AN INTRODUCTION TO OPHTHALMIC IN SITU GEL: A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT
Eye is one of the sensitive organs of the human body. It is sometimes infected by bacterial, viral or any other infections. To treat those infections conventional dosage forms are available. Due to some disadvantages of these dosage forms, Novel dosage forms are available in the market nowadays. In situ gelling system is the dosage form in solution form in normal conditions and converts in to gel form at physiological conditions. Temperature sensitive, pH triggered and ion sensitive gels are most common in situ gelling system. In situ gels are evaluated for clarity, gelling time, gelling strength and capacity, rheological properties, mucoadhesive strength, in vitro drug release, In vivo ocular irritancy, sterility, Isotonisity, ex vivo studies and stability study. In situ gelling systems are one of the best alternatives to conventional preparations.

KEYWORDS: In situ gelling system, Ophthalmic in situ gel, phase transition system, Temperature sensitive gel, pH triggered gel, ion sensitive gel.

INTRODUCTION

From the eras of past 10-20 years, ophthalmic drug delivery is the most interesting and challenging drug delivery system for pharmaceutical researchers. Eye is the vital organ of our body. It is a sensory organ that converts light to an electric signal and the brain interprets it. Eye exquisitely impervious to foreign substances viz. microbes due to anatomy, physiology and biochemistry of eye. The challenge to the investigator is to circumvent the protective barriers of the eye without causing permanent tissue damage. The conventional ophthalmic dosage forms which are widely used, are eye drops, ointment, cream, suspension, emulsion. Due to some disadvantages like

Rapid precorneal elimination of solution
No sustained effect
Loss of drug by drainage
Blurred vision and sticking of eyelids in ointments
Less patient compliance
For the therapeutic treatment of most of the ophthalmic problems or diseases, topical dosage forms are clearly preferred, because in case of systemic administration of drugs, only a very small fraction of dose reaches to the eye. Thus by topical administration, can achieve an optimum concentration of drug.

Various problems faced in poor bioavailability of the eye instilled drugs are:

- Binding by the lachrymal proteins
- Drainage of the instilled solutions
- Lachrymation and tear turnover
- Limited corneal area and poor corneal metabolism
- Non-productive absorption/adsorption

To improve the bioavailability of drug, various approaches have been used which increase in the duration of drug action. There are mainly two different approaches are categorised. The first one is based on to provide the controlled and continuous ophthalmic drug delivery which is known as sustained drug delivery systems. The second involves maximizing corneal drug absorption and minimizing precorneal drug loss.

Ideal ophthalmic drug delivery system must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolonged period of time. Consequently it is imperative to optimize ophthalmic drug delivery, recently some novel ophthalmic dosage forms are available like erodible, non-erodible ophthalmic inserts, medicated lenses or in situ gelling systems to prolong the drug duration.

**Introduction to human eye**

The human eye is an organ that is able to distinguish form, color and distant of the object with the aid of brain which translates this information in to what we are refers to as vision. This is a very complex process which requires a highly developed organ, with its unique organization, architecture and physiological process. The eye has many protective mechanisms to maintain normal functions, but at times due to anatomic and different physiological conditions or to frank pathologic conditions, vision is compromised.

Eye has four most important fluid-fill components

- Tear chamber
- Anterior chamber
- Posterior chamber
- Vitreous chamber
THE TEAR CHAMBER

It is the outermost portion of the eye that interfaces with outside environment. It sometimes refers to as the precorneal area. It consists of eyelids which open to the atmosphere and conjunctiva all tissues in this chamber are continuously bathed by tear.

**The eyelids:** The eyelids are two thin and movable flaps of soft tissue covering the eye ball with the upper being larger and movable amongst two. Lower eyelid is steady. At the end of both eyelids it has eye lashes which serves in protective manner to sweep foreign particles and perspiration from the eye.

**The conjunctiva:** The conjunctiva is a loose flap made up of soft tissues that can be pulled away manually from the chamber of eye because it is attached to the anterior surface of the lid at one end and to the scleral tissue near the cornea at the other end.

**The sclera:** The white portion which is very next to the cornea and beneath the conjunctiva of the eye is generally known as the sclera. This is a fibrous dense tissue that is very rigid and more vascular.

**The cornea:** The cornea is the transparent window of the eye in curved shape. It allows light rays to enter the eye and become focused as an image on the retina which start the vision process. This tissue is very important for proper vision and must be maintain in a healthy state.
three principle layers in the cornea each of which is separated from the other by a very thin membrane.

Epithelium
Substantial propria (stroma)
Endothelium

There are mainly two membranes which separates the above various layers. First is the Bowman’s membrane, which separates the epithelium and stroma. Second is the Descemet’s membrane which separates the stroma and endothelium.

Tears: the tears are required to keep the cornea surface with the correct refractive index and in a proper state of health. The surface is continuously bathed with tears. Under the normal circumstances tears not to move themselves across the cornea but must be assisted by blinking. Tears then collects and are moved to the drainage apparatus for elimination from eye.

ANTERIOR CHAMBER

Immediately black of the cornea is the anterior chamber. It is bounded anterior by the lens and the iris and contains the transparent fluid aqueous humor.

The Iris: The iris is a tissue of eye that expands and contracts when exposed to light and chemicals. This alters the size of the pupil. Miosis and mydriasis that are observed in the iris as a biochemical event. Iris is porous and very vascular.

The ciliary processes: It contains muscles which change the degree of curvature of the lens surface to accommodate light that is, they adjust the refractive capacity of the crystalline lens for the varying distance of near vision. Moreover, the ciliary processes contribute to formulation of aqueous humor.

The lens: The lens must remain optically transparent and must have the correct index of refraction for near vision. Lens must be more rounded for great refraction or bending of light rays. This tissue is very dense so that nutrients must be supplied by the bathing fluid.

The aqueous humor: The crystal clear fluid in anterior chamber is referred to as an aqueous humor. It is mainly important for maintenance of intraocular pressure so that the cornea retains an optically useful shape. Secondly it nourishes the lens and cornea under normal circumstances.

THE POSTERIOR CHAMBER

The posterior chamber is a narrow space between the iris and the lens containing aqueous humor. Communication between anterior chamber and the posterior chamber is around the lens.

THE VITREOUS CHAMBER
The vitreous chamber contains a transparent material that keeps the eyeball in its rounded shape. This assures proper form to the retinal tissue at the rear of the eyeball.

**Mechanism of ocular drug absorption**

The drugs administered into the eye by instillation must penetrate the eye and do primarily through the corneal followed by the non-corneal permeation. This non-corneal permeation involves drug diffusion across the conjunctiva and sclera of the eye. It appears to be particularly important for drugs which are poorly absorbed across the cornea.

**Figure 2: Mechanism of ocular drug absorption**

**Corneal permeation**

From the precorneal space the drugs cross the corneal membrane. Thus, the mixing and kinetic behavior of drug disposition in tears has a direct bearing on efficiency of drug absorption into the inner eye. The productive absorption of ophthalmic drugs occurs by diffusional process across the cornea. The flux of the any ophthalmic drug molecule across the corneal membrane depends on the physiochemical properties of pertaining molecule and some interactions with the corneal membrane. The extent to which the absorption process occurs is also a function of physiological mechanism of precorneal drainage.

**Non corneal permeation**

Non corneal permeation occurs mainly by sclera and conjunctival membrane. The structure of the scleral tissue is more similar to corneal stroma so the drug can easily diffuse across the intercellular aqueous media. The conjunctival membrane is made up of epithelium tissue as cornea, so it is less resistance to permeation of ophthalmic drug.

**In situ gelling system**
In situ gelling systems are three-dimensional, cross-linked networks containing water-soluble polymers. Several terms have been coined for this system, such as ‘hydrogels’, ‘intelligent gels’, ‘smart hydrogels’. In situ gelling systems 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.\(^6\)

In-situ ophthalmic gelling system is a viscous liquid that shifts to a gel phase upon exposure to ocular environment. It is highly advantageous over the conventional preformed gels as it easily instilled in liquid form. By the physiological, physical and chemical stimuli, it can be convert from solution to gel phase.

Gelation occurs via the polymer crosslinking by covalent or non-covalent bond formation. This occurs due to chemical and physical crosslinking respectively.\(^7\)

**Advantages of in situ gelling system**\(^8\)

1. To sustain the drug release.
2. To improve systemic absorption.
3. To increase ocular bioavailability and improve therapeutic response.
5. Remain contact with corneal membrane for longer period of time.
6. To circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.
7. To provide comfort and better patient compliance.

**Drug release mechanism from in situ gelling system**\(^4\)

In situ gelling system has a unique combination of characteristics that make them useful in drug delivery applications. Due to their hydrophilicity, in situ gelling system can imbibe large amounts of water. Therefore, the molecule release mechanisms from systems are very different from hydrophobic polymers. Both simple and sophisticated models have been previously developed to predict the release of an active agent from a hydrogels device as a function of time. These models are based on the rate limiting step for controlled release and are therefore categorized as diffusion, swelling & chemically controlled mechanism.
Types of In situ gelling system

In situ gelling system can be classified into four different types:

a. **Physiological stimuli**
   1. Thermo sensitive gel
   2. pH triggered gel

b. **Physical stimuli in biomaterial**
   Solvent exchange and swelling

c. **Chemical stimuli**
   Enzymatic and photo initiated polymerization

d. **Ion exchange approach**

**Thermo sensitive gel**
Thermo sensitive gels are also known as temperature dependent in situ gelling system. It is probably the most commonly studied class of physiological stimuli. It is the very interesting approach for sol to gel transition by increasing the temperature. Formulation is liquid in the room temperature (20°C - 25°C) which undergoes gelation with contact to body fluid at 35°C to 37°C. Temperature increases the degradation of polymeric chain which leads to formulation of hydrophobic domains and transition of an aqueous liquid to in situ gel network. There are three main strategies to design temperature dependent sol to gel transition temperature. Temperature
Sensitive systems are classified into negatively thermo sensitive, positively thermo sensitive and thermo reversible gel.

Negative temperature sensitive in situ gels have a lower critical solution temperature (LCST) and contract upon heating above LCST. Polymers with LCST, transition between ambient and physiologic temperature. Positive temperature sensitive in situ gels have an upper critical solution temperature (UCST) such in situ gel contract upon cooling below UCST. Poloxamer, cellulose derivatives, Polymethacrylates, xyloglucan are used as temperature dependent polymers.

**pH triggered gel**

It is another physiological stimuli gel. In pH triggered systems sol to gel transition occurs when pH raised 5.5 to 7.4. At higher pH polymers forms hydrogen bonds with mucin which leads to formation of in situ gel networks. Carbopol, cellulose acetate phthalate, poly vinyl acetal diethyl amino acetate are used as pH dependent polymers. All pH dependent polymers contain cationic and anionic pendant groups that either accept or release the protons in response to environmental pH. Swelling of in situ gels increase in the case of weakly acidic groups but decreases if polymers having weakly basic groups.

The formulation is in solution form at pH 4 to 5 and converts in to gel form at 7 to 7.4. Carbopol forms low viscosity gel at neutralized pH as well as pH 4 of solution can damage the surface of eye. To overcome all these problems it is necessary to add HPMC as a viscosity enhancing agent in the formulation and pH is adjusted around 5.5 which is non-irritant to eye.

**Ion exchange approach**

Formulation undergoes into gel transition under influence of an increase in ion exchange. Gel formation takes place because of complexation with polyvalent cations in tear fluid. Chitosan, alginates, Gellan gum, Xanthan gums are used as ion exchange polymers. Alginate is used as gelling agent with combination of HPMC as a viscosity enhancing agent. Gellan gum is used in this approach by exchange of mono or divalent cations present in tear fluid. It is also used in combination of sodium alginate as the gelling agent.

**Solvent exchange method**

Solvent exchange method mainly depends on diffusion. In this diffusion of solvent occurs from polymeric solution to surrounding tissues of eye which results in solidification of polymeric matrix. For this solvent exchange method, N-methyl-pyrolidone is mostly used as solvent.

**Swelling**
In this method polymer or material adsorbs water from the surrounding of eye and then expands to convert into gel transition. Myverol18-99 (glycerol mono-oleate) is used as swelling material. It is the substance which is polar 1400 lipid that swells in water to form lyotropic liquid crystalline phase structures. This polymer has bioadhesive properties and can be degraded in vivo by enzymatic action.

**Evaluations of In situ gel**

**Visual appearance**

Examine the colour of formulation.

**Clarity:** Clarity is the important parameter of ophthalmic preparations. Examine clarity of all the formulations visually against white & black background.

**Texture Analysis**

The consistency, firmness and cohesiveness of in situ gelling system is assessed by using texture profile analyzer. Higher values of adhesiveness of gels are needed to maintain intimate contact with mucus surface. Texture analysis provides information on mechanical properties of gel.

**Sol-gel transition temperature and gelling time**

For thermo sensitive in situ gelling system the sol-gel transition temperature may be defined as that temperature at which the phase transition of sol meniscus is first noted when kept in the sample tube at specific temperature and then heated at specified rate. Gel formation is indicated by a lack of movement of sol on tilting the tube. Gelling time is the time for first detection of gelation as defined above.

**pH**

pH is one of the important parameter of in situ gelling system. pH should be lied nearer to ophthalmic pH 7.0 to 7.4. Measure the pH of formulation by digital pH meter.

**Gelling capacity**

Place a drop of formulation in the vial containing 2 ml of phosphate buffer 7.4. Notethe time required to form a gel and also note the time taken by the formed gel to dissolve.

**Rheological property**

Rheological properties measured by Brookfield viscometer at different RPM. The formulation having viscosity 5 to 1000 mPas in solution form and after converting to gel it should be 50 to 50000 mPas. Analyze the samples at room temperature and at 37°C. All the formulations should exhibit Newtonian and Pseudoplastic flow characteristics before and after gelling respectively.

**Gel strength**
Gel strength is one of the most important parameters for an in situ gel. Place the gel in a glass vial. Measure the time required to penetrate the plunger up to 5 cm from the initial point.

**In vitro diffusion study**

The in vitro diffusion study is carried out through dialysis membrane (Molecular weight 12000-14000 daltons) using a Franz diffusion cell. The previously soaked dialysis membrane is kept between the donor and receptor compartments. The receptor compartment is filled with phosphate buffer 7.4. And 1 ml gel is placed in the donor compartment. Aliquots each of 1 ml are taken up to 8 hours and are analysed by UV-VIS spectrophotometer at respective nm against blank. Calculate % cumulative drug release. Further calculate the data to plot Zero order, first order, Higuchi model and Korsemeyer Peppas model.

**Mucoadhesive strength**

The mucoadhesive strength is measured using a modified two arm balance for laboratory scale. The corneal mucosa is fixed to the outer surface of the bottom of the 10 ml of beaker with adhesive. The beaker is inverted and then it is kept on one side of the balance. Another corneal mucosa is attached to another beaker and it is kept over the inverted beaker. 1 gm of gel is placed between the two corneal mucosa and they are attached. Both the sides of pan are balanced with weights. Additional weights are then put on the pan and amount of weight required to detach the mucosa is noted.

**Sterility testing**

Ophthalmic preparations must be sterile. So sterility test should be performed for an in situ gelling system. It is performed by direct inoculation method as per IP. 1 ml formulation is added in fluid thioglycolate media (FTGM) and soya bean casein digest media (SCDM) (10 ml each) aseptically. FTGM is incubated at 32-35 °C and SCDM at 20-25 °C for 7 days.

**In vivo ocular irritancy test**

The test is performed with rabbits. One group containing two animals is prepared. The optimized ophthalmic in situ gel is placed in the conjunctival sac of one eye of each animal after gently pulling the lower lid away from the eyeball. The lids are then gently held together for about one second in order to prevent loss of the material. The other eye, which remains untreated, serves as a control. Ocular irritation from the formulation is determined by observations of any ocular sensitivity and reactions such as redness, swelling or watering from eye after following time periods: 5, 10, 30 min and 1, 6, 24, 48 hours.

The ocular irritation effect of the in situ gel is graded as: a) Conjunctival edema: no swelling 0, any swelling 1, Prominent swelling along with partial lid eversion 2, swelling with half closed
Isotonicity Test\textsuperscript{19}
Isotonicity is the main characteristic of ophthalmic preparations. Isotonicity has to be maintained for prevention of ophthalmic tissue damage or irritation. That is why in situ gelling system is subjected to Isotonicity test. Take one drop of blood on the glass slide. One drop of formulation is mixed with it. RBCs are examined under microscope and compare with hypotonic, isotonic and hypertonic control solutions.

Antimicrobial efficacy\textsuperscript{20}
It is determined by the agar diffusion test with cup plate technique. Marketed eye drops and developed formulation each of 1 ml was added in to cups bored in to sterile nutrient agar previously seeded with \textit{Staphylococcus aureus} or other bacteria. After allowing diffusion of the solutions for 2 hours, the agar plates are incubated at 37\degree C for 24 hours. The zone of inhibition (ZOI) is measured around each cup. The entire operation except incubation is carried out in a laminar air flow unit.

Ex \textit{vivo} permeation study\textsuperscript{21}
The ex \textit{vivo} study is carried out through goat cornea using Franz diffusion cell. Goat corneal membrane is kept between the donor and receptor compartment. Receptor compartment is filled up with phosphate buffer 7.4. And 1 ml gel is placed in the donor compartment. Aliquots each of 1 ml are taken up to 8 hours and is analysed by UV- VIS spectrophotometer.

Stability study\textsuperscript{22}
Stability is defined as the extent to which a product retains, within specified limits and throughout its period of storage, the same properties and characteristics that it possessed at the time of its manufacture. Stability testing is performed to ensure that drug products retain their fitness for use until the end of their expiration dates. Formulation is subjected to stability studies at room temperature and 40\pm 1\degree C and 75\% RH for a period of one month. The samples are withdrawn after 30 days and are evaluated for drug content and \textit{In vitro} drug release, gelling capacity, pH, appearance.

CONCLUSION
In situ gelling system has very simplest ways of preparation. It is a sol to gel transition system which converts in to gel in physiological conditions. It provides sustained release effect. It has
better precorneal residence time. It increases in the ocular bioavailability. It has better patient compliance. That is why in situ gelling system is the best alternative to marketed eye drops.

REFERENCES


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