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Ophthalmic In-Situ Gel: An Overview

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ABSTRACT

One of the most difficult and fascinating fields for pharmaceutical scientists is ocular medication delivery. Ophthalmic in situ gels use a variety of polymers. Hydrogels are typically employed. These polymers will raise the viscosity of the solution. One of the most difficult and fascinating fields for pharmaceutical scientists is ocular medication delivery. The field has greatly progressed over the last 10 to 20 years.[1] When creating a new product, consideration must be exercised due to the delicate nature of the site and the numerous restrictions of the application site.[2] The eye's physiology states that it is impervious to outside chemicals. It is challenging to formulate a medicine that can sufficiently overcome the eye's protective barriers to reach the site of action.[1] The biological barrier that may prevent effective ocular drug administration was the focus of novel drug delivery technologies.[3] A significant problem for the formulator during formulation is breaking through the protective barrier without harming the permanent tissue. Blepharitis, conjunctivitis, keratitis, trachoma, glaucoma, etc. are a few common conditions that can be treated via topical medication delivery. Poor bioavailability, increased precorneal elimination, and considerable variability in efficacy are, respectively, the main drawbacks of conventional formulations including solutions, suspensions, emulsions, ointments, etc.[5] The most recommended medication formulation for ophthalmic chemotherapy is optical application because of its ease and safety.

INTRODUCTION:

To promote drug retention on the ocular surface, polymers that increase solution viscosity are used. [6] Hydrogels create a polymeric network due to the chemical or physical cross-linking of their polymer chains, which allows them to absorb vast amounts of water while staying insoluble in aqueous solutions. They resemble natural living tissue the closest of any class of synthetic biomaterials because of their high water content, which also helps the material to be biocompatible. It exhibits less tendency to absorb proteins from bodily fluids as a result of low interfacial tension.[7] The use of a dry swelling polymeric network as a drug delivery method for oral, nasal, and other routes of administration is made possible by hydrogels' capacity for drug loading and release.

HYDROGELS[8,9]

The most common way to improve drug retention on the corneal surface is undoubtedly by using polymers to increase solution viscosity. Hydrogels are polymers endowed with the ability to swell in water or aqueous solvents and induce a liquid-sol transition. Currently, two groups of hydrogels are distinguished:

- Preformed gel, and
- In situ forming gels

Preformed gels can be defined as simply viscous solutions which do not undergo any modifications after administration. In situ forming gels are formulations, applied as solutions, sols, or suspensions, that undergo gelation after installation due to physicochemical changes inherent to the eye.

The use of preformed hydrogels has some drawbacks that can limit their interest for ophthalmic drug delivery or as tear substitutes. They do not allow accurate and reproducible administration of quantities of drugs and, after administration, they often produce blurred vision, crusting of eyelids, and lachrymation. A new approach is to try to combine the advantages of both solutions and gels, such as the accuracy and facility of administration of the former and prolonged residence time of the latter. Thus, in situ hydrogels can be instilled as eye drops and undergo immediate gelation when in contact with the eye.

IN SITU GELLING SYSTEM[9,10]

The word in situ is derived from Latin which means 'in its original place or in position'. This novel drug delivery system promotes the important ease and convenience of administration, deliverance of accurate dose as well as prolonged residence time of drug in contact with mucosa, that problems generally encountered in semisolid dosage forms. In situ forming hydrogels are liquid upon instillation and undergo a phase transition in the ocular cul-de-sac to form a viscoelastic gel and this responds to environmental changes.

Advantages of in situ forming a gel

▪ Less blurred vision as compared to ointment.

▪ Decreased nasolacrimal drainage of the drug which may cause undesirable side effects due to systemic absorption (i.e., reduced systemic side effects).

▪ The possibility of administering accurate and reproducible quantities, in contrast to already gelled formulations and promoting precorneal retention. ▪ Sustained, Prolonged drug release and maintaining a relatively constant plasma profile.

▪ Reduced dosing frequency compared to preformed gel. Reduced number/frequency of applications hence improved patient compliance and comfort.

▪ Generally, more comfortable than insoluble or soluble insertion. ▪ Increased bioavailability due to increased precorneal residence time and absorption.

▪ Avoidance of hepatic first pass.

Approaches for in situ gelling system[8-11]

Ideally, an in-situ gelling system should be a low viscous, free-flowing liquid to allow for reproducible administration to the eye as drops, and the gel formed following phase transition should be strong enough to withstand the shear forces in the cul-de-sac and demonstrated long residence times in the eye. To increase the effectiveness of the drug a dosage form should be chosen that increases the contact time of the drug in the eye. This may then prolong the residence time of the gel formed in situ along with its ability to release drugs in a sustained manner will assist in enhancing the bioavailability, reducing systemic absorption, and reducing the need for frequent administration leading to improved patient compliance.

There are three broadly defined mechanisms used for triggering the in-situ gel formation of biomaterials:

A. Physiological stimuli (e.g., temperature and pH),

B. Physical changes in biomaterials (e.g., solvent exchange and swelling),

C. Chemical reactions (e.g., enzymatic, chemical, and photo-initiated polymerization).

A. In situ formation based on physiological stimuli:

a. Thermally triggered system: These are the in-situ systems, which are liquid at room temperature (20-25^{o}C) and form semisolid at physiological temperature (35-37^{o}C). Examples of temperature-sensitive polymers are xyloglucan, methyl cellulose, poly oxy ethylene-polypropylene copolymer (poloxamers), n-isopropyl acryl amide (NIPAM), etc.

b. pH triggered system- Are in situ systems, which are liquid under non-physiological conditions and forms semisolid gel when exposed to the physiological (pH 7.5) conditions. pH-sensitive polymers are cellulose acetate phthalate (CAP), carbomer (carbopol).

B. In situ formation based on physical mechanism:

a. Swelling- In situ formation may also occur when material absorb water from the surrounding environment and expand. One such substance is glycerol mono oleate.

b. Diffusion- This method involves the diffusion of the solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix.

C. In situ formation based on chemical reaction:

a. Ionic cross linking- Are in-situ systems, which are liquid under non physiological conditions and form semisolid gel after contact with the monovalent and divalent ions present in tears. Polymers used are Gellan gum, Sodium alginate, etc.

b. Enzyme cross-linking- Are in-situ systems, where in situ formation is catalysed by enzymes. E.g., cationic pH sensitive polymers containing immobilised insulin and glucose oxidase can swell in response to blood glucose level.

c. Photopolymerization- Is commonly used for in situ formation of biomaterials. A solution of monomer or reactive macromere and initiator can be injected into a tissue site and

application of electromagnetic radiation used to form gel. Acrylate or similar polymerizable functional groups are typically used as the polymerizable groups on the individual monomers and macromers, because they rapidly undergo polymerization in the presence of suitable initiator.

In situ gelling polymers[12-13]

Various polymers are used that can undergo phase transition at physiological conditions of the eye and remain as a liquid at non-physiological conditions (Table 5).

Table 1: Polymers used in In situ gelling system

External Stimuli	Mechanism	Examples
Temperature	The formulation is liquid at room temperature(20-25°C) which undergoes gelation in contact with body fluid (35-37°C) Temperature increases the degradation of polymer chains which leads to the formation of hydrophobic domains & transition of an aqueous liquid to hydrogel network	• Poloxamer/ Pluronics • Copolymers of Polyethylene oxide and PEO • Copolymers of Polypropylene oxide and PPO • Polyesters Xyloglucan Cellulose derivative
Ionic Interactions	Formulation undergoes liquid-gel transition under the influence of an increase in ionic strength Gel formation takes place because of complexation with polyvalent cations (like Ca2+) in the lacrimal fluid.	Chitosan, Gellan gum, Alginate
pH Change	Sol to gel transition when pH raised from 4.2 to 7.4(physiological pH) At higher pH polymer forms hydrogen bonds with mucin which leads to the formation of a hydrogel network	Pseudo latexes, Acrylate (carbopol), Cellulose acetate phthalate (CAP), Polyox

EVALUATION PARAMETERS: -

1. Clarity: - With the help of visual inspection under black and white background the clarity of formulation is determined.[14]

2. Texture analysis: - To determine consistency, firmness and cohesiveness of in situ gel is determined by using a texture profile analyzer which indicates gel strength and ease of application. In vivo to maintain the intimate contact of gel with mucus surface, polymer should have high adhesiveness value.[15]

3. sol-gel transition temperature and gelling time: - This evaluation test is carried out for the formulations which are formulated by using thermo-sensitive polymer. For these tests the sample is kept in tube and kept the sample tube at specific temperature and then heated at specified rate. The conversion in gel is checked by tilting the test tube, no movement of sample seen one can say that gel is formed. Gelling time can be defined as time required for first detection of gelation as mentioned above.[16]

4. Gel strength: - For evaluation of gel strength rheometer is used. The gel is prepared in beaker as mentioned in the formulation from sol form. The gel-containing beaker is raised at certain rate, to push the probe slowly down through the gel. The changes in load from gel to empty space can be measured as a function of depth of immersion of probe below the gel surface.[16]

5. In vitro drug release studies: - Franz diffusion cell is used to determine in vitro release study of in situ gel. In this instrument, two compartments are present, in which formulation is placed in donor compartment and freshly prepared stimulated tear fluid in receptor compartment. The dialysis membrane is placed (0.22 µm pore size) between receptor donor compartments. The whole assembly is placed on the thermostatically controlled magnetic stirrer. The temperature is maintained at 37ºc± 0.5ºc. 1 ml sample is withdrawn at time interval of one hour for six hours. This sample is diluted to 10 ml volumetric flask with suitable solvent and analyzed by UV using reagent blank. With the help of standard calibration curve drug content is calculated. The % cumulative drug release is also calculated.[17]

6. Ocular irritancy test: - These studies are performed on male albino rabbits (weight 1-2kg). The modified Draize technique is used for checking ocular irritation potential.[18] The formulation is placed in lower cul-de-sac and irritancy is tested at time interval of 1hr, 2hr,

48hr, 72hr, and 1 week after administration.[19] then observes the rabbits are observed periodically for redness, swelling & watering of eyes.[20]

7. Gelling capacity: - In proportion of 25:7 the in-situ gel is mixed with simulated tear fluid respectively. The gelation is accessed visually by noting time taken for gelation and time taken for dissolution of formed gel. [21]

8. Rheological studies: - With the help of Brookfield viscometer, cone and plate viscometer the viscosity of the formulation is determined. the viscosity of Formulation should be 5-100mPas, before gelling and after ion gel activation by eye will have viscosity ranging from 50-50,000 mPas.[22,23]

9. Isotonicity evaluation: - In case of ophthalmic preparations isotonicity is maintained prevent tissue damage or irritation of eye. The formulation is mixed with few drops of blood & observed under a microscope at 45x magnification and compared with standard marketing formulations.[24]

10. Sterility testing: - To carry out sterility testing formulation should be incubated at 300-350 degree Celsius for not less than 14 days in fluid thioglycolate media. Incubation of formulation at 200-250 degree Celsius in soya bean casein digest medium. Thioglycolate medium used to find growth of bacteria whereas soya bean casein medium is for fungi in formulation.[25]

11. Accelerated stability studies: - Place formulation in amber color vial and sealed it with aluminum foil for accelerated stability studies at 40± 20 c and relative humidity 75±5% as mentioned in ICH and placed the vial for stability studies. After every month sample is analyzed for clarity, pH, gelling capacity, drug content, rheological evaluation and in vitro dissolution.[2]

12. Texture analysis: - With the help of texture profile analyzer the consistency, firmness and cohesiveness of in situ gel can be analyzed. These studies may indicate gel strength and easiness in administration. For intimate contact of gel with mucus membrane the value of adhesiveness should be high.[21]

Mechanisms of Ocular Drug Absorption[26-35]

Topical delivery into the cul-de-sac is, by far, the most common route of ocular drug delivery. Adsorption from this site may be corneal or noncorneal.

A. Corneal Permeation:

Corneal absorption represents the major mechanism of absorption for most therapeutic entities. Topical absorption of these agents, then, is considered to be rate limited by the cornea. The anatomical structures of the cornea exert unique differential solubility requirements for drug candidates. Figure 5 illustrates a cross-sectional view of the cornea. In terms of transcorneal flux of drugs, the cornea can be viewed as a trilaminate structure consisting of three major diffusional barriers: epithelium, stroma, and endothelium. The epithelium and endothelium contain on the order of 100-fold the amount of lipid material per unit mass of the stroma. Depending on the physiochemical properties of the drug entity, the diffusional resistance offered by these tissues varies greatly.

The outermost layer, the epithelium, represents the rate-limiting barrier for transcorneal diffusion of most hydrophilic drugs. The epithelium is composed of five to seven cell layers. The basement cells are columnar in nature, allowing for minimal paracellular transport. The epithelial cells, however, narrow distal to Bowman's membrane, forming flattened epithelial cells with zonulae occludentes inter-junctional complexes. This cellular arrangement precludes paracellular transport of most ophthalmic drugs and limits lateral movement within the anterior epithelium. Corneal surface epithelial intracellular pore size has been estimated to be about 60 Å. Small ionic and hydrophilic molecules appear to gain access to the anterior chamber through these pores; however, for most drugs, paracellular transport is precluded by the interjectional complexes.

Sandwiched between the corneal epithelium and endothelium is the stroma (substantiapropria). The stroma constitutes 85–90% of the total corneal mass and is composed of mainly of hydrated collagen. The stroma exerts a diffusional barrier to highly lipophilic drugs owing to its hydrophilic nature. There are no tight junction complexes in the stroma, and paracellular transport through this tissue is possible.

The innermost layer of the cornea, separated from the stroma by Descermet's membrane, is the endothelium. The endothelium is lipoidal in nature; however, it does not offer a significant barrier to the transcorneal diffusion of most drugs. Endothelial permeability depends solely on molecular w eight and not on the charge of hydrophilic nature of the compound.

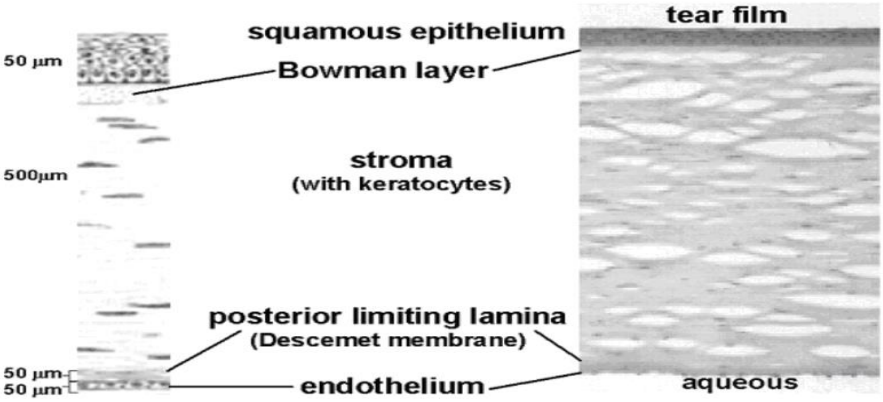

Figure 1: Cross sectional view of the corneal membrane depicting various barriers to drug absorption.

Transcellular transport across the corneal epithelium and stroma is the major mechanism of ocular absorption of topically applied ophthalmic pharmaceuticals. This type of fickian diffusion is dependent upon many factors, i.e., surface area, diffusivity, the concentration gradient established, and the period over which concentration gradient can be maintained.

B. Non-corneal Permeation:

The noncorneal route of absorption involves penetration across the sclera and conjunctiva into the intraocular tissues. This mechanism of absorption is usually nonproductive, as drug penetrating the surface of the eye beyond the corneal-scleral limbus is taken up by the local capillary beds and removed to the general circulation. This noncorneal absorption in general precludes entry into the aqueous humour. The noncorneal route of absorption may be significant for poorly cornea-permeable drugs.

Fate of formulation administered through eye[26-35]

The general process of absorption into the eye from the precorneal area (dose site) following topical ocular administration is quite complex. The classical sequence of events involves drug instillation, dilution in tear fluid, diffusion through mucin layer, corneal penetration (epithelium, stroma, endothelium), and transfer from cornea to aqueous humour. Following absorption, drug distributes to the site of action e.g., iris-Ciliary body.

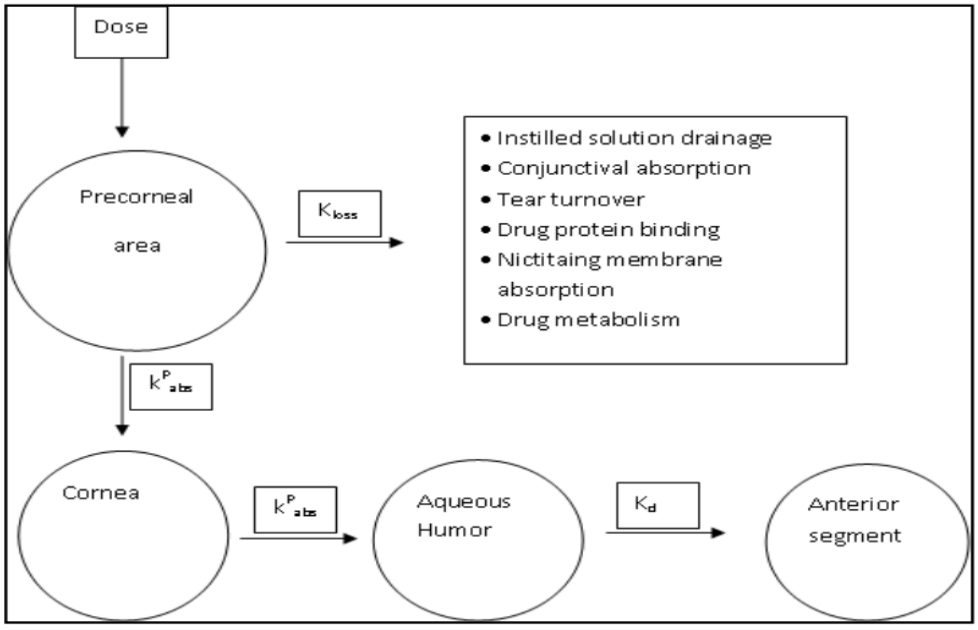

Figure 2: Model showing precorneal and intraocular events following topical ocular administration of the drug.

Parallel absorption via the conjunctiva/sclera provides an additional pathway to eye tissues but, for most drugs, is minor compared with corneal absorption. Also, nonproductive, competing, and parallel pathways (e.g., nasolacrimal drainage or systemic absorption via the conjunctiva) work to carry the drug away from the eye and limit the time allowed for the absorption process. Moreover, in some species, such as the rabbit, non-productive absorption into the nictitating membrane can occur. Figure 6 presents a summary of these precorneal events, along with a relatively simplified view of the kinetics in the cornea, aqueous humor, and anterior segment.

BARRIERS TO OCULAR DELIVERY [30]

1. Drug loss from the ocular surface

After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of the eye. Even though the lacrimal turnover rate is only about 1 µl /min the excess volume of the instilled fluid is flown to the nasolacrimal duct rapidly in a couple of minutes. Another source of non-productive drug removal is its systemic absorption instead of ocular absorption. Systemic absorption may take place either directly from the conjunctival sac via local blood capillaries or after the solution flow to the nasal cavity.

2. Lacrimal fluid-eye barriers

Corneal epithelium limits drug absorption from the lacrimal fluid into the eye. The corneal epithelial cells form tight junctions that limit the paracellular drug permeation. Therefore, lipophilic drugs have typically at least an order of magnitude higher permeability in the cornea than hydrophilic drugs. In general, the conjunctiva is leakier epithelium than the cornea and its surface area is also nearly 20 times greater than that of the cornea.

3. Blood-ocular barriers

The eye is protected from the xenobiotics in the bloodstream by blood-ocular barriers. These barriers have two parts: blood-aqueous barrier and blood-retina barrier. The anterior blood-eye barrier is composed of the endothelial cells in the uvea (The middle layer of the eye beneath the sclera. It consists of the iris, Ciliary body, and choroid). This barrier prevents the access of plasma albumin into the aqueous humour, and also limits the access of hydrophilic drugs from plasma into the aqueous humour. The posterior barrier between bloodstream and eye is comprised of retinal pigment epithelium (RPE) and the tight walls of retinal capillaries. Unlike retinal capillaries, the vasculature of the choroid has extensive blood flow and leaky walls. Drugs easily gain access to the choroidal extravascular space, but thereafter distribution into the retina is limited by the RPE and retinal endothelial.

APPROACHES FOR THE ENHANCEMENT OF OCULAR BIOAVAILABILITY[28]

- **Early attempts to enhance ocular bioavailability**

Initial attempts to overcome the poor bioavailability of topically instilled drugs typically involved the use of ointments based on mixtures of white petrolatum and mineral oils and suspensions. Ointments ensure superior drug bioavailability by increasing the contact time with the eye, minimizing the dilution by tears, and resisting nasolacrimal drainage. Because these vehicles have the major disadvantage of providing blurred vision, they are mainly used for either night time administration or for treatment on the outside and edges of the eyelids. Use of suspensions as ophthalmic delivery systems relies on the assumption that particles may persist in the conjunctival sac. The efficiency of suspensions has shown high variability, which occurred as a result of inadequate dosing, probably mainly due to the lack or patients compliance in adequately shaking the suspension before administration. These disadvantages have led to other approaches being investigated. One of the common methods to optimize prolonged pre-corneal residence time is to use hydrogels, liposomes, micro and nanocarrier

systems. In comparison with traditional formulations, these systems have the advantages of increased contact time, prolonged drug release, reduction of systemic side effects, reduction of the number of applications, and better patient compliance.

- **Recent formulation approaches to improve ocular bioavailability**

Various approaches that have been attempted to increase the bioavailability and the duration of therapeutic action of ocular drugs can be divided into two categories:

A. Based on the use of the drug delivery system, which provides the controlled and continuous delivery of ophthalmic drugs.

B. Based on maximizing corneal drug absorption and minimizing precorneal drug loss.

A more desirable dosage form would be one that can be delivered in a drop form. Creates little to no problem for vision, and needs to be dosed no more frequently than once or twice daily. Major progress has been made by ophthalmic gel technology in the development of droppable gels (in situ forming gels). The principle advantage of this formulation is the possibility of administering accurate and reproducible quantities, in contrast to already gelled formulations and promoting precorneal retention.[28]

CONCLUSION:

Ophthalmic in situ gels were introduced in this review. Several different types of polymers are utilized for gelling. Various stimuli cause the sol to become the gel. Also mentioned is the medication release from the gels. Drugs are absorbed into the eye by corneal or non-corneal penetration. This review also covers numerous evaluation parameters.

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