A REVIEW ON IN SITU OCULAR DRUG DELIVERY

Sumayya. R, Smt. Anupama Jayaraj, Dr Umesh Kumar Sharma

Department of Pharmaceutics, Mar Dioscorus College of Pharmacy, Thiruvananthapuram, Kerala

Email id:sumayyasufi93645@gmail.com

ABSTRACT: Eye is the most sensitive 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 .Designing of ocular drug delivery system is the most challenging field for pharmaceutical scientists as less than 5% of administered drug enters the eye due to the complicated anatomical structure of the eye, small absorptive surface and low transparency of the cornea, lipophilicity of corneal epithelium, pre corneal loss due to nasolacrimal drainage, bonding of the drug with proteins contained in tear fluid, blinking, low capacity of conjunctival sac, that restricts the entry of drug molecule at the site of action and ultimately leads to poor ocular therapy. To improve ophthalmic drug bioavailability, a novel in-situgel approach as a means to localize and prolong drug activity at its site of action. These are solutions, instilled as drops into the eye and undergo a sol to gel transition in the cul-de-sac, improved ocular bioavailability by increasing the duration of contact with corneal tissue, thereby reducing the frequency of administration required in case of conventional ophthalmic solutions, thus optimizing ocular therapy.

KEYWORDS: In situ gels, pH-triggered *Insitu* system, Ion-activated *Insitu* system, polymer.

INTRODUCTION: Gel is a substance containing liquid and solid components. Gel consists of three-dimensional solid tissue. One example of a gel used for treatment is hydrogel. Hydrogels form polymeric chains of 3-D macromolecules so they can be easily formed in various shapes and sizes. Hydrogels have a good absorbing ability. Hydrogels are polymers that have ability to transition between liquid-gel. Hydrogel itself is a type of preparation that is hydrophilic because it has a network of physics and chemistry, commonly called "crosslink" serves to accommodate a very large amount of air. The rheology associated with the hydrogel preparation is based on the properties and concentrations of polymers which are the laws of Newton. Hydrogel consists of two groups: preformed gel and *in situ* gel. Preformed gel and *in situ* gel that can improve residence time and bioavailability. solution

INSITUGEL *In situ* gel is a gelatinous when interacting with the eye due to changes in the physical properties of chemistry by the eye so as to not cause problems like the previous gel. Administration route for gel preparation *in situ* usually through oral, ocular, rectal, vaginal, injectable and intraperitoneal. In the preparation of *in situ* gel required a trigger to form the gel when contacts with the target organ as in the eye. There are four mechanisms used to trigger *in situ* gel formation of biomaterials, physiological stimulation (temperature and pH), physical changes (exchange of solvents and swelling), chemical reactions, and photo-initiated polymerizations. There are three gel forming systems in the *in situ* gel preparation when in contact with target organs, ie thermoreversible *in situ* gels, pH sensitive *in situ* gels and ion sensitive *in situ* gels.

Anatomy and function of the eye.

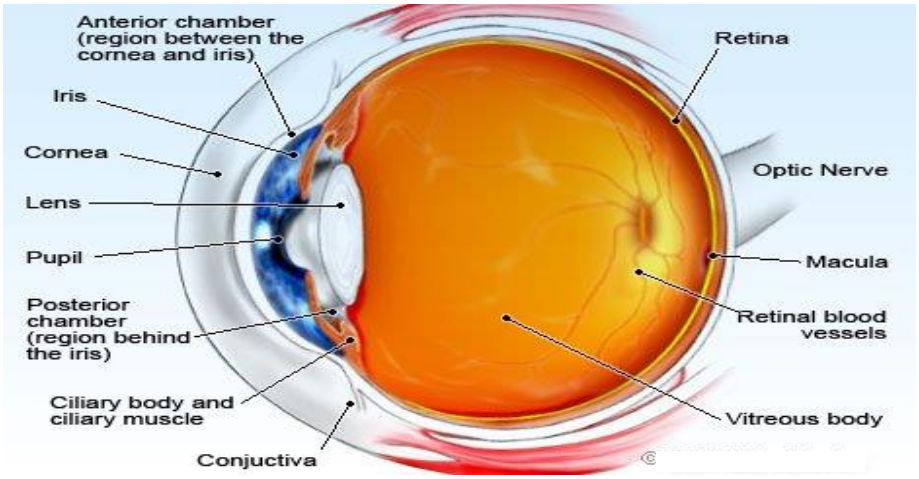

FIG.1:ANATOMY AND FUNCTIONS OF EYE

An eye is a spherical structure with a wall made up of three layers: the outer part sclera, the middle parts choroid layer, ciliary body and iris and the inner section nervous tissue layer retina. The sclera is tough fibrous coating that protecting the inner tissues of eye which is white except for the transparent area at the front, that is cornea allows light to enter to the eye. The choroid layer, situated in the sclera, contains many blood vessels that modified at front of the eye as pigmented iris the colored part of the eye (blue, green, brown, hazel, or grey). The clear transparent bulge cornea situated at the front of the eye that conveys images to the back of the nervous system. The adult cornea has a radius of approximately 7-8mm that is a vascular tissue to which provides nutrient and oxygen are supplied via lachrymal fluid and aqueous humor as well as from blood vessels of the junction between the cornea and sclera. The cornea is made of five layers as epithelium, bowman's layer, stroma, descemet's membrane and endothelium which are main pathways of the drug permeation to eye. The main barrier of drug absorption into the eye is the corneal epithelium, in comparison to many other epithelial tissues (intestinal, nasal, bronchial, and tracheal) that is relatively impermeable. The epithelium is squamous stratified, (5-6 layer of cells) with thickness of around 50-100 μm. The basal cells are packed with a tight junction forming not only an effective barrier to dust particle and most microorganisms, and also for drug absorption. The transcellular or paracellular pathway is the main pathway to penetrate drug across the corneal epithelium. The lipophilic drugs choose the transcellular route whereas the hydrophilic one chooses paracellular pathway for penetration (passive or altered diffusion through intercellular spaces of the cells).

Ocular absorption of drug

The common method of ocular drug delivery is topical administration of ophthalmic dosage formulation drops into the lower cul-de-sac. Eye drops outflow quickly due to the eye blinking reflux, and the precorneal region returns to maintain resident volume of around 7μl. The available concentration of drug in precorneal fluid provides the driving force for passive transport of drug across the cornea. However, the epithelium is the predominant rate limiting barrier for hydrophilic drugs and where as stroma is rate limiting step for most of the lipophilic drugs.

Mechanism of drug release

The medicine used through the attention organs should have the tissue layer to be followed by non-corneal permeation. This non corneal permeation can involve the diffusion of the drug throughout the mucosa and also the eye sclerotic coat. it's necessary to grasp that medications area unit less absorbed within the tissue layer.

1. Diffusion

The drug are free unendingly into the watering liquid. If associate insertion is created from a solid body that may not be worn with pores and spread medicine. The drug unleash by this method happens through diffusion through the pores.

2. Osmosis

In this mechanism, there's associate water-resistant elastic membrane which is able to insert into 1st compartment and also the second compartment; within the first compartment is delimited by a semi-permeable membrane, and also the second compartment are restricted by associate water-resistant material. there's a drug unleash hole on the water-resistant wall of insertion. within the 1st compartment system containing solutes, that can't have the semi-permeable membrane otherwise on the second compartment provides a reservoir for the drug, once more in liquid or gel type. within the binary compound surroundings the attention are inserted, at which period the water can diffuse into the primary compartment and stretch the elastic membrane that has operate to expand the primary compartment and contract the second compartment so the drug is forced through the drug unleash hole.

3. Bio-erosion

In this mechanism, there's associate insertion body configuration fashioned from a matrix of bioerodible materials used. as an area of medication to be spread. The teardrops can get contact with the inserts that may lead to the continual unleash of the drug by the bioerosion matrix then drug are equally spread, however if the drug is focused on the matrix it'll be obtained a additional controlled unleash. Preformed gel incorporates a straight forward viscousness that may not modification when administration. Mean while, the in place gel undergoes gelation when administration supported chemistry properties. In preformed gel on repair of refined cell tissue then inserted into polymer then drug and biological signals area unit inserted at the same time then injected into the body as a result of the character of colloidal gel within the kind of "sustain release" the drug are issued bit by bit supported patient's vital sign.

Polymer : The most important ingredients in the manufacture of *in situ* and preformed gel is the polymer. The formulation of *in situ* gel using various polymers such as hydroxy ethyl cellulose, carbopol, sodium alginate, and gums such as guar hydroxypropyl, xanthum gum. As for the properties that need to be present in the *in situ* gel formulation is first, the formulation must be a free flowing liquid which may facilitate the administration of a reproducible dose. Secondly, after gradual preparation of *in situ* gel must gel has the type according to gel formation. The preparation method is to mix the polymer with water. This solution is stirred periodically until the solution is homogeneous and cooled to 4°C. then added another polymer like HPMC to the solution. The sample was then transferred to the bottle and stored in the refrigerator overnight which was finally sterilized by autoclaving at 121°C at 15psi for 20 minutes30. The polymer used in the preparation of *in situ* gel differs by *in situ* gelling system.

, this polymer will form a small micellar subunit in solution that will lead to increased viscosity leading to swelling to form a large cross-crossed micellar tissue. Examples of polymers for this system are poloxamer.

The mechanism is based on the mucoadhesive properties caused by form sol-to-gel with the transition phase and thirdly, the *in situ* gel preparation may form a strong gel so sufficient to withstand shear forces in the cul-de-sac functioning to extend the residence time drug. The polymer used for the preparation of *in situ* gel must be in accordance with the criteria, ie non-toxic and not absorbed from the gastrointestinal tract, does not cause irritation to the mucous membranes, and the cost used is not too high. The polymer used in each formulation is not the same because *in situ*

Polymer used in thermo reversible *in situ* gelling system.

The system of this polymer consists of a central polypropylene oxide surrounded by polyethylene oxide. At room temperature (25^{o}C), this polymer is a viscous liquid and will then turn into a transparent gel when temperature increases (37^{o}C). At low temperatures.

Polymer used in pH sensitive *in situ* gelling system.

electrostatic interactions or hydrophobic interactions, hydrogen bonding. This is an acidic molecule. When the polymer is dispersed into water, the carboxylic group of molecules will partially dissociate and form a coil. Because of the polymer sensitive pH, the increase of the pH of the solution results in polymer swelling.

Polymer example with this system is **Polymer used in ion sensitive *in situ* gelling system.**

The mechanism of this system is a monomer of alginate β-DMannuronic acid and α-L glucuronic acid arranged as an M-M block .

Mechanism of Sol-Gel Formulation:

In situ forming hydrogels are liquid preparations upon instillation undergoing phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental changes. In situ gel forming ophthalmic drug delivery systems prepared from polymers that exhibit reversible phase transitions (sol–gel–sol) and pseudo plastic behavior to minimize interference with blinking. Such carbopol29.

a system can be formulated as a liquid dosage form suitable to be administered by instillation into the eye which, upon exposure to physiological conditions, changes to the gel phase, thus increasing the pre-corneal residence time of the delivery system. The vast majority of the In situ forming drug delivery systems reported is based on polymeric materials which forms gel matrices upon administration. Polymers that have been investigated includes [1] polysaccharides like alginate, gellan and xyloglucan, [2] polyesters like PLA and PLGA, [3] polyethers like PEG-PPG-PEG (Poloxamers) or [4] mixed polyesters and polyether's such as PEG-PLGAPEG

CLASSIFICATION OF OPHTHALMIC DRUG DELIVERY SYSTEMS

I. Conventional delivery systems

Eye drops

Ointments and Gels

Ocuserts and Lacrisert

II. Drug delivery to anterior segment

Contact lens

Cal du sac inserts

Subconjuctival/ Episcleral implants

III. Drug delivery to posterior segment

Intravitreal implants (e.g, Duraser Technology system, Novadu Technology, I- vatio TA, NT-501)

Injectable Particulate Systems (RETAAC, Cortiject, Visudyne**)**

IV. Physical devices

Iontophoresis

Micro- electromechanical intra ocular drug delivery devices

V. Vesicular system

Liposomes

Niosomes

Discomes

Pharmacosomes

VI. Controlled delivery systems

In situ gel systems/ Phase transition systems

Iontophoresis

Dendrimer

Contact lens

Collagen shield

Microemulsion

Nanosuspensions

Microneedle

VII. Particulates

Nanoparticles

Microparticles

Microemulsion

Nanosuspensions

Microneedle

VII. Particulates

Nanoparticles

Microparticles.

VIII. Advanced delivery systems

Cell encapsulation

Gene therapy

Stem cell therapy

Protein and Peptide therapy

Scleral plug therapy

siRNA therapy

Oligonucleotide therapy

Aptamer

FATE OF FORMULATION ADMINISTERED THROUGH EYE .

The general process of drug absorption into the eye from the precorneal area (dose site) following topical ocular administration is quite complex. The classical sequence of events involves drug instillation, dilution in tear fluid, diffusion through mucin layer, corneal penetration (epithelium, stroma, endothelium), and transfer from cornea to aqueous humor. Following absorption, drug distributes to the site of action (e.g., iris-ciliary body).

Parallel absorption via the conjuctiva/sclera provides an additional pathway to eye tissues but, for most drugs, is minor compared with corneal absorption. Also, nonproductive, competing, and parallel pathways (e.g., nasolacrimal drainage or systemic absorption via the conjuctiva) work to carry drug away from the eye and limit the time allowed for the absorption process.

Moreover, in some species, such as the rabbit, non-productive absorption into the nictitating membrane can occur.

In situ gel forming systems are drug delivery systems thatare in solution form before administration in the body but once administered, undergo gelation in situ, to form a gel triggered by external stimulus such as temperature, pH etc and release the drug in sustained or controlled manner. This novel concept of producing in situ gel was suggested for the first time in the early 1980s. Gelation occurs via the cross-linking of polymer chains that can be achieved by covalent bond formation (chemical cross-linking) or non-covalent bond formation (physical cross-linking). In situ gel-forming systems can be described as low viscosity solutions that undergo phase transition in the conjunctival cul-de-sac to form viscoelastic gels due to conformational changes of polymers in response to the physiological environment. The rate of in situ gel formation is important because between instillation in the eye and before a strong gel is formed, the solution or weak gel is produced by the fluid mechanism of the eye 8. Both natural as well as synthetic polymers can be used for the fabrication of *in situ* gels .

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IN SITU GELLING SYSTEM

ADVANTAGES OF IN SITU GELS

*Less blurred vision as compared to ointment.

* Decreased nasolacrimal drainage of the drug which may cause undesirable side effects due to systemic absorption (i.e. reduced systemic side effects).The possibility of administering accurate and reproducible quantities, in contrast to already gelled formulations and moreover promoting precorneal retention.

* Sustained, Prolonged drug release and maintaining relatively constant plasma profile.

* Reduced frequency of applications hence improved patient compliance and comfort.

* Generally more comfortable than insoluble or soluble insertion.

* Improved local bioavailability due to increased precorneal residence time and absorption.

Its production is less complex and thus lowers the investment and manufacturing cost

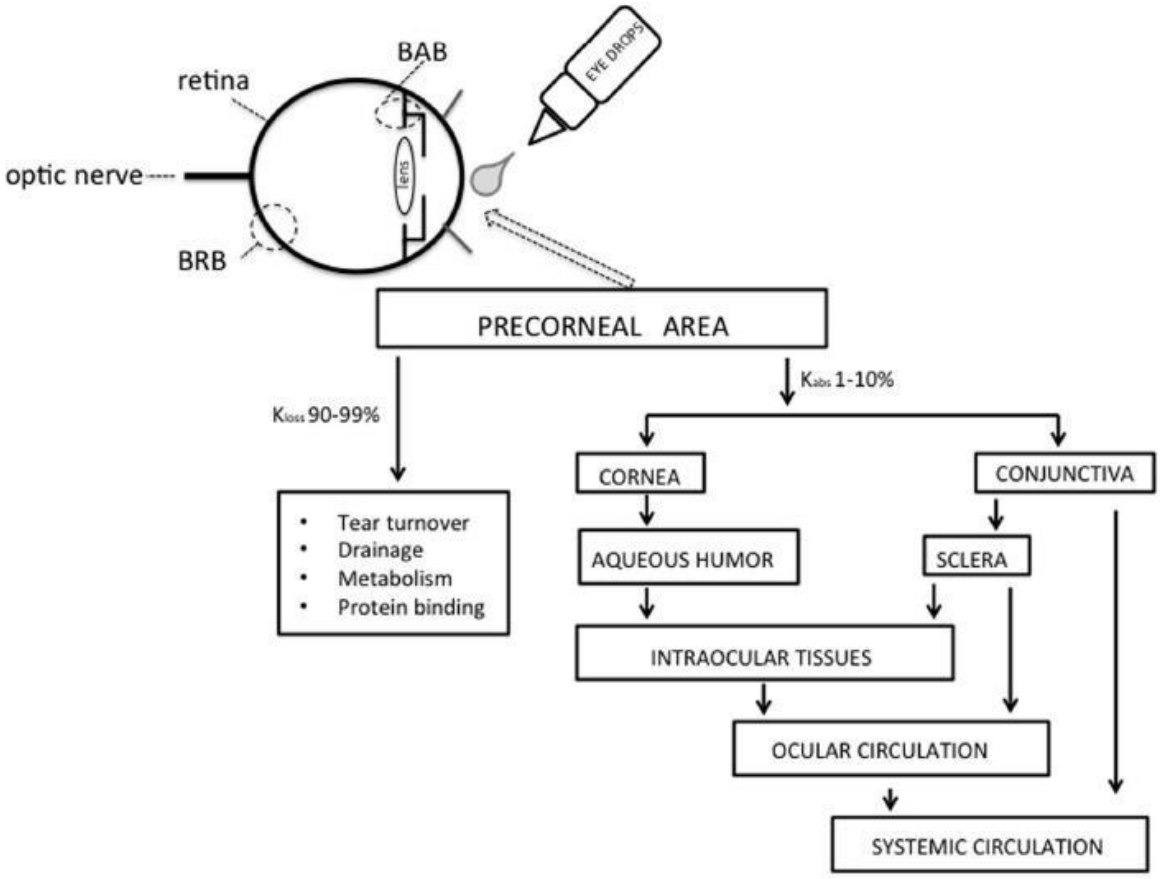

FIG.2: PRECORNEAL AND OCULAR DRUG MOVEMENT FROM TOPICAL INSTILLED DOSE

***In situ* gels may be evaluated and characterized for the following parameters;**

Clarity

The clarity of formulated solutions determined by visual inspection under black and white background.

Texture analysis

The firmness, consistency and cohesiveness of formulation are assessed using texture analyzer which mainly indicates the syringeability of sol so the formulation can be easily administered in-vivo. Higher values of adhesiveness of gels are needed to maintain an intimate contact with surfaces like tissues.

Sol-Gel transition temperature and gelling time

For in situ gel forming systems incorporating thermoreversible polymers, the sol-gel transition temperature may be

defined as that temperature at which the phase transition of sol meniscus is first noted when kept in a sample tube at a specific temperature and then heated at a specified rate. Gel formation is indicated by a lack of movement of meniscus on tilting the tube. Gelling time is the time for first detection of gelation as defined above.

Gel-Strength This parameter can be evaluated using a rheometer. Depending on the mechanism of the gelling of gelling agent used, a specified amount of gel is prepared in a beaker, from the sol form. This gel containing beaker is raised at a certain rate, so pushing a probe slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below the gel surface.

Viscosity and rheology

This is an important parameter for the *in situ* gels, to be evaluated. The viscosity and rheological properties of the polymeric formulations, either in solution or in gel made with artificial tissue fluid (depending upon the route of administrations) instead of 5% mannitol, were determined with 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.

In-vitro drug release studies

For the *in situ* gel formulations to be administered by oral, ocular or rectal routes, the drug release studies are carried out by using the plastic dialysis cell. The cell is made up of two half cells, donor compartment and a receptor compartment. Both half cells are separated with the help of cellulose membrane. The sol form of the formulation is placed in the donor compartment. The assembled cell is then shaken horizontally in an incubator. The total volume of the receptor solution can be removed at intervals and replaced with the fresh media. This receptor solution is analyzed for the drug release using analytical technique. For injectable *in situ* gels, the formulation is placed into vials containing receptor media and placed on a shaker water bath at required temperature and oscillations rate. Samples are withdrawn periodically and analyzed.

Histopathological studies

Two mucosa tissue pieces (3 cm2) were mounted on in vitro diffusion cells. One mucosa was used as control (0.6 mL water) and the other was processed with 0.6 mL of optimized organogel (conditions similar to in vitro diffusion). The mucosa tissues were fixed in 10% neutral carbonate formalin (24 hours), and the vertical sections were dehydrated using graded solutions of ethanol. The subdivided tissues were stained with haematoxylin and eosin. The sections under microscope were photographed at original magnification ×100. The microscopic observations indicate that the organogel has no significant effect on the microscopic structure of the mucosa. The surface epithelium lining and the granular cellular structure of the nasal mucosa were totally intact. No major changes in the ultra structure of mucosa morphology could be seen and the epithelial cells appeared mostly unchanged.

Isotonicity evaluation

Isotonicity is important characteristic of the ophthalmic preparations. Isotonicity has to be maintained to prevent tissue damage or irritation of eye. All ophthalmic preparations are subjected to isotonicity testing, since they exhibited good release characteristics and gelling capacity and the requisite viscosity. Formulations are mixed with few drops of blood and observed under microscope at 45X magnification and compared with standard marketed ophthalmic formulation

Drug polymer interaction study and thermal analysis

Interaction study can be performed with Fourier Transform Infra Red (FTIR) spectroscopy. During gelation process the nature of the 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

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 antibiotic. To carryout microbiological assay serial dilution method is employed.

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 eye is normally 100µl placed into the lower *culdesac* with observation of the various criteria made at a designed required time interval of 1hr, 24hrs, 48 hrs, 72hrs, and 1week after administration. Three rabbits (male) weighing 1.5 to 2kg are used for the study. Formulations are placed in ambient colour vials and sealed with aluminium foil for a short term accelerated stability study at 40±2°C and 75±5% RH as perInternational Conference on Harmonization (ICH) states Guidelines. Samples are analyzed every month for clarity, pH, gelling capacity, drug content, rheological evaluation, and *in vitro* dissolution.

Statistical analysis

The results obtained from the experiments of mucoadhesive strength and release studies were analysed statistically using multivariate tests. A statistically

drug, good stability and biocompatibility characteristics make the *in situ* gel dosage forms very reliable. These are easy to instill at the same time improves ocular bioavailability by increasing the duration of contact with corneal tissue, thereby

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

Accelerated stability studies

significant difference was conducted by usingvarious SPSS software and difference was considered to be significant at $P<0.05$.

CONCLUSION

The primary requirement of a successful controlled release product focuses on increasing patient compliance which the *in situ* gels offer. Exploitation of polymeric insitu gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Sustained and prolonged release of the reducing the frequency of administration required in case of conventional ophthalmic solutions, thus optimizing ocular therapy. Use of biodegradable and water soluble polymers for the *in situ* gel formulations can make them more

acceptable and excellent drug delivery systems.

Ocular drug delivery system is burgeoning field in which most of the researchers are taking challenges to combat various problems associated to this delivery. Steady advancement in the understanding of principles and processes governing ocular drug absorption and disposition and continuing technological advances have surely brought some improvements in the efficacy of ophthalmic delivery systems. The primary requirement of a successful controlled release product focuses on increasing patient compliance which the *insitu* gels offer. *In situ* gelling systems are promising ocular delivery systems because they can overcome the drawbacks associated with conventional ocular dosage forms thus in the recent years ophthalmic *in situ* gelling drug delivery systems have drawn much attention of researchers. They are easy to administer with improved patient compliance. The principal advantages of these systems are the possibility of administering accurate and reproducible quantities of drugs, increased precorneal contact time, prolonged drug release, drug delivery to deeper tissues, and reduced frequency of administration. Further, drug loaded nanoparticles, liposomes or other colloidal drug carriers can also be incorporated in these systems to obtain sustained drug delivery in a much improved and effective manner. Future use of biodegradable and water soluble polymers for the in situ gel formulations can make them more acceptable and excellent drug delivery systems. Moreover, in situ gels have ease of commercialization which adds advantage from industrial point of view.

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