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IN - SITU OPHTHALMIC DRUG DELIVERY SYSTEMS – AN OVERVIEW

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Abstract:

Eye is the most vital organ of the body. To achieve effective ocular therapy, an adequate amount of active ingredients must be delivered and maintain at the site of action within the eye. Ocular drug delivery is the most challenging and interesting field for the pharma scientists due to the unique anatomy of the eye. The major disadvantage of ocular drug delivery is lachrymal drainage of the drug leads to poor bioavailability. 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. dendrimers, There are various new dosage forms like insitu gel, collagen shield, minidisc, ocular film, ocusert, nanosuspension, nano particulate system, liposomes, niosomes, dendrimers, ocular iontophoresis etc.

Key words: *In-situ gel, ocusert, liposomes, niosomes, dendrimers, iontophoresis.*

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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 [1].

Development of ophthalmic drug delivery systems has always been challenging because of the drawbacks with ocular route like non-productive absorption, drainage, induced lacrimation, tear turn over, impermeability of drugs to cornea[2]. Topical application of drugs to the eye is the well established route of administration for the treatment of various eye diseases like dryness, conjunctivitis, keratitis, eye flu etc. New approaches have been investigated for delivery of drugs to the eye by means of polymeric delivery of drugs to the pre and intra ocular tissues, have been attempted to increase the bioavailability and the duration of therapeutic action of ocular drug. Therefore, it is necessary to develop safer, efficacious and more acceptable ocular therapeutic system. The ocular bioavailability of the drugs can be improved by prolonging their residence time in the cul-de-sac and by increasing their corneal permeability. There are various new dosage forms like In situ gel, collagen shield, niosomes, liposomes, dendrimers and implants [3].

Disadvantages of Conventional Ophthalmic Delivery Systems [4]:

- Poor ocular bioavailability
- Poor therapeutic response
- Rapid precorneal elimination of the drug
- High frequency of administration
- Patient non-compliance
- Blurred vision
- Nasolacrimal drainage of the drug
- Irritation to the eye
- Cellular damage eat the ocular surface
- Toxic side effects.

Advantages of *In-situ* gel:

- Less blurred vision as compared to ointment
- Increased precorneal residence time
- Increased bioavailability
- Decreased nasolacrimal drainage of the drug
- Drug effect is prolonged
- Accuracy and reproducible quantities
- Promoting precorneal retention.
- Generally more comfortable than insoluble inserts.
- Chance of undesirable side effects arising due to systematic absorption of drug through nasolacrimal duct is reduced.
- Drug effect is prolonged hence frequent instillation of drug is not required.

Challenges in Ocular Drug Delivery Formulation:

1. Anatomical
- Special anatomy
- Protective mechanisms
- Limited area of absorption.

2. Biopharmaceutical
- Hydro and lipophillicity
- Molecule size
- Protein binding.

3. Patient
- Easy handling
- Self administration
- No discomfort
- No blurred vision
- No visual disorders
- Be non invasive
- Low price.

Mechanism of Drug Absorption:

1. Non Corneal Absorption:

Penetration across sclera and conjuctiva into intra ocular tissues.

Non productive because penetrated drug is absorbed by general circulation.

2. **Corneal Absorption:**

Outer epithelium is a rate limiting barrier, with a pore size 60° only access to ionic and lipophilic molecules.

Transcellular transport**:** transport between corneal epithelium and stroma.

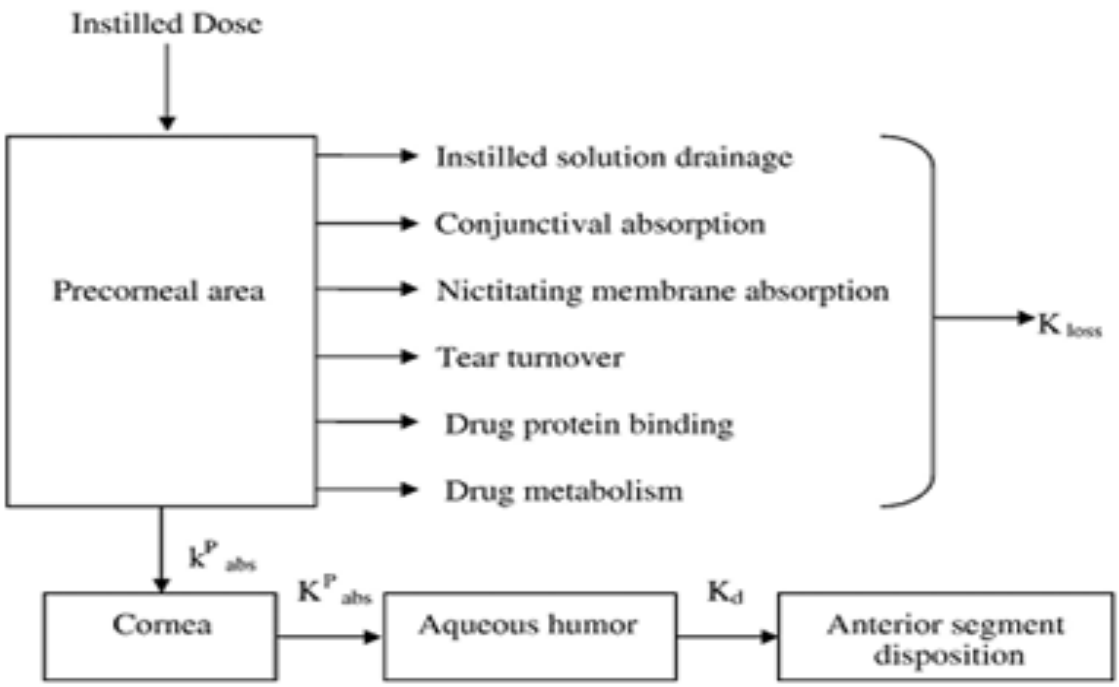

Fig 1: Model Depicting Precorneal and Intraocular Drug Movement from Topical Dosing[5].

Various Approaches of *In-Situ* Gelation [6]:

There are four broadly defined mechanisms used for triggering the *in situ* gel formation of biomaterials:

- Physiological stimuli (e.g., temperature and pH),
- Physical changes in biomaterials (e.g., solvent exchange and swelling),
- Chemical reactions (e.g., enzymatic, chemical and photo-initiated polymerization)

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

1. *In Situ* Formation Based On Physiological Stimuli

Thermally trigged system:
The system is designed to use Poloxamer as a vehicle for ophthalmic drug delivery using *in-situ* gel formation property. The gelation temperature of graft copolymers can be determined by measuring the temperature at which immobility of the meniscus in each solution was first noted. The bioadhesive and thermally gelling of these graft copolymers expected to be an excellent drug carrier for the prolonged delivery to surface of the eye. Other example of Poloxamer-407 (a polyoxyethylene polyoxypropylene block copolymer) is a polymer with a solution viscosity that increases when its temperature is raised to the eye temperature [7,8].

pH- Triggered System:
Polyacrlic acid (Carbopol 940) is used as the gelling agent in combination with hydroxy propyl-methylcellulose (Methocel E50LV) which acted as a viscosity enhancing agent. The formulation with pH-triggered *in-situ* gel is therapeutically efficacious, stable, non-irritant and provided sustained release of the drug for longer period of time than conventional eye drops. Another example cellulose acetate phthalate (CAP) is a polymer undergoing coagulation when the original pH of the solution (4.5) is raised to 7.4 by the tear fluid [9,10,11].

2. *In Situ* Formation Based On Physical Mechanism [12]:

Swelling:
In situ formation may also occur when material absorbs water from surrounding environment and expand to occur desired space. One such substance is myverol 18-99 (glycerol mono-oleate), which is polar 1400 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.

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.

3. *In situ* Formation Based on Chemical Reactions [12]:
Chemical reactions that results in situ gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes.

Ionic Cross Linking
Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion-sensitive ones .While k-carrageenan forms rigid, brittle gels in reply of small amount of K+, icarrageenan forms elastic gels mainly in the presence of Ca2+. Gellan gum commercially available as Gelrite® is an anionic polysaccharide that undergoes in situ gelling in the presence of mono- and divalent cations, including Ca2+, Mg2+, K+ and Na+. Gelation of the low-methoxy pectins can be caused by divalent cations, especially Ca2+. Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations eg. Ca2+ due to the interaction with glucuronic acid block in alginate.

Enzymatic Cross-Linking:
In situ formation catalyzed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators. Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion. Adjusting the amount of enzyme also provides a convenient mechanism for controlling the rate of gel formation, which allows the mixtures to be injected before gel formation.

Photo-Polymerization:
Photo-polymerization is commonly used for *in situ* formation of biomaterials. A solution of monomers or reactive macromer and initiator can be injected into a tissues site and the application of electromagnetic radiation used to form gel. Acrylate or similar polymerizable functional groups are typically used as the polymerizable groups on the individual monomers and macromers because they rapidly undergo photo polymerization in the presence of suitable photo initiator. Typically long wavelength ultraviolet and visible wavelengths are used. Short wavelength ultraviolet is not used often because it has limited penetration of tissue and biologically harmful. A ketone, such as 2,2-dimethoxy-2-phenyl acetophenone, is often used as the initiator for ultraviolet photo-polymerization, where as camphorquinone and ethyl eosin initiators are often used in visible light systems. The photo-reactions provide rapid polymerization rates at physiological temperature. Furthermore, the systems are easily placed in complex shaped volumes leading to an implant formation.

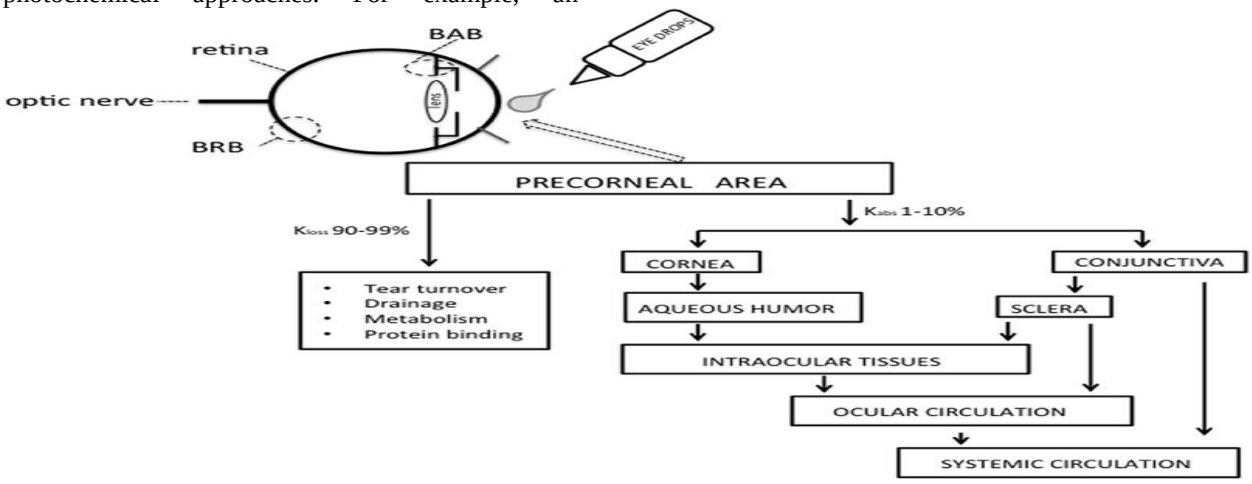

Fig 2: Movement of Drug into the Eye after Topical Administration [13]

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 determined 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 [9,14].

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 [15,16].

***In Vitro* Drug Release Studies:**

In vitro drug release study of *in-situ* gel solution was carried out 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 [9].

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 [17].

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 [18].

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 [17].

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 [19].

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 culde-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 [20].

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 [21].

Commercial Formulations of *In-Situ* Polymeric Systems At A Glance [22] :

Regel: Depot-Technology

Regel is one of the Macromed's proprietary drug deliverysystem and based on triblock copolymer, composed of poly (lactide-co-glycolide)-poly (ethylene glycol)-poly(lactide-co-glycolide). It is a family of thermally reversible gelling polymers developed for parenteral delivery thatoffers a range of gelation temperature, degradation rates and release characteristics as a function of molecular weight, degree of hydrophobicity and polymer concentration. Following injection, the physical propertiesof polymer undergo a reversible phase change resulting information of a water insoluble, biodegradable gel depot.Oncogel is a frozen formulation of paclitaxel in Regel. It isa free flowing liquid below room temperature which uponinjection forms a gel in-situ in response to bodytemperature. hGHD-1 is a novel injectable depotformulation of human growth hormone (hGH) utilizingMacromed's Regel drug delivery system for treatment ofpatients with hGHdeficiency**.**

Cytoryn

This is one of the Macromed's products, which is a novel,peritumoral, injectable depot formulation of interleukin-2(IL-2) for cancer immunotherapy using Regel drug delivery system. It is a free flowing liquid below room temperature that instantly forms a gel depot upon injection from which the drug is released in a controlled manner.Cytoryn enhances the immunological response by safely delivering four times the maximum tolerated dose allowedby conventional IL-2 therapy. Cytoryn also activates the systemic antitumor immunity. Regel system stabilizes andreleases IL-2 in its bioactive form. The release of drugs is controlled by the rate of diffusion from and degradation of the depot.

Timoptic-XE

It is a timolol maleate ophthalmic gel formulation ofMerck and Co. Inc., supplied as a sterile, isotonic,buffered, aqueous gel forming solution of timolol maleate.This formulation is available in two dosage strengths0.25% and 0.5% in market. The pH of the solution is approximately 7.0, and the osmolarity is 260-330 mOsm. Each ml of Timoptic-XE 0.25% contains 2.5 mg of timolol(3.4 mg of timolol maleate). Inactive ingredients include gellan gum, tromethamine, mannitol, and water forinjection and the preservative used is benzododecinium bromide 0.012%. Timoptic- XE, when applied topically onthe eye, reduces the elevated, as well as normal intraocular pressure, whether or not accompanied by glaucoma.

Table 1: List of Drugs Used With Their Mechanism of Gelation [23]

Drug Used	Mechanism of Gelation
Azithromycin	Thermoreversible
Brimonidine Tartrate	Temperature dependent
Gatifloxacin	pH triggered
Ketorolac Tromethamine	Ion-activated
Lomefloxacin HCl	pH induced
Naphazoline Hydrochloride	pH induced

CONCLUSION:

The main effort in ocular drug delivery is to prolong the residence time of drugs. The development of ophthalmic drug delivery systems is easy because we can easily target the eye to treat ocular diseases. The eye has specific characteristics such as eye protecting mechanism, which make ocular delivery systems extremely difficult. The most widely developed drug delivery is represented by the conventional and non-conventional ophthalmic formulations to polymeric hydrogels, nanoparticle, nanosuspensions, microemulsions, iontophoresis and ocular inserts. In future an ideal *in situ* ophthalmic gel system may be able to achieve an effective drug concentration at the target tissue for an extended period of time, while minimizing systemic exposure and the system may be both comfortable and easy to use.

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