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REVIEW ARTICLE

Formulation and Evaluation of *In-Situ* Ophthalmic Drug Delivery System

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ABSTRACT

In ocular delivery the physiological constraints imposed by the protective mechanisms of the eye lead to low absorption of drugs, resulting in a short duration of the therapeutic effect. Thus with the use of these *In-situ* gelling systems, residence time of the drug in the eye is increased. Continuous delivery of drugs in a controlled manner to the anterior chamber of the eye will eliminate the requirement for frequent drug administration, causing better patient compliance and resulting in extended duration of action .The present article describes the formulation and evaluation of an *In-situ* ophthalmic drug delivery system based on the concept of pH triggered *In-situ* gelation ,temperature dependent *In-situ* gelation and ion activated *In-situ* gelation by using different polymers.

Key words: *In-situ* gel, pH triggered *In-situ* gelation, Temperature dependent *In-situ* gelation; Ion activated *In-situ* gelation.

INTRODUCTION

Eye drops that are conventional ophthalmic delivery systems often result in poor bioavailability and therapeutic response because high tear fluid turnover and dynamics cause rapid precorneal elimination of the drug. A high frequency of eye drop instillation is associated with patient non-compliance. Inclusion of excess drug in the formulation in an attempt to overcome bioavailability problem is potentially dangerous if the drug solution drained from the eye is systemically absorbed from the nasolacrimal duct. Various ophthalmic vehicles such as inserts, ointments, Suspensions, and aqueous gels, have been developed in order to lengthen the residence time of instilled dose and enhance the ophthalmic bioavailability. These ocular drug delivery systems, however, have not been used extensively because of some drawbacks such as blurred vision from ointments or low patient compliance from inserts [11,18].

Several *In-situ* gel forming system have been developed to prolong the precorneal residence time of a drug and improve ocular bioavailability. These systems consist of polymers that exhibit sol -to-gel phase tansititions due to change in specific physico chemical parameter (pH, temperature), in their environment, the cul-de-sac in this case.

Advantages of *In-situ* forming gel:

- Generally more comfortable than insoluble or soluble insertion. Less blurred vision as compared to ointment.
- Increased bioavailability due to – Increased precorneal residence time Decreased nasolacrimal drainage of the drug which causes undesirable side effects arising due to systemic absorption of the drug through naso-lacrimal duct is reduced.
- Drug effect is prolonged hence frequent instillation of drug is not required.

The principle advantage of this formulation is the possibility of administering accurate and reproducible quantities, in contrast to already gelled formulations and moreover promoting precorneal retention.

Various approaches of *In-situ* gelation:

Depending upon the method employed to cause sol to gel phase transition on the ocular surface, the following types of systems are recognized [16]:

- **pH-triggered systems**:
  In case of pH sensitive *in-situ* gels, the pH-sensitive polymer contains pendent acidic or basic groups that either accept or release protons in response to change in environmental pH. Swelling of *in situ* gel increases as the external pH increase in the

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case of weakly basic groups. Sol to gel transition takes place when pH is raised from 4.2 to 7.4 (eye pH). At higher pH polymer forms hydrogen bonds with mucin which leads to formulation of hydrogen network.

Example: cellulose acetate phthalate (CAP) latex, carbopol, polymethacrilic acid (PMMA), polyethylene glycol (PEG), pseudo latexes.

- **Temperature dependent systems***:*
  Temperature dependent *in-situ* gel system is probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research. These *in-situ* gels are able to swell or deswell as a result of changing in the temperature of the surrounding fluid. This type of formulation is liquid at room temperature (20°-25°c) which undergoes gelation in contact with body fluid (35-75°c).
  Example: chitosan, pluronics, tetronics, xyloglucans, hydroxyl propylmethyl cellulose or hypromellose (HPMC).
- **Ion-activated systems (osmotically induced gelation)*:***
  In this polymer may undergo phase transition in presence of various ions. Gellan gum commercially available as gelrite is an anionic polysaccharide Ca2+, Mg2+, k+ and Na+. Formulation undergo liquid- gel transition under influence of an increase in ionic strength and gel formation take place because of complexation with polyvalent cations in lacrimal fluid.
  Example: gelrite, gellan, hyaluronic acid, alginates.

EVALUATION AND CHARACTERIZATION OF *IN-SITU* OPHTHALMIC GEL:

Physical parameter:

The formulated *In-situ* solution is tested for clarity, pH, gelling capacity and drug content estimation**.**

Gelling capacity:

Gelling capacity of prepared formulation is determine by placing the drop of formulation in vial containing 2.0 ml of freshly prepared simulated tear fluid and visually observed. The time taken for gelling was noted [1, 3]**.**

Rheological parameter:

The viscosity measurements can be calculated by using Brookfield viscometer, cone and plate viscometer. The *In-situ* gel formulation was placed in sampler tube. The formulation before gelling should have viscosity from 5 to 1000 mpas. After ion gel activation in the eyes it will have viscosity of about 50-50,000 mpas. The samples are analysed both at room temperature at 25 °c and thermo stated at 37 °c ± 0.5 °c by a circulating bath connected to viscometer adaptor prior to each measurement [4,5].

In vitro drug release studies:

In vitro drug release study of *In-situ* gel solution was carried by using Franz diffusion cell. Formulation placed in donor compartment and freshly prepared stimulated tear fluid in the receptor compartment. Between donor and receptor dialysis membrane is placed .Then whole assembly is placed in thermostatically controlled magnetic stirrer. The temperature of medium was maintained at 37 °c ±0.5 °c. 1 ml of sample is withdrawn at predetermine time interval of 1 hr to 6 hr and same volume of fresh is replaced. The withdrawn sample is diluted to 10 ml of volumetric flask with respective solvent and analysed by UV spectrophotometer at respective nm using blank reagent. The drug content is calculated using equation generated from standard calibration curve. The % cumulative drug release is calculated. The data obtained is further subjected to curve fitting for drug release data [1].

Texture analysis:

The consistency, firmness and cohesiveness of *In situ* gel are assessed by using texture profile analyzer which mainly indicates the gel strength and easiness in administration in vivo. The higher value of adhesiveness of gel needed to maintain an intimate contact with mucus surface [6].

Isotonicity evaluation:

Isotonicity is important characteristics of the ophthalmic preparation. Isotonicity has to be maintained to prevent tissue damage or irritation of eyes. All ophthalmic preparations are subjected to isotonicity testing, since they exhibit good release characteristics and gelling capacity and the requisite viscosity. Formulation is mixed with few drops of blood and observed under microscope at 45x magnification and compared with standard marketed ophthalmic preparation [7].

Drug polymer interaction study and thermal analysis:

Interaction study was performed with Fourier Transform Infra Red (FTIR) spectroscopy. During gelation process the nature of interacting forces can be evaluated using the technique by employing kBr pellet method. Thermo Gravimetric Analysis (TGA) can be conducted for *in- situ* forming polymeric system to quantitate the percentage of water in hydrogel. Differential Scanning Calorimetry (DSC) conducted to observe if there are any changes in thermograms

as compared with pure active ingredients used for gelation [6].

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 antibiotics. To carry out microbiological assay serial dilution method is employed [8].

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 eyes is normally 100µl placed into the lower *cul-de-sac* with observation of the various criteria made at a designed required time interval of 1 hr, 24hrs, 48 hrs, 72 hrs and 1 week after administration. Three rabbits (male) weighing 1.5 to 2 kg 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 [9, 10].

Accelerated stability studies:

Formulations are placed in ambient coloured vials and sealed with aluminium foil for a short terms accelerated stability study at 40 ±2°c and 75±5% RH as per International Conference on Harmonization (ICH) states guidelines. Samples are analysed every month for clarity, pH, gelling capacity, drug content, rheological evaluation, and *in vitro* dissolution [7].

CONCULSION

The *In-situ* ophthalmic gels prepared provide number of advantages over conventional dosage forms like sustained and prolonged release of drug, good stability and biocompatibility characteristics make this *in situ* gel very useful. These *In-situ* gels can administered in drop form and produce appreciably less inconvenience with vision .This type of dosage form is used in the treatment of glaucoma, dry eyes syndrome, shoran's syndrome, trachoma etc.

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