorneal area[20].

2. pH triggered systems

pH triggered systems can be defines as those oculars *in-situ* gel-forming systems that upon installation conventionally as an eye drop within a short period gets converted to a gel due to its exposure to different pH level (here it is pH of precorneal area).This happens due to the presence of pH-sensitive substances or polymers in the formulation. At low pH (pH 4- 4.4) the prepared formulation remains as a free-flowing solution but upon instillation, it gets converted to a viscous gel due to a higher pH of lachrymal fluid that is pH 7.4[21].

Polymers used in pH triggered systems:

Carbopol (Polyacrylic acid): Carbopol is a synthetic high molecular weight polymer of acrylic acid also known as polyacrylic acid. Carbopol may be cross linked with an allyl ether of pentaerythritol or allyl ether of propylene or maybe homopolymers of acrylic acid. The groups present mainly carboxylic group in the carbopol, releases or accept protons at a high and low value of pH, respectively. It shows gel phase transition from sol to gel when the pH is raised above 5.5[22].

3.Temperature triggered systems

Temperature triggered systems can be defined as those oculars *in-situ* gel-forming systems that have the ability to transform from a free-flowing liquid to a viscous gel, due to the temperature of the ocular region. The phase transition of the formulation to a gel from a solution is basically due to the temperature-sensitive polymers incorporated in it. Temperature triggered *in-situ* systems are the most widely studied topic among other ocular *in-situ* gel-forming systems. At lower temperature, this formulation is in the form of the free-flowing solution but upon exposure to the ocular region with the rise in temperature gets converted to a viscoelastic gel. The required temperature for phase transition for a temperature-triggered system is the normal physiological or ocular temperature no external heat for temperature rise is needed[22,23].

Polymers used in Temperature triggered in-situ systems:

Chitosan: Chitosan is sugar that is basically produced from the outer skeleton of shellfish, shrimp, lobster, and crabs. Generally used as a dietary supplement. It is made by treating the chitin shells of the above-mentioned crustaceans with an alkaline substance, for example, sodium hydroxide. Chemically it a linear polysaccharide composed of randomly distributed β-(1→40)-linked D-glucosamine and N-acetyl-D glucosamine which is deacetylated and acetylated units, respectively. Chitosan possesses advantageous features like mucoadhesiveness, biocompatibility, low cytotoxicity, and

biodegradability, due to which it is widely used in the biomedical field[23].

Xyloglucan: Xyloglucan, another polysaccharide, is a hemicellulose which is obtained from the primary cell wall of vascular plants generally from tamarind seeds; therefore, sometimes referred to as tamarind seed polysaccharide. It has a backbone of β→4-linked glucose residue, most of which is substituted with 1-6 linked xylose side chain. Xyloglucan when it degrades partially byβ-galactosidase forms gel in an aqueous solution[23,24].

Poloxamers (Pluronic): Poloxamers consist of a non ionic triblock copolymer composed of a central hydrophobic chain of polyoxypropylene (polypropylene oxide) guarded by two hydrophilic chains of polyoxyethylene (polyethylene oxide). Due to the presence of both hydrophilic units(ethylene oxide) and hydrophobic units (propylene oxide), it is amphiphilic in nature. This polymer undergoes a phase transition above 15% (w/w) concentration from sol-to-gel at normal body temperature. The most possible reasons for this sol-to-gel transition must be the slow desolvation and increased aggregation of the micelle along with the additional entanglement within the polymer of the polymeric system[24,25].

EVALUATION

In-situ gels can be evaluated for the following parameters:

1. pH measurement

The pH of the ocular *in-situ* gel-forming systems is usually measured with the help of a pH meter which has to be pre-calibrated. The calibration of the pH meter is done using buffers of pH 7 and 4 as per the standard procedures[26].

2. Gelling capacity

This evaluation is necessary to know the time taken by the formulation to phase transit from sol to gel. The gelling capacity of the *in-situ* formulations is usually determined by making use of simulated tear fluid or STF. 0.5-1 ml of a formulation is placed in the 2.0- 3.0 ml of STF, and the time taken by the dropped formulation to transform to a gel is noted[27].

3. Visual appearance and clarity

Visual appearance and clarity of ocular *in-situ* gelling systems are done to check the presence of any small, particulate substances by utilizing fluorescent light against a black and white background[28].

4. In-vitro drug release study

In-vitro drug release study is done by utilizing the Franz diffusion cell. In the receptor compartment, freshly prepared artificial tear fluid is placed. Dialysis membrane is placed in between receptor and donor compartments. The whole assembly is kept on the thermostatically controlled magnetic stirrer to simulate *in-vivo* conditions and the temperature of medium is maintained at 37°C ± 0.5°C. Medium is continuously stirred at 20 rpm. 1ml of a formulation is placed in the donor compartment. 0.5ml of Sample is withdrawn at a predetermined time interval and after every withdrawal; it is replaced by artificial tear fluid. These Samples are then analysed either on HPLC or Ultraviolet spectrophotometer[29].

5. Rheological studies

Viscosity determination of *in-situ* formulation is carried out on Brookfield viscometer having a small volume adapter. The measurement of Viscosity is done before and as well as after the gel formation by increasing angular velocity gradually from 0.5 to 100 rpm[30].

6. Accelerated stability study

The stability study for the *in-situ* formulation is carried out as per ICH guidelines to determine the physical stability of the formulation under accelerated storage conditions. Formulation is subjected to elevated temperatures and humidity conditions of 25±1°C/ 60%RH, 30±1°C/ 65%RH and 40 ± 2oC/ 75 ± 5 % RH. Samples are withdrawn at the end of 0, 30, 60 and 90 days and then evaluated for active drug content[31].

7. Drug content

For drug content evaluation firstly, in a 100ml phosphate buffer,2 to 3 ml of the formulation is dissolved after that the solution is analysed in a UV spectrophotometer[31].

Table 1: Some of the marketed products of ocular *in-situ* systems

Sl. No.	Manufacturing company	Name of the product	Drug used in the formulation	References
1.	Spectrum Thea Pharmaceuticals	Virgan	Ganciclovir	32
2.	Alcon Laboratories Inc.	Pilopine HS	Pilocarpine hydrochloride	32
3.	Insite vison	Azasite	Azithromycin	33
4.	Merck and Co. Inc	Timoptic-XE	Timolol	34

SOME OF THE ADVANTAGES OF OCULAR IN-SITU GEL-FORMING SYSTEMS

- By increasing the precorneal residence time increases the ocular bioavailability
- Provide better fit and housing of the delivery system.
- Due to the decreased loss of the active drug from the ocular region increases accurate dosing.
- Provides prolong, sustained and ultimately controlled drug delivery.
- Due to ease to administer and increased comfort, provides better patient compliance.
- Due to increased precorneal residence time, dosing frequency is significantly decreased.
- Absorption of the drug or trans-barrier (protective barriers of the eye) permeation is enhanced.
- Provides targeted drug delivery in the ocular region and prevents the loss of drug to other ocular tissues[35,36].

CONCLUSION

In ophthalmology, many efforts have been made to develop a delivery system with prolonged residence time in the ocular region, which could ultimately result in the increased ocular bioavailability by making many changes and modifications in the product formulation and product content like by incorporating mucoadhesive polymers, and by modifying the viscosity. One of the major efforts was the development of a delivery system that could transform from sol-to-gel after they are instilled in the ocular region which was named ocular *in-situ* gel-forming systems. These systems are considered to be the most promising and impressive ones and a large number of studies and experiments are carried out in this field as this system could increase the ocular bioavailability and decrease the systemic toxicity, additionally, offer great patient compliance due to its sustained a prolonged drug-releasing nature resulting in low dosing frequency. However, despite being such an impressive and promising drug delivery system only a hand full of drugs in the form of ocular in-situ gel are in clinically use, having said that, it is important that many other ophthalmic drugs that are crucially needed in ocular patient care and in ophthalmology should be further studied, experimented, and used in the form of an in-situ gel.

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