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In Situ Gels- A Novel Approach For Ophthalmic Drug Delivery System

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ABSTRACT
Ophthalmic drug delivery is a fascinating and challenging endeavour for pharmaceutical scientists. Traditional ocular drug delivery systems such as solutions, suspensions, and ointments have drawbacks such as increased precorneal elimination, high variability in efficiency, and blurred vision, so an advanced drug delivery system was developed. To overcome the drawbacks of traditional drug therapy, in situ forming polymeric formulations were developed. These systems are in solution form before being administered in the body, but once administered, these systems gel. Gel formation is influenced by factors such as changes in a specific physicochemical parameter (pH, temperature, ion-sensitive) that allows the drug to be released in a sustained and controlled manner. Drug content, clarity, pH, gelling capacity, viscosity, in vitro drug release tests, texture analysis, sterility testing, isotonicity evaluation, accelerated studies, and irritancy test were all tested for these systems. To determine the compatibility of drugs and polymers, FT-IR spectroscopy was performed.

Keywords: *In situ* gel, ophthalmic drug delivery, pH triggered *in situ* gelation, Temperature dependent *in situ* gelation, Ion activated *in situ* gelation.

INTRODUCTION

The eye is the most fascinating organ because of how drugs affect it. Due to its ease and safety for ocular chemotherapy, topical administration of medications is typically the method of choice. It is a huge difficulty for the formulator to get around (bypass) the eye's defences without enduring long-term tissue damage. Ocular delivery systems with high treatment efficacy continue to be made possible by the development of better, more sensitive diagnostic procedures and innovative therapeutic substances. Traditional ophthalmic formulations, such as solution, suspension, and ointment, have a number of drawbacks that contribute to the drug's poor ocular cavity bioavailability.[1]

The primary drawback of using ocular formulation is the quick loss of suspended solids and solutions. Ophthalmic ointments cause impaired vision, which makes patients less accepting of them.[2] Utilizing an in situ gel-forming ocular drug delivery system made of polymer that exhibits sol-to-gel phase transition due to a change in a certain physico-chemical parameter can solve these issues (pH, temperature, ion- sensitive).[3]

The pH, temperature, or ion activated systems can all change, causing the sol-gel transition. For improving ocular bioavailability, this form of gel combines the benefits of solutions (precise and repeatable drug administration) and gels (prolonged residence time).[4]

THE BENEFITS OF IN SITU OCULAR DRUGS DELIVERY SYSTEMS

1. To provide controlled and sustained drug delivery.[5]
2. To improve drug ocular bioavailability by increasing corneal contact time.
3. Because the drug's effect lasts longer, it is not necessary to administer it on a regular basis.[6]
4. To improve patient compliance and drug therapeutic performance.
5. More comfortable in general than insoluble or soluble insertion
6. The system is simple to administer.[7]

IDEAL CHARACTERISTICS OF POLYMERS FOR PREPARATION OF *IN SITU* OPHTHALMICGELS

1. Biocompatibility is required.
2. It has the ability to stick to the mucous membrane
3. Preferred pseudo plastic behavior of polymer.
4. Better optical clarity and good tolerance are preferred.
5. It ought to affect how tears behave.
6. The polymer ought to be able to reduce viscosity as shear rate rises.[8]

MECHANISM OF IN SITU GELS

In situ formation based on physical mechanism

Swelling

In situ formation can also occur when a material absorbs water from its surroundings and expands to fill a desired space. Myverol (glycerol mono-oleate) is a polar lipid that expands in water to form lyotropic liquid crystalline phase structures. It possesses some bioadhesive properties and can be degraded in vivo through enzymatic action.[9]

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Diffusion
The diffusion of solvent from the polymer solution into the surrounding tissue results in the precipitation or solidification of the polymer matrix. N-methyl pyrrolidone (NMP) has been demonstrated to be a suitable solvent for such a system.[10]

***In situ* formation based on chemical reaction mechanism**
Precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes are examples of chemical reactions that result in situ gelation.[11]

VARIOUS APPROACHES OF *IN SITU* GELATION
PHtriggered *in situ* gelation
pH sensitive polymers are those that contain acidic or alkaline functional groups and respond to changes in pH. The pH is a significant signal that can be addressed with pH responsive materials. A change in pH causes the solution to gel; at pH 4.4, the formulation is a free-running solution that coagulates when the pH is raised to pH 7.4 by the tear fluid. The pH change of about 2.8 units after instillation of the formulation (pH 4.4) into the tear film causes the highly fluid latex to almost instantly transform into a viscous gel. Polyelectrolytes are polymers with a large number of ionizable groups. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups.[13]

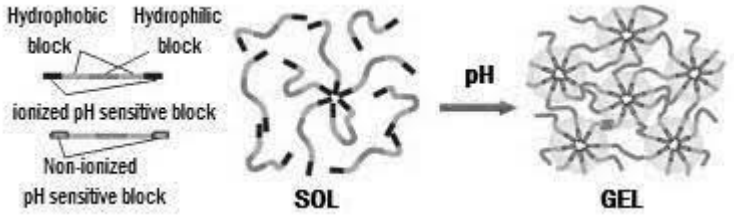

Fig 1: Mechanism of pH sensitive system.

Temperature triggered in situ gel
The most frequently employed stimulus in environmentally sensitive polymer systems is temperature. In addition to being reasonably simple to control, the temperature change is also conveniently applicable both in vitro and in vivo. In this method, a change in temperature causes the fluid to gel, continuing the drug release. These hydrogels are liquid at room temperature (20–25 °C), but due to a rise in temperature when they come into contact with bodily fluids (35–37 °C), they begin to gel. An appealing method of approaching in situ formation is the use of biomaterials whose transitions from sol-gel are induced by increase in temperature. Poloxamer or pluronics, cellulose derivatives (methyl cellulose, HPMC, ethyl (hydroxyl ethyl) cellulose (EHEC), and xyloglucan, among others, are polymers that exhibit temperature-induced gelation.[12]

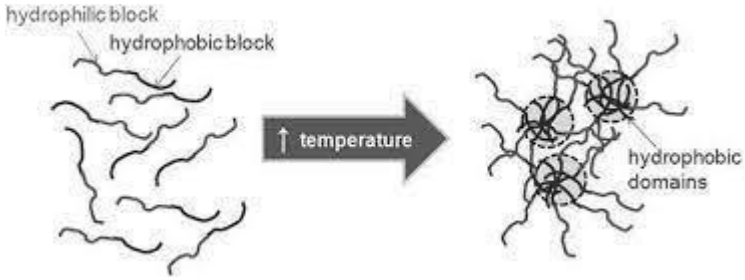

Fig 2: Mechanism of temperature sensitive system.

Ion activated *in situ* gelation
The gelling of the instilled solution is triggered by a change in ionic strength in this method. It is assumed that the rate of gelation is affected by the osmotic gradient across the gel's surface. In the presence of monovalent or divalent cations found in tear fluids, the aqueous polymer solution forms a clear gel. When instilled as a liquid solution in the conjunctival cul-de-sac, the electrolyte of the tear fluid, particularly Na+, Ca2+, and Mg2+ cations, is particularly suited to initiate polymer gelation. Gelrite or Gellan gum, Hyaluronic acid, and Alginates are examples of polymers that exhibit osmotically induced gelation.[14]

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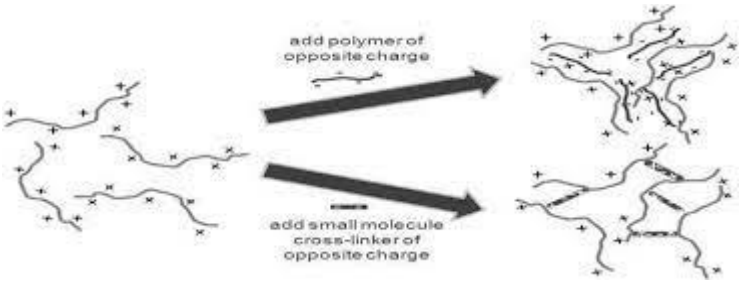

Fig 3: Mechanism showing Ion activated system.

EVALUATION OF OCULAR *IN SITU* GEL

These formulations were tested for clarity, pH, gelling capacity, drug content, rheological study, in vitro diffusion study, isotonicity, in vivo ocular testing in rabbits, and accelerated stability studies. The pH of the in situ gel solution should be 7.4 for all formulations. The formulation should have an optimal viscosity that allows for easy instillation into the eye as a liquid (drops) and a rapid soltogel transition (triggered by pH, temperature or ion exchange)

1. Test for Clarity test / Appearance

The formulations were evaluated for their overall appearance, including colour, odour, and the presence of suspended particulate matter. The preparation's clarity was tested against a black and white background.[15]

2.Determination of pH

The pH of all formulations was determined immediately after preparation using a calibrated digital pH metre.

3.Gelling capacity

A drop of the formulation is placed in a vial containing 2.0 ml of freshly prepared simulated tear fluid and visually observed to determine gelling capacity. It is noted how long it takes to gel.

4. Drug content

The drug content was determined by precisely placing 100l of formulations in a test tube and diluting with simulated tear fluid (STF) to a concentration of 10g/ml. The drug concentration was determined using a UV-Visible spectrophotometer.

5. Rheological studies

The viscosity and rheological properties of in situ forming drug delivery systems can be evaluated using a Brookfield rheometer or another type of viscometer, such as an Ostwald's viscometer. The viscosity of these formulations should be such that no difficulties are anticipated during patient administration, particularly parenteral and ocular administration.

6. In vitro Drug release studies

The Franz diffusion cell is used to conduct an in vitro release study of an in situ gel solution. The formulation was placed in the donor compartment, while freshly prepared simulated tear fluid was placed in the receptor compartment. Dialysis membrane (0.22m pore size) is placed between the donor and receptor compartments. The entire assembly is placed on the magnetic stirrer, which is thermostatically controlled. The medium's temperature is kept constant at 37°C + 0.5°C. 1ml of sample is withdrawn every 1 hour for 6 hours, and the same volume of fresh medium is replaced. The withdrawn samples are diluted in a volumetric flask with the appropriate solvent to a specific volume before being analysed by UV spectrophotometer at the appropriate nm with a reagent blank. The drug content is calculated using the equation generated by the standard calibration curve, and the % cumulative drug release (%CDR) is calculated after that. The collected data is then subjected to curve fitting for drug release data.

7. Texture Analysis

The texture profile analyzer was used to assess the consistency, firmness, and cohesiveness of in situ gel, which primarily indicated gel strength and ease of administration in vivo. Gels with higher adhesiveness values are required to maintain intimate contact with the mucus surface.

8.Sterility Testing

According to the Indian Pharmacopoea, aerobic and anaerobic bacteria and fungi were tested for sterility using fluid thioglycolate and soybean casein digest medium, respectively. The direct inoculation method was used for sterility testing. 100 ml of culture medium was mixed with 10 ml of culture. Both media were incubated at 320°C for 7 days to see if any microbial growth occurred.[16]

9. Evaluation of Isotonicity

Isotonicity is an important property of ophthalmic preparations. To avoid tissue damage or eye irritation, isotonicity should be maintained. Isotonicity testing is performed on all ophthalmic preparations. Formulations are mixed with a

few drops of blood, observed under a microscope at 45X magnification, and compared to standard marketed ophthalmic formulations.

10.Ocular irritancy test

The Draize irritancy test is intended to assess the ophthalmic product's potential for ocular irritation prior to marketing. The amount of substance applied to the eye is normally 100l placed into the lower cul de sac with 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, according to the Draize test. The study employs three male rabbits weighing 1.5 to 2 kg. The sterile formulation is instilled twice daily for 7 days, followed by a cross-over study (3 day washing period with saline prior to the cross-over study). Rabbits are observed periodically for redness, swelling, watering of the eye

11. Accelerated stability studies

Formulations are placed in ambient colored vials and sealed with aluminium foil for a short term accelerated stability study at 40±2°C/75±5% RH, Intermediate stability study 30°C ± 2°C/65% ± 5%RH and Long term at 25°C ± 2°C/60% ± 5% RH as per International Conference on Harmonization (ICH) guidelines. Samples were tested every month for clarity, pH, gelling capacity, drug content, rheological evaluation, and in vitro dissolution. Storage conditions and study lengths should be sufficient to cover storage, shipment, and subsequent use.[17]

COCLUSION AND FUTURE PROSPECTS

The eye is the most essential and sensitive part of the body, the safety issues of ophthalmic formulations is critically important. The majority of the cytotoxicity and irritability experiments that were examined in this study revealed no appreciable alterations or indications of toxicity brought on by the use of in-situ gel. However, more research is needed to determine the potential toxicity of the materials and applications used to prepare nanoparticles in nano-gel systems. Additionally, the increased viscosity of in-situ gel may restrict the patient and result in discomfort and obscured vision, which would speed up elimination through reflex tears and blinks.In order to lower the restrictions to a manageable level, important control of the viscosity should be taken into account when creating and optimising the in-situ gel formulation.

Despite the in-situ gel's significant promise for ocular drug delivery, few few in-situ gel-based medications are currently being used in clinical settings. As a result, more research should be done to examine this method of drug delivery for the therapeutic use of other ophthalmic medications.

Most ophthalmic in-situ gels are currently designated only for formulations containing a single active ingredient. In the future, some more appropriate strategies should be developed for formulas containing multiple ingredients, which requires a multi-target approach to produce their action. Finally, we anticipate the development of new and more dependable in-situ forming polymers in the future, which may be responsible for some biochemical markers associated with eye disease conditions.

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