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REVIEW ON APPROACHES OF *IN-SITU* OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT

The eye is the most complex and precious organ of the body due to its immediate pre-corneal elimination of dosage form. In order to overcome this, researchers developed a new system; in-situ gel forming system. This formulation undergoes a phase transition in the eye to form a gel, thus prolonging the precorneal contact time which will result in improved ocular bioavailability. The conventional ocular drug delivery systems like solutions, suspensions, and ointments show drawbacks such as increased precorneal elimination, high variability in efficiency, and blurred vision respectively so there was a need for developing advanced drug delivery system. *In situ* forming polymeric formulations were developed to overcome the conventional drug therapy drawbacks these systems are in solution form before administering in the body, but once administered these systems undergo gelation. The formation of gels depends on factors like change in a specific physicochemical parameter (pH, temperature, ion-sensitive) by which the drug gets released in a sustained and controlled manner. These systems were evaluated for drug content, clarity, pH, gelling capacity, viscosity, in vitro drug release studies, texture analysis, sterility testing, isotonicity evaluation, accelerated studies and irritancy test. FT-IR spectroscopy was used to know drug and polymer incompatibilities.

KEYWORDS: *In situ* forming polymeric, improved ocular bioavailability, gelling capacity, eye, polymer.

INTRODUCTION

The eye is most interesting organ due to its drug disposition characteristics. Generally, topical application of drugs is the method of choice under most circumstances because of its convenience and safety for ophthalmic chemotherapy. A significant challenge to the

formulator is to circumvent (bypass) the protective barriers of the eye without causing permanent tissue damage. Development of newer, more sensitive diagnostic techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. Conventional ophthalmic formulations like solution, suspension, and ointment have many disadvantages which result into poor bioavailability of drug in the ocular cavity.[1]

The basic disadvantage associated with the use of ocular formulation is a rapid loss of both solutions and suspended solids. Ophthalmic ointments give blurred vision, leading to poor patient acceptance.[2] These problems can be overcome by using *in situ* gel forming ocular drug delivery system, prepared from polymer, exhibit sol-to-gel phase transition due to a change in a specific physicochemical parameter (pH, temperature, ionsensitive).[3]

The sol-gel transition can be induced by a shift in pH, temperature or ion activated systems. This type of gel combines the advantage of a solution (accurate and reproducible administration of the drug) and gels (prolonged residence time) for enhancing ocular bioavailability.[4]

Advantages of *In Situ* Ocular Drug Delivery Systems

- Sustained and controlled drug delivery.
- Improve the ocular bioavailability of the drug by increasing the corneal contact time.
- For patient compliance and enhance the therapeutic performance of the drug.
- Generally more comfortable than insoluble or soluble insertion
- System provides ease of administration[5]

Ideal Characteristics of Polymers For Preparation of *In Situ* Ophthalmic Gels

- It should be biocompatible.
- It should have pseudoplastic behavior.
- It should have a good tolerance.
- It should be capable of adherence to mucus.
- The polymer should be capable of decreasing.
- viscosity with increasing shear rate thereby lowering viscosity during blinking.[6]

MECHANISM OF *IN SITU* GELS

In situ formation based on physical mechanism

Swelling

In situ formation may also occur when a material absorbs water from surrounding environment and expand to desired space. One such substance is myverol (glycerol mono-oleate), which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some bioadhesive properties and can be degraded *in vivo* by enzymatic action.[7]

Diffusion

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of the polymer matrix. N-methyl pyrrolidone (NMP) has been shown to be useful solvent for such system.[8]

In situ formation based on chemical reactions mechanism

Chemical reactions that result *in situ* gelations may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes.[6]

APPROACHES IN *IN-SITU* GEL DRUG DELIVERY

Temperature-triggered *in-situ* gel

In temperature triggered method, transmission of sol-to-gel occurs when it comes in contact with tear fluid. The system is designed to use poloxamer and pluronics as a polymer for ophthalmic drug delivery using *in-situ* gel formation. The Bioadhesive gelling properties of these polymers are expected to an excellent drug carrier for prolonged drug delivery to the surface of the eye. Other examples, Poloxamer-407, chitosan, tetronics, xyloglucans, HPMC are the polymers with a viscosity that increases when its temperature is raised to the eye temperature.

pH-triggered *in-situ* gel

In the pH-triggered system, the main polymer used for the preparation is Carbopol 940 which is used as a gelling agent in combination with HPMC which is a viscosity enhancer. The formulation with pH-triggered *in-situ* gel is therapeutically stable, non-irritant and efficient and it will show a delaying in the release of drug for a prolonged period of time than conventional eye drops. Another example is cellulose acetate phthalate which may form a gel

by phase transition system where there is a change in pH. Other examples - polyethylene glycol, pseudo latexes.

Ion activated system

Gellan gum is the most important polymer which form gel depends on Ion activated system. Gellan gum is an anionic Exo-cellular polysaccharide which is water soluble and undergoes cation-induced gelation. Which is available as Gelrite. The solution to gel transition process is induced by the presence of monovalent or divalent ions such as Na + and Ca+, some other parameters influence the phase transition such as the concentration of polysaccharide, the temperature of the preparation, and the nature and the concentration of cations.[9]

EVALUATION OF OCULAR *IN SITU* GEL

1. Test for Clarity test / Appearance

The formulations were observed for general appearance i.e. color, odour and for the presence of suspended particulate matter. The clarity of the preparation was checked using against black and white background.[9]

2. Determination of pH

The pH of all formulations was recorded using a calibrated digital pH meter immediately after preparation.[11]

3. Gelling capacity

The gelling capacity 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 noted.[8]

4. Drug content

The drug content was determined by accurately placing 100µl of formulations in a test tube and suitably diluted with simulated tear fluid (STF) to obtain a concentration of 10µg/ml. By using UV-Visible spectrophotometer the drug concentration was determined.[12]

5. Rheological studies

Viscosity and rheological properties of *in situ* forming drug delivery systems can be assessed by using Brookfield rheometer or some other type of viscometers such as Ostwald's viscometer. The viscosity of these formulations should be such that no difficulties are

envisaged during their administration by the patient, especially during parenteral and ocular administration.[6]

6. *In vitro* drug release studies

In vitro release study of *in situ* gel solution is 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 is placed on the thermostatically controlled magnetic stirrer. The temperature of the medium is maintained at 37°C ± 0.5°C. 1ml of the sample is withdrawn at a predetermined time interval of 1hr for 6 hrs and the same volume of fresh medium is replaced. The withdrawn samples are diluted in a volumetric flask with a respective solvent to a specific volume and analyze by UV spectrophotometer at respective nm using reagent blank. The drug content is calculated using the equation generated from standard calibration curve then the % cumulative drug release (%CDR) is calculated. The data obtained is further subjected to curve fitting for drug release data.[11]

7. Texture analysis

The consistency, firmness, and cohesiveness of *in situ* gel are assessed by using texture profile analyzer which mainly indicated gel strength and easiness in administration *in vivo*. Higher values of adhesiveness of gels are needed to maintain an intimate contact with mucous surface.

8. Sterility Testing

Sterility testing was performed for aerobic and anaerobic bacteria and fungi by using fluid thioglycolate and soybean casein digest medium respectively as per the Indian Pharmacopoeia. The method used for sterility testing was direct inoculation method.10 ml culture was added to 100 ml of culture medium. Both medias were kept for incubation at 320C for 7 days and observed for any microbial growth.

9. Isotonicity evaluation

Isotonicity is an important characteristic of the ophthalmic preparations. Isotonicity should be maintained to prevent tissue damage or irritation of the eye. All ophthalmic preparations undergo isotonicity testing, Formulations mixed with few drops of blood and observed under a microscope at 45X magnification and compared with standard marketed ophthalmic formulation.

10. Ocular irritancy test

The Draize irritancy test is 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 the observation of the various criteria made at a designed required time interval of 1 hr, 24 hrs, 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 crossover study is carried out (3 day washing period with saline was carried out before the crossover study). Rabbits are observed periodically for redness, swelling, watering of the eye.[6]

11. Accelerated stability studies

Formulations are placed in ambient color vials and sealed with aluminum 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* dissolution. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

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