A Novel Approach for Sustained Ocular Drug Delivery: *In-Situ* Gel

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**Abstract**

To achieve effective ocular therapy, an adequate amount of active ingredients must be delivered and maintain at the site of action within the eye. The anatomical structure and the protective physiological process of the eye exert a formidable defense against ophthalmic drug delivery, leads to poor precorneal drug loss results in poor ocular by availability and ultimately poor ocular therapy. Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientists, the major problem encountered to pharmaceutical scientist is rapid precorneal elimination of the drug, resulting in poor bioavailability and therapeutic response, because of high tear fluid turnover and dynamics. To improve ophthalmic drug bioavailability, there are considerable efforts directed towards newer drug delivery systems for ophthalmic administration. Since Conventional delivery systems often result in poor bioavailability and therapeutic response because of high tear fluids turn over and dynamics cause rapid elimination of the drug from the eyes. Newer research in ophthalmic drug delivery systems is directed towards a amalgamation of several drug delivery technologies, that includes to build up systems which is not only extend the contact time of the vehicle at the ocular surface, but which at the same time slow down the removal of the drug.

**Key words:** Eye, *In-Situ*, Hydrogel, Ophthalmic

**Introduction**

The main aim of pharmacotherapeutics is the attainment of effective drug concentration at the intended site of action for a sufficient period of time to elicit the response. A major problem being faced in ocular therapeutics is the attainment of optimal concentration the site of action. Poor bioavailability of drugs from ocular dosage forms is mainly due to the tear production, transient residence time, and impermeability of corneal epithelium. The poor bioavailability and therapeutic response exhibited by conventional ophthalmic solutions due to rapid precorneal elimination of the drug may be overcome by the use of a gel system that are instilled as drops into the eye and undergo a sol-gel transition from the instilled dose. In the development of ocular drug delivery system lot of complications and difficulties are found. The conventional drug delivery such as suspension, ointment, solution shows some drawbacks like increase pre-corneal drainage, blurred vision, low bioavailability low residence time. Various problems encountered in poor bioavailability of the eye installed drugs are:

1. Binding by the lachrymal proteins,
2. Drainage of the instilled solutions,
3. Lachrimation and tear turnover,
4. Limited corneal area and poor corneal metabolism,
5. Non-productive absorption/adsorption

The poor bioavailability and therapeutic response exhibited by conventional ophthalmic solutions due to rapid precorneal elimination of the drug may be overcome by the use of a gel system that are instilled as drops into the eye and undergo a sol-gel transition in the *cul-de-sac*. This new system developed is called *in-situ* gelling system. This system shows various advantages like:

1. Improved Patient Compliance
2. Reduce Dose Frequency
3. Increase Bioavailability
4. Sustain And Controlled Delivery
In-Situ Gelling System

In-situ forming hydrogels are refer to polymer solution which can be administered as liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental changes. Gelation can be triggered by temperature, pH, ions; solvent induced and may be UV induced. Three methods have been employed to cause phase transition on the surface: change in temperature, pH, and electrolyte composition. In-situ hydrogels are providing such ‘sensor’ properties and can undergo reversible sol-gel phase transitions upon changes in the environmental condition. It is widely accepted that increasing the viscosity of a drug formulation in the pre-corneal region will lead to increased bioavailability, due to slower drainage rate from the cornea. Moreover, the efficacy of ophthalmic hydrogels is mostly based on an increase of ocular residence time via enhanced viscosity and mucoadhesive properties. Since resulted swollen hydrogel is aqueous based, it is very comfortable in the human eye. In-situ gels are preferred since they are conveniently dropped in the eye as a solution, where undergo transition into a gel. 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. In order to increase the effectiveness of the drug a dosage form should be chosen which increases the contact time of the drug in the eye. This may then prolonged residence time of the gel formed in-situ along with its ability to release drugs in sustained manner will assist in enhancing the bioavailability, reduce systemic absorption and reduce the need for frequent administration leading to improved patient compliance. Different polymers used for this in-situ gelling system according to their sensitivity for example-sodium alginate and gelrite, carbopol, poloxamer9,10.

Evaluations of In-Situ Gel

The prepared in-situ gel formulations were evaluated for clarity, pH measurement, gelling capacity, drug content, rheological study, in vitro diffusion study, isotonicity, antibacterial activity, in-vivo ocular testing in rabbits and accelerated stability studies. The formulation should have an optimum viscosity that will allow for easy instillation into the eye as a liquid (drops), which would undergo a rapid sol-to-gel transition (triggered by pH, temperature or ion exchange).

1. Texture analysis
   The firmness, consistency, and cohesiveness of hydrogels are evaluate by using texture analyser which mainly indicates the syringeability of sol so can formulation can easily be administered in-vivo. Higher values of adhesiveness are needed to maintain the intimate contact with the tissues11.

2. Physical parameters
   The formulated in-situ gel solution is tested for clarity, pH, gelling capacity, and drug content estimation.

3. Rheological studies
   The viscosity measurements can be calculated using Brookfield viscometer, Cone and Plate viscometer. The in-situ gel formulations were placed in the sampler tube. From the literature it was evident that, the formulation before gelling should have a viscosity of 5 to 1000 mPas. And after ion gel activation by the eye, will have a viscosity of from about 50- 50,000 mPas. The samples are analyzed both at room temperature at 25°C and thermo stated at 37°C ± 0.5°C by a circulating bath connected to the viscometer adaptor prior to each measurement. The angular velocity of the spindle was increased 20, 30, 50, 60, 100, 200 and the viscosity of the formulation is measured. All the formulations exhibited Newtonian and pseudoplastic flow characteristics before and after gelling in the simulated tear fluid respectively12,13.

4. Gelling capacity
   The gelling capacity of the prepared formulation is determined by placing a drop of the formulation in a vial containing 2.0 ml of freshly prepared simulated tear fluid and visually observed. The time taken for its gelling is noted16.

5. In vitro drug release studies
   In vitro release study of in-situ gel solution was carried out by using Franz diffusion cell. The formulation placed in donor compartment and freshly prepared simulated tear fluid in receptor compartment. Between donor and receptor compartment dialysis membrane is placed (0.22µm pore size). The whole assembly was placed on the thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37°C ± 0.5°C. 1ml of sample is withdrawn at predetermined time interval of 1hr for 6 hrs and same volume of fresh medium is replaced. The withdrawn samples are diluted to 10ml in a volumetric flask with respective solvent and analyzed by UV spectrophotometer at respective nm using reagent blank. The drug content calculated using the equation generated from standard calibration curve. The % cumulative drug release (%CDR) calculated. The data obtained is further subjected to curve fitting for drug release data. The best fit model is checked for Krosmeyers Peppas and Fickinian diffusion mechanism for their kinetic8,14.

6. Ocular irritancy test
   The Draize irritancy test was designed for the ocular irritation potential of the ophthalmic product prior to marketing. According to the Draize test, the amount of substance applied to the eye is normally 100µl
placed into the lower cul-de-sac with observation of the various criteria made at a designed required time interval of 1hr, 24hrs, 48 hrs, 72hrs, and 1 week after administration. Three rabbits (male) weighing 1.5 to 2kg are used for the study. The sterile formulation is instilled twice a day for a period of 7 days, and a cross-over study is carried out (a 3 day washing period with saline was carried out before the cross-over study). Rabbits are observed periodically for redness, swelling, watering of the eye.5,15

7. Isotonicity Evaluation
Isotonicity is important characteristic of the ophthalmic preparations. Isotonicity has to be maintained to prevent tissue damage or irritation of eye. All ophthalmic preparations are subjected to isotonicity testing, since they exhibited good release characteristics and gelling capacity and the requisite viscosity. Formulations are mixed with few drops of blood and observed under microscope at 45X magnification and compared with standard marketed ophthalmic formulation13,16.

8. Antibacterial activity
The microbiological growth of bacteria is measured by concentration of antibiotics and this has to be compared with that produced by known concentration of standard preparation of antibiotic. To carryout microbiological assay serial dilution method is employed11,17.

9. Accelerated stability studies
Formulations are placed in ambient colour vials and sealed with aluminium foil for a short term accelerated stability study at 40±2 °C and 75±5% RH as per International Conference on Harmonization (ICH) states Guidelines. Samples are analyzed every month for clarity, pH, gelling capacity, drug content, rheological evaluation, and in vitro dissolution18,19.

Recent Advances
One of the challenges facing today's pharmaceutical industry centers on coming up with efficient treatment options that are readily acceptable to physicians and patients. Delivery systems must also contribute to a better therapeutic outcome if they are going to provide viable alternatives to pharmaceuticals currently delivered by other routes. In situ gel formulations are one of the challenging drug delivery systems19. Various biodegradable polymers are used for formulation of in situ gels, but there are fabrication problems, difficult process ability, and use of organic solvents for their preparation (especially for synthetic polymer based systems), burst effect and irreproducible drug release kinetics. Natural polymers satisfy the characteristics of an ideal polymer but batch to batch reproducibility is difficult therefore synthetic polymers are used. The recent advancement of biotechnologies has led to the development of labile macromolecular therapeutic agents that require complex formulations for their efficient administration N-stearoyl L-alanine (m) ethyl ester s when mixed with a vegetable oil and a biocompatible hydrophilic solvent led to the formation of injectable, in situ forming organ gel. Following subcutaneous injection, leuprolide-loaded organ gel degraded and gradually released leuprolide for 14 to 25days20-24.

Conclusion
The complications in eye formulation are mainly due to specific anatomical and physiological features of eye. The primary requirement of a successful controlled release product focuses on increasing patient compliance which the in situ gels offer. The development of in-situ stimuli activated gel-forming systems for ophthalmic drug delivery provides simplest and best gel-forming systems. Exploitation of polymeric in situ gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the in situ gel dosage forms very reliable. This system is preferred over other systems for ocular delivery because it can be administered in drop form and creates significantly fewer problems with vision as well as have sustained release. It is an ideal system that maintains effective level of drug for the longer duration following a single application and offers the primary requirement of a successful controlled release product that increases patient compliance. These gels are easy to instill at the same time improved ocular bioavailability by increasing the duration of contact with corneal tissue, thereby reducing the frequency of administration required in case of conventional ophthalmic solutions, thus optimizing ocular.

References