



## Insitu Ophthalmic Drug Delivery Systems

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### ABSTRACT

Eyes are considered as one of the most important organs of the body. The main hurdle for achieving effective ocular treatment is the maintenance of adequate quantity of drug at the site of action within the eye. Maintaining the concentration of drug in the eye is a difficult task as the anatomy and physiology of the eye leads to the draining of the drug from the eye. This leads to poor ocular bio availability and there by poor ocular therapy. The ocular bio availability can be improved by increasing the ocular retention time of the formulation. Insitu gel formation technology is a promising technique to prevent the lacrimal drainage of the drug rapidly from the eyes. Insitu gel preparation will be in liquid form when prepared, they are administered into the Cul-de-sac of the eye. Due to the environmental characteristics of the eye such as temperature, pH, Ionic concentration etc. the liquid formulation changes to gel form. This will increase the residence time and contact time of the drug with the mucosa of the eye. Insitu gels can increase the ocular bioavailability of the drug. The primary requirement of a successful control release product focuses on increasing patient compliance, good stability and bio compatibility. Insitu gels are used now a days as vehicles for both local and systemic drug therapies. This review deals with the study of a novel insitu gel approaches as a means to localize and prolong drug activity at its site of action.



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### INTRODUCTION

Nowadays insitu gels are used commonly to deliver the drug into the eye. These insitu gels have certain advantages like ,

a) Improving the retention time of the drug in eye,

b) Prevents fast drainage of instilled drug from the outer site.

The eye is a complicated organ consists of different layers and structures, with particular physiological roles. (Figure 1) The eye's natural reaction eliminates the foreign bodies rapidly when it is applied to the eye. Therefore, the instillation of the drug into the eye topically is quite difficult.

The eye drop has a disadvantage, i.e. poor drug bioavailability, this is due to different reasons like,

a) Lachrymation,

b) Reduction in the residence time (less than 5mins) because of the nasolacrimal drainage and metabolic degradation,

c) also cover rapid elimination from the pre corneal area due to the nasolacrimal drainage and lacrimal secretion. (Diebold *et al.*, 2007; Zimmer and Kreuter, 1995; Almeida *et al.*, 2014).

This problem causes reduction in time for the drug to be in connection with cornea and only below 5% of the applied drugs penetrate through the cornea and get to the intraocular tissues. This issue can be solved by utilising the insitu building technique that are administered as drops into the eye, which undergoes a solution to gel transition in the cul-de-sac. (Figure 2) Here, the drug is converted into nanoparticles and combined with insitu gel has an intended action in the ocular tissues and produces greater bioavailability (Lee and Robinson, 1986; Ludwig, 2005).

### Advantages

1. The frequency of administration can be reduced (Evelyn et al., 2012).
2. Bioavailability increases due to the increase in precorneal residence time, absorption (Patel et al., 2011).
3. Better patient compliance (Evelyn et al., 2012).
4. Avoids hepatic first pass effect (Evelyn et al., 2012).
5. The local or systemic side effects of a drug can be reduced (Evelyn et al., 2012).
6. Provides sustained, prolonged drug release which maintain reasonably steady plasma profile (Kute et al., 2015).
7. When comparing to ointment, it provides less blurred vision (Patel et al., 2011; Nerkar et al., 2013).
8. Easy and convenient (Sweetman, 2005).
9. The application of this medication does not need any trained personnel (Sweetman, 2005).
10. Needle free drug application (Sweetman, 2005).
11. Better penetration of hydrophilic, ability to attain the low molecular wt drugs through the eye (Sweetman, 2005).
12. The ocular administration of appropriate drugs is an effective method in an emergency when compared to other administrative routes, due to its rapid absorption and quick onset of action (Sweetman, 2005).

### Disadvantages

1. It has some stability issues which results in chemical degradation, needs huge amount of fluids.

2. Improper storage of preparations leads to degradation.
3. Increased drains of the doses into the lachrymal duct resulting in unwanted systemic in side effects.
4. The blinking of the eye causes fast elimination of the drug (Sweetman, 2005).

### Polymer characteristics

The polymers used in the formulations are selected based on their,

1. Biocompatibility with the drug.
2. The capacity of the polymer to adhere into the mucus membrane.
3. Polymer should have pseudo plastic behaviour.
4. Enhanced clarity optically as well as tolerability.
5. Tear behaviour should be observed.
6. Since the polymer used decreases in viscosity with the increase in shear, blinking results in less viscosity (Van, 1993).

### Mechanisms of physical formation of insitu gel

#### Swelling

Myverol (glycerol mono oleate) is one of the materials which is useful in the insitu formation, it has the capacity to expand and enlarge to the desired region by absorbing water from its surrounding. It can be defined as a lipid which is polar and develops into lyotropic liquid crystalline structures in liquid. It possesses certain characteristics of bio adhesiveness and also undergoes enzymatic decomposition in vivo (Parekh et al., 2012).

#### Diffusion

It can be expressed as the process which involves movement of solvent from the polymer solution to the neighbouring tissue resulting in the polymeric matrix precipitation or solidification.

N – Methyl pyrrolidone has been suggested as a better solvent in such a system (Nirmal et al., 2010).

### Insitu formation based on chemical reaction

#### Ionic cross linking

Among different ions, polymers follow transition of phase where most polysaccharides enter into those that are ion sensitive. Rigid and fragile gels can be made from K-carrageenan in the presence of Minor quantities of K<sup>+</sup>, in the presence of Ca<sup>2+</sup> it produces gels of elasticity. Gelrite which is also known

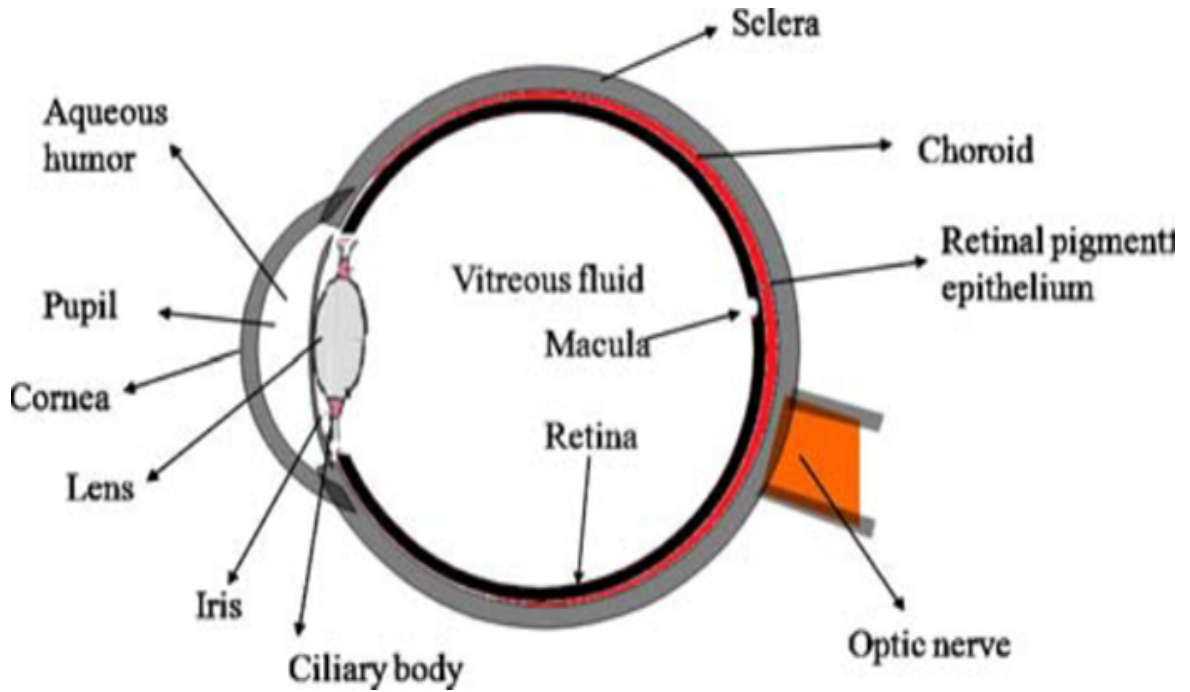


Figure 1: Structure of Eye

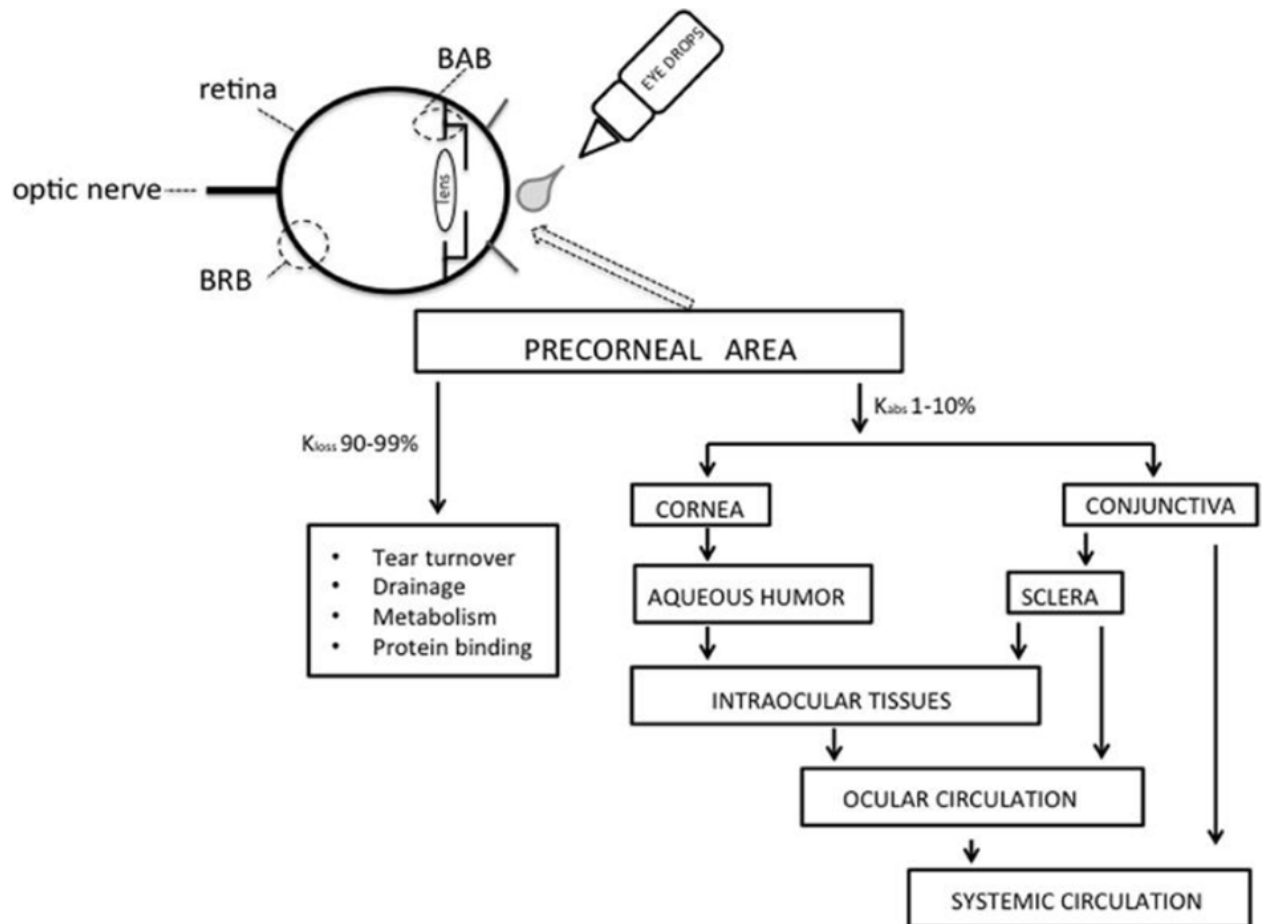


Figure 2: Topical Administration and the progress of drug absorption into the Eye.

as gellan gum is a polysaccharide in anionic form and in the presence of a mono or a divalent cation such as Ca<sup>2+</sup>, K<sup>+</sup>, Na<sup>+</sup> results in the formation of an insitu gel. The gelation process may be initiated in the presence of divalent cations Ca<sup>2+</sup> on low methoxy pectins. A similar reaction is observed with alginic acids where gelation is induced by divalent/polyvalent cation, for example alginate chains gets blocked when Ca<sup>2+</sup> interacts with glucuronic acid. Hence it can be deduced that when the tearfluid contains certain cations, it induces gelation which can be achieved using compounds of polymeric content such as gellan gum or sodium alginate. The gel is formed when the anionic polymers associate with cationic ions (Nirmal *et al.*, 2010).

### Enzymatic cross linking

The formation of insitu gel following the catalysis process induced by natural enzymes has not been studied extensively, yet appears to possess a number of advantages over conventional photochemical and chemical processes.

Eg; The functioning of enzymes under the physiologic states without the additional requirements of monomer or an initiator has proven its efficacy. Novel delivery systems involving stimuli have been devised with hydrogels releasing insulin.

Polymers containing cationic polymers have been found to contain insulin in the immobilised form And glucose oxidase with the property of enlargement along with the levels of glucose in the blood And which subsequently releases the insulin previously trapped. The formation of gel rates can be Monitored and controlled by altering the amount of enzyme which causes the injection of the mixture Prior to formation of gel (Nirmal *et al.*, 2010).

### Photo polymerisation

It is one of the frequently used technique for production of biomaterials. In this process, a monomer Mixture or macromere which is one of high reactivity along with a suitable initiator can be taken and Instilled on a particular site of tissue and subsequently introduction of an electromagnetic radiation to Induce gel formation. Some functional groups related to acrylate and other such polymerizable functional groups are commonly implemented on monomers or macromers in the presence of photo initiator to undergo photo polymerisation. Most commonly larger wavelengths of UV-VIS radiation are used because the shorter wavelengths due to its limits in penetrating tissues and is also considered a biologic hazard.

Among initiators 2, 2 dimethoxy 2 phenyl acetophenone (a ketone) is most commonly used in UV photo

polymerisation. In visible light, camphor quinone and ethyl eosin are commonly Implemented. Both these systems can undergo degrade by processes such as enzymatic or chemical or Maybe continued for further use in invivo. these systems which are polymerizable convert into photo Cured insitu gel with additional support from cables of fiber optics, when taken to the desired spot via Injection, and then releases the drug extended time interval. At physiological temperature the photo Reactions can produce quick polymerization. These systems are effortlessly positioned in the form of Complex shape levels, which lead to the formation of an implant (Nirmal *et al.*, 2010).

### Stimuli-responsive in situ gel system

#### Insitu gel induced by temperature changes

In environmentally responsive polymeric systems, one of the most common used stimulus is Temperature which can be under control in both invitro and invivo conditions and the release rate of Drug can be altered according to the temperature conditions. A class of gels referred to as hydrogels Do not get up at normal room temperature, however in contact with fluids of the body they undergo Gelation. Another imminent method of stimulation of gel formation can be performed by activating The transition of solid to get along with temperature increase by bio materials. Some notable polymers Which can undergo gelling based on temperature are poloxamers, xyloglucan and derivatives of Cellulose such as methyl cellulose and ethyl hydroxyl ethyl cellulose (Sreenivas *et al.*, 2006).

#### Systems which can be triggered by pH modification

The insitu gel formation can be induced by physiological stimuli such as alteration of pH. The Common characteristic of polymers which are pH sensitive is that based on the environment, they Accept of give protons. Polymers containing high proportions of ionisable groups are referred to as Polyelectrolytes. Groups which are weakly acidic, in response to an increase in pH, has a tendency of undergoing Swelling. But in cases where the polymer consists of weak bases, the swelling tendency decreases. Some examples of polymers which are sensitive to pH are polyvinyl acetal diethyl amino acetate derivatives. Drugs formulated in liquid form possess certain drawbacks namely low bioavailability, tendency to be Washed by tear fluid. In order to overcome such limitations and to improve usage of this particular delivery system, The PAA solution to create the gel at pH 7 as with lower pH can cause problems to the eye surface prior to lacrimal fluid neutralisation. Hence to overcome this problem,

PAA can be mixed with HPMC which formed gel at pH 7.4 and normally consists of a pH 4. Another possible method of inducing gelation is the mixture of polyethylene glycol along with poly methacrylic acid (Nirmal *et al.*, 2010).

## EVALUATION PARAMETERS

### Gelling Capacity

Analysis of this parameter can be performed by application of a drop of the formulation in a vial Already containing stimulated tear fluid around 20ml. Time required for gelling was observed (Pandit *et al.*, 2007).

### Clarity

Clarity of the formulation was established by visual examining it under a white or black background (Nirmal *et al.*, 2010).

### Anti-bacterial activity

The antibacterial activity of a drug is determined by comparing its antimicrobial activity at a concentration compared to the same concentration at the standard preparation. Serial dilution method is employed to carry out the microbial assay (Rathore, 2010).

### Ocular irritancy

The ocular irritancy study for an appointed formulation can be performed on albino rabbits [male] weighing around 2-3 kg. A formulation consisting of 1ml of optimized moxifloxacin was administered into the cul-de sac region consecutively for 14 days and the parameters of the eye were noted including redness, swelling (Draize, 1944).

### Stability testing studies (accelerated)

This study was carried out by placing the formulation in a close vial along with butylated rubber Closures and sealed by means of a cap madeup of aluminium, in an instability chamber with controlled temperature conditions of  $40 \pm 2^\circ\text{C}$  and  $75 \pm 5\%$  (Matthews, 1999).

### Drug release analysis in in-vitro models

Frans diffusion cell was utilised for this study on insitugels where the donor compartment consisted of the prepared formulation and the receptor compartment is filled with stimulated tear fluid. A thin membrane is kept between the two with about  $0.22 \mu\text{m}$  pore size. This arrangement is placed along with a magnetic stirrer with thermostat control of  $37^\circ\text{C} \pm 0.5^\circ\text{C}$ . The sample is withdrawn once every 6hrs with a volume of 1ml and replenished. The volume withdrawn is then analysed under a specific

wavelength using a reagent blank and drug concentration can be calculated from the calibration curve. The percentage drug release is calculated followed by curve fitting (Vengurlekar *et al.*, 2014).

### Testing of pH levels

Digital pH meter can be utilized to record the pH (Bucolo *et al.*, 2012).

## CONCLUSION

It has a specific characteristic such as eye protecting mechanisms which makes extremely Difficult. In order to overcome such difficulties, there have been a number of proposed methods of Enhancing the bioavailability as well as the response of the drugs when applied along ocular globe. Nanoparticles have been shown to be excellent carriers for enhancing the bioavailability of Ophthalmic drugs, bio compatibility, non irritation, sustained release, enhancement of the amount of Drug penetrating into the ocular tissues. Insitu gelling system is a successful strategy for improving. The bio availability of ophthalmic drugs, because insitu gel promotes the absorption, accurate, more Accurate sustained release without any irritation to the eye.

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### Conflict of Interest

The authors declare that there are no conflicts of interest involved in this review. The authors alone are responsible for the content and writing of the paper.

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### Author's contribution

Dineshkumar M : the lead author and synthesis of the literature.

Tallapaneni V: Involved in drafting.

Karri V V S R: Conceptual input, design and critical revision of the manuscript.

All authors read and approved the final paper.

### Ethical approval

This article does not contain any studies with human or animal subjects performed by any of the authors.

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