

# ***IN SITU* GELS- A NEW TRENDS IN OPHTHALMIC DRUG DELIVERY SYSTEMS**

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## **ABSTRACT**

Ophthalmic drug delivery is one of the most interesting and challenging endeavor facing the pharmaceutical scientist. 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 physico-chemical 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* gel, pH triggered *in situ* gelation, Temperature dependent *in situ* gelation, Ion activated *in situ* gelation.

## **INTRODUCTION**

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.<sup>1</sup>

The basic disadvantage associated with the use of ocular formulation is rapid loss of both solutions and suspended solid. Ophthalmic ointments give blurred vision, leading to poor patient acceptance.<sup>2</sup> 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 physico-chemical parameter (pH, temperature, ion-sensitive).<sup>3</sup>

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 drug) and gels (prolonged residence time) for enhancing ocular bioavailability.<sup>4</sup>

## **ADVANTAGES OF *IN SITU* OCULAR DRUG DELIVERY SYSTEMS**

1. To provide sustained and controlled drug delivery.<sup>5</sup>
2. To increase the ocular bioavailability of drug by increasing the corneal contact time.
3. Drug effect is prolonged hence frequent instillation of drug is not required.<sup>6</sup>
4. For patient compliance and enhance therapeutic performance of drug.
5. Generally more comfortable than insoluble or soluble insertion
6. System provides ease of administration.<sup>7</sup>

## **IDEAL CHARACTERISTICS OF POLYMERS FOR PREPARATION OF *IN SITU* OPHTHALMIC GELS**

1. It should be biocompatible.

2. It is capable of adhering to the mucus membrane.
3. Preferred pseudo plastic behavior of polymer.
4. Good tolerance and optical clarity is more preferred.
5. It should influence the tear behavior.
6. The polymer should be capable of decreasing the viscosity with increasing shear rate<sup>8</sup>

### MECHANISM OF *IN SITU* GELS

#### *In situ* formation based on physical mechanism

##### Swelling

*In situ* formation may also occur when 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.<sup>9</sup>

##### Diffusion

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-methyl pyrrolidone (NMP) has been shown to be useful solvent for such system.<sup>10</sup>

#### *In situ* formation based on chemical reactions mechanism

Chemical reactions that results *in situ* gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes.<sup>11</sup>

### VARIOUS APPROACHES OF *IN SITU* GELATION

#### **PH**triggered *in situ* gelation

Polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH sensitive polymers. The pH is an important signal, which can be addressed through pH responsive materials. Gelling of the solution is triggered by a change in pH at pH 4.4 the formulation is a free-running solution which undergoes coagulation when the pH is raised by the tear fluid to pH 7.4. The pH change of about 2.8 units after instillation of the formulation (pH 4.4) into the tear film leads to an almost instantaneous transformation of the highly fluid latex into a viscous gel. The polymers with a large number of ionizable groups are known as polyelectrolyte. 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.<sup>13</sup>

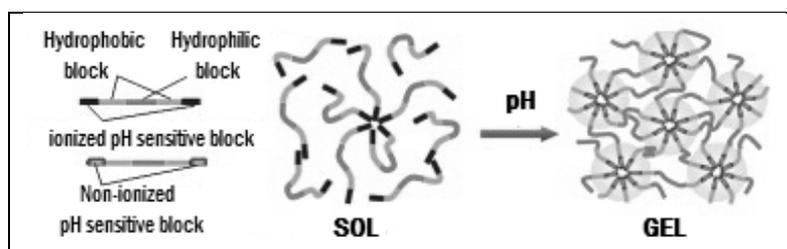
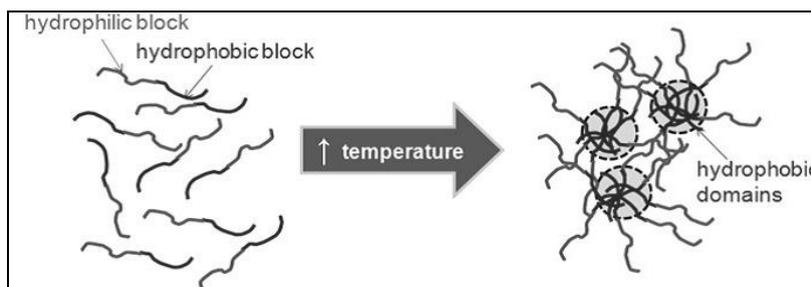


Fig 1: pH sensitive system.

#### **Temperature** triggered *in situ* gel

Temperature is the most widely used stimulus in environmentally responsive polymer systems. The change of temperature is not only relatively easy to control, but also easily applicable both *in vitro* and *in vivo*. In this system, gelling of the solution is triggered by change in temperature, thus sustaining the drug release. These hydrogels are liquid at room temperature (20–25 °C) and undergo gelation when in contact with body fluids (35– 37 °C), due to an increase in temperature. The use of biomaterial whose transitions from sol-gel is triggered by increase in temperature is an attractive way to approach *in situ* formation. The polymers which show temperature induced gelation are Poloxamer or pluronics, cellulose derivatives (methyl cellulose, HPMC, ethyl (hydroxyl ethyl) cellulose (EHEC) and xyloglucan etc.

Fig 2: Mechanism of temperature sensitive system.<sup>12</sup>**Ion activated *in situ* gelation:**

In this method, gelling of the solution instilled is triggered by change in the ionic strength. It is assumed that the rate of gelation depend on the osmotic gradient across the surface of the gel. The aqueous polymer solution forms a clear gel in the presence of the mono or divalent cations typically found in the tear fluids. The electrolyte of the tear fluid and especially Na<sup>+</sup>, Ca<sup>2+</sup> and Mg<sup>2+</sup> cations are particularly suited to initiate gelation of the polymer when instilled as a liquid solution in the conjunctival cul-de-sac. The polymer which shows osmotically induced gelation is Gelrite or Gellan gum, Hyaluronic acid and Alginates etc.<sup>14</sup>

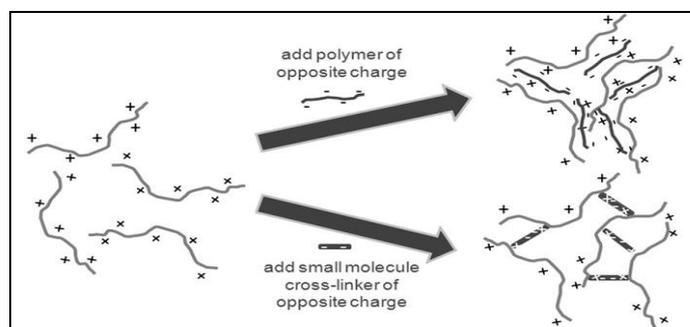


Fig 3: Mechanism showing Ion activated system.

**EVALUATION OF OCULAR *IN SITU* GEL**

These formulations were evaluated 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 *in situ* gel solution should be 7.4 for all the formulations. 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. 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.<sup>15</sup>

**2. Determination of pH**

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

**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.

**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.

**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. *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 (0.22 $\mu$ m pore size). The whole assembly is placed on the thermostatically controlled magnetic stirrer. The temperature of the medium is maintained at 37°C  $\pm$  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 in a volumetric flask with respective solvent to 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.

### 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 mucus 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 32<sup>0</sup>C for 7 days and observed for any microbial growth.<sup>16</sup>

### 9. Isotonicity evaluation

Isotonicity is important characteristic of the ophthalmic preparations. Isotonicity should be maintained to prevent tissue damage or irritation of eye. All ophthalmic preparations undergo isotonicity testing, Formulations mixed with few drops of blood and observed under 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 100 $\mu$ l 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. 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 (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.

### 11. Accelerated stability studies

Formulations are placed in ambient colour vials and sealed with aluminum foil for a short term accelerated stability study at 40 $\pm$ 2°C and 75 $\pm$ 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.<sup>17</sup>

## REFERENCES

- [1] Kumar L. Singh R.P. Singh S.G. and Kumar D. In situ Gel: A Novel System for Ocular Drug Delivery, Int. j. pharm. Sci. rev & res., 2011,9,(2):83-91.
- [2] Patel P.B. Shastri D.H. Shelat P.K. and Shukla A.K. Development and Evaluation of PH Triggered In situ Ophthalmic Gel Formulation of Ofloxacin, Am. J. Pharm. Tech. Res., 2011, 1(4):430-445.
- [3] Zarikar N. Katedeshmukh R. Kulkarni A. and Patel R. Ophthalmic In situ Drug Delivery System: A Review, Int. J. Pharm. Res. & Dev., 2013, 5(5):48 – 55.
- [4] Talat F. Sadhana R.S. Azmat M.S. Nityanand Z. and Syed A. Formulation Development and Evaluation of In situ Ophthalmic Gel of Sodium Cromoglycate. Der Pharmacia Sinica, 2013, 4(2):109-118.
- [5] Gupta A. and Manocha N. Formulation and Evaluation of In Situ Ophthalmic Drug Delivery System, Int. J. Pharm. Bio. Arch., 2012, 3(4):715-718.
- [6] Agarwal K. Mehta N. Namdev A. and Gupta A.K. In Situ Gel Formation for Ocular Drug Delivery System: An Overview, Asian J. Bio Pharm Sci., 2011, 1(4):01-07.
- [7] Rajeshwari N. Patil R. and Kumar S. In situ Gelling System: Novel Approach for Ophthalmic Drug Delivery, World J. Pharm. Pharma. Sci. 2014, 3(7):423-440.
- [8] Nittur J. R. kunchu k. Theetha G. and Tamizh M. Review on In situ Ophthalmic Gels: A Developing Trend, Int. J. Pharma. Sci. Rev. & Res., 2011, 7(1):08-14.
- [9] Parekh H.B. Rishad J. Jivani N.P. Patel L.D. Makwana A and Sameja K. Novel In situ Polymeric Drug Delivery System: A Review, J. Drug Deliv. & Therap., 2012, 2(5):136-145.
- [10] Nirmal H.B. Bakliwal S.R. and Pawar S.P. In Situ Gel: New Trends in Controlled and Sustained Drug Delivery System, Int. J. Pharm. Tech. Res., 2010, 2(2):1398-1408.
- [11] Nerkar T.S. Gujarathi N.A. Bhushan R. Bakliwal S. R. and Pawar S.P. In situ Gel: Novel Approach in Sustained and Controlled Drug Delivery System, Pharma. Sci. monitor, 2013, 4(4):1-18.

- [12] Rajoia G and Gupta A. In situ Gelling System: A Novel Approach for Ocular Drug Delivery, Am. J. Pharm. Tech. Res., 2012, 2(4):25-53.
- [13] Rathore K.S. In situ Gelling Ophthalmic Drug Delivery System: An Overview, Int. J. Pharm. Pharm. Sci., 2011, 2(4):30-34.
- [14] Bhardwaj L. Sharma P. K. and Malviya R. A Short Review on Gastro Retentive Formulations for Stomach Specific Drug Delivery: Special Emphasis on Floating In situ Gel Systems, African J. Basic & Applied Sci., 2011,3(6): 300-312.
- [15] Sampathi S. Design, Development and Characterization: In situ Gels of Lomefloxacin Hydrochloride for Ocular Drug Delivery, World J. Pharm. Pharma. Sci., 2014, 3(2):2350-2364.
- [16] Vengurlekar P. Singh A. and Rathod S. Microspheric In situ Gel for Ocular Drug Delivery System of Bromfenac Sodium, Int. J. Pharma. Sci. Res., 2014, 5(4):179-185.
- [17] Gambhire S. bhalerao K. and Singh S. Review on In situ Hydrogel: Different Approaches to Ocular Drug Delivery, Int. J. Pharm. Pharm. Sci.,2013,5(2):27-36.