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OPHTHALMIC IN-SITU GEL: AN OVERVIEW

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ABSTRACT

Ocular drug delivery has been a major challenging and interesting field for the pharmaceutical scientists due to unique anatomy and physiology of eye. The major problem encountered in ocular drug delivery is the rapid loss of the drug through lachrymal drainage which results in poor bioavailability and therapeutic response of the drug. There are some static (different layers of the eye i.e. cornea, sclera, retina) and dynamic (blood aqueous and blood retinal barrier) barriers which also affect the bioavailability of the drug. In-situ gels are the liquid preparations which upon instillation undergoes phase transition in cul-de-sac of the eye to form a viscous gel and this occurs due to the environmental changes in the eye (i.e. due to change in temperature, change in pH and ion induced change). This review is to specify the basic anatomy and physiology of human eye, various approaches used for formulation of in-situ gels and polymers used in the formulation of in-situ gels.

INTRODUCTION

Eye is the most vital organ of the body.[1] It is the sensory organ that converts light to anelectric signal that is treated and interpreted by the brain.[2] Ophthalmic drug delivery is thechallenging endeavor faced by the pharmaceutical researchers today.The structural andfunctional aspects of the eye render this organ highly impervious to foreign substances.[3] In the earlier period,drug delivery to the eye has been limited to topical application,redistribution into the eye following systemic administration or direct intraocular/per ocular injections.[4] But the conventional ocular drug delivery systems like solutions,suspensions and ointments show drawbacks such as increased precorneal elimination, high variability and blurred vision.[1]So to overcome the problems caused by these conventional dosage forms and to improve the ocular bioavailability, recently there are considerable efforts directed towards controlled and sustained drug delivery in modern pharmaceutical field.[5]Ophthalmic in-situ gel is one of those efforts undertaken by the pharmaceutical researchers.

Overview Of Anatomy And Physiology Of Human Eye

The eye is most important organ of human body. The cornea, lens, and vitreous body are transparent media with no blood vessels. Oxygen and nutrients are transported to these nonvascular tissues by the aqueous humour. The aqueous humour has a high oxygen tension and about the same osmotic pressure as blood. The cornea also derives part of its oxygen need from the atmosphere and is richly supplied with free nerve endings. The transparent cornea is continued posterior into opaque white sclera, which consists of tough fibrous tissue. Both cornea and sclera withstand the intra-ocular tension constantly maintained in the eye. The eye is constantly cleansed and lubricated by the lachrymal apparatus, which consists of four structures: Lachrymal glands, lachrymal canals, lachrymal sac, naso- lachrymal duct. The lachrymal fluid secreted by the lachrymal glands is emptied on the surface of the conjunctiva of the upper eyelid at a turnover rate of 16% per min. It washes over the eyeball and is swept up by the blinking action of the eyelids. Thus the eyeball is continually irrigated by a gentle stream of lachrymal fluid that prevents it from becoming dry and inflamed. The lachrymal fluid in humans has a normal volume of 7µl and is an isotonic aqueous solution of bicarbonate and sodium chloride (pH 7.4) that serves to dilute irritants or to wash the foreign bodies out of the conjunctival sac. It contains lysozyme, whose bactericidal activity reduces the bacterial count in the conjunctival

sac. The rate of blinking varies widely from one person to another, with an average of approximately 20 blinking movements per min. During each blink movement the eyelids are closed for a short period of about 0.3 sec.[1]

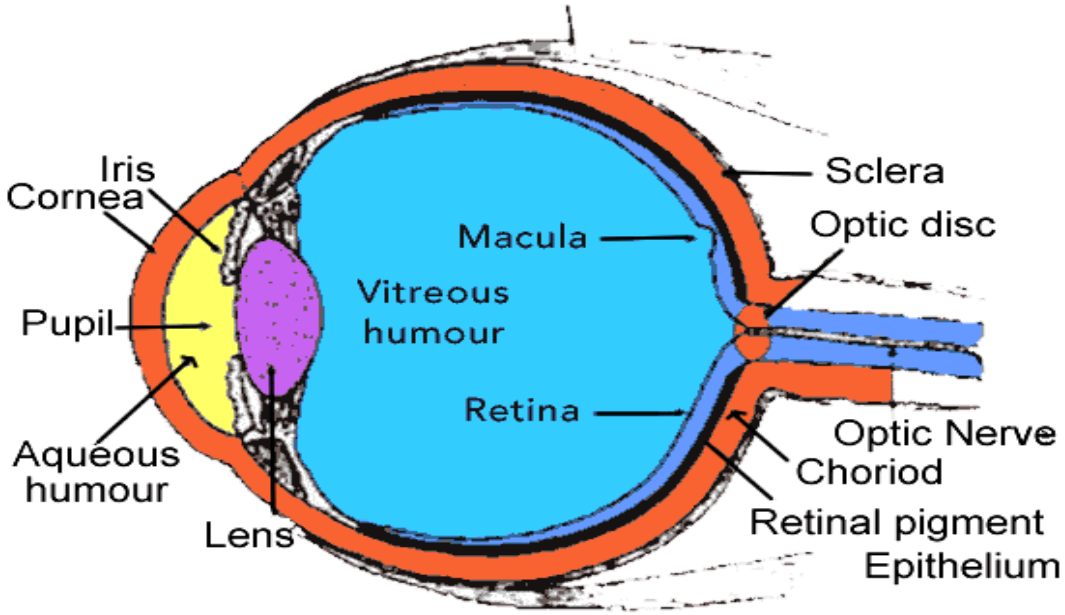

Figure No:(1) Anatomy of Eye

Various Problems Encountered In Poor Bioavailability of Drugs Instilled Through Eye are[1,2,6,7]

• Binding by the lachrymal proteins

• Drainage of the instilled solutions

• Lachrimation and tear turnover

• Limited corneal area and poor corneal penetration

• Non-productive absorption/adsorption

Characteristics Required To Optimize Drug Delivery Systems[1,5]

• Good corneal penetration.

• Prolonged contact time with corneal tissue.

• Simplicity of installation for the patient.

• Non- irritative and comfortable form (the viscous solution should not provoke Lachrimation and reflex blinking).

In-Situ Gelling System

A more desirable dosage form would be one that can deliver drug in a solution form, create little to no problem of vision and need be dosed no more frequently than once or twice daily. In situ

activated gel forming systems are those which are when exposed to physiological conditions will shift to a gel phase. 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 and synthetic polymers can be used for the production of in situ gels.[1]

ADVANTAGES OF IN-SITU GEL[1]

- 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 number/frequency of applications hence improved patient compliance and comfort.
- Generally more comfortable than insoluble or soluble insertion.
- Increased bioavailability due to increased precorneal residence time and absorption.

Approaches For In-Situ Gelling System

A new approach is to try to combine advantages of both solutions and gels, such as accuracy and ease of administration of the former and prolonged residence time of the latter. Thus, in situ hydrogels can be instilled as eye drops and undergo an immediate gelation when in contact with the eye. In situ-forming hydrogels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental change.[9]The main approaches for in-situ gelling system can be classified as follows.

A) Physiological stimuli approach[1]or Stimuli-responsive in situ gel systems[10]

This approach is further subclassified as.

a.Temperature induced in-situ gelling system.

b.pH induced in-situ gelling systems.

B) Physical change in biomaterial approach[1]

This approach can be further subclassified as:

a.Swelling mechanism.
b.Diffusion mechanism.

C) Chemical reaction approach[1]or Chemically induced in situ gelling system[10]

This approach can be further subclassified as:

a.Ionic cross linking.
b.Photo-polymerisation.
c.Enzymatic cross-linking.

Above mentioned approaches for in-situ gels can be explained in detail as follows.

A) Physiological stimuli approach or stimuli-responsive in-situ gel systems.

Stimuli responsive polymers are defined as polymers that undergo relatively large and abrupt physical or chemical changes in response to small external changes in the environmental conditions.[10]

a. Temperature induced in situ gelling system

Temperature is the most widely used stimulus in environmentally responsive polymer systems as it is easy to control whenever needed and it is applicable to both in vitro and in vivo systems.[10]The ideal critical temperature for this system is ambient and physiologic temperature.[1] In these systems, gelling of the solution is triggered by change intemperature,thus sustaining the drug release.[1,10]These hydrogels are liquid at room temperature(20-25ºC) and undergo gelation when in contact with body fluids(35-37ºC) due to change in temperature.[1,10,11]Temperature sensitive gels are of three types: positive temperature sensitive gel,negative temperature sensitive gel and thermally reversible gel. Negative temperature sensitive gels have Lower Critical Solution Temperature (LCST), such gels contracts on heating above LCST.Positive temperature sensitive gel has Upper Critical Solution Temperature(UCST),such gels contracts on cooling below UCST.[11]

b.pH induced in-situ gel systems

Polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH sensitive polymers.[10]In this system, sol to gel transition takes place when pH is raised from 4.2 to 7.4(eye pH).At higher pH,polymer forms hydrogen bonds with mucin which leads to hydrogel formation.[1,11]

Mechanism

All the pH sensitive polymers contain pendant acidic or basic groups that can either accept or release protons in response to changes in environmental pH. The polymers with a large number of ionisable groups are known as polyelectrolytes.Swelling of polymer increases as the external pH increases in the case of weakly acidic(anionic) groups,also known as polyacids,but decreases if polymer contains weakly basic(cationic) groups termed as polybases.[1,10,11]

B) Physical change in biomaterial approach

a.Swelling mechanism

In this approach, in-situ gel is formed when material absorbs water from surrounding environment and expand to occur 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.[1,12]

b.Diffusion mechanism

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N methylpyrrolidone (NMP),dimethylsulfoxide(DMSO),tetrahydrofuran,2 pyrrolidone and triacetin has been shown to be useful solvents for such system.

C) Chemical reaction approach

Ionic cross linking-Certain ion sensitive polysaccharides undergo phase transition presence of various ions such as K+,Ca2+,Mg2+,Na+.These polysaccharides fall into the class of ion sensitive ones.[1]

b.Photo-polymerisation

A solution of monomers or reactive macromer and initiator can be injected into a tissue site and to this site electromagnetic radiation is applied due to which the gel is formed.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. Photopolymerizable systems when introduced to the desired site via injection get photocured in situ with the help of fiber optic cables and thenrelease the drug for prolonged period of time.[1]

b. Enzymatic cross-linking

This approach is still under investigation as natural enzymes are responsible for forming the in-situ gel. But it is estimated that this method will be more advantageous than chemical and photochemical approaches. For example, intelligent stimuli-responsive delivery systems using hydro gels that can release insulin have been investigated.[1]

Principle Applications of In-Situ Gelling System

a) In Situ Forming Drug Delivery System for Parenteral Administration[13]

Controlled parenteral systems used in drug delivery are implants, microspheres and liposomes. These suffer from limitations such as surgical implantation, complex manufacturing process, high production cost and drug leakage. Injectable in situ gel forming drug delivery system represents an attractive alternative to microspheres and implants as parenteral depot systems and has following advantages over conventional parenteral system:

- Less invasive technique
- Direct delivery to a target area
- Biodegradable and biocompatible
- Economical

b) In situ forming drug delivery system for ocular administration

The poor bioavailability and therapeutic response exhibited by conventional ophthalmic dosage form (eye drops, eye gels, eye ointments) due to rapid precorneal elimination of the drug may be overcome by the use of a gel system instilled as drops into the eye and undergo a sol-gel transition in the cul de sac. For in situ gel based ocular delivery, natural polymers such as gellan gum, alginic acid and xyloglucan are most commonly used polymers. Local ophthalmic drug delivery has been used for various compounds such as antimicrobial agents, anti-inflammatory agents and autonomic drugs used to relieve intraocular tension in glaucoma.[13]

c) In situ forming drug delivery system for oral administration

Pectin, xyloglucan and gellan gum are the natural polymers used for in situ forming oral drugdelivery systems. The potential of an orally administered in situ gelling pectin formulation forthe sustained delivery of Paracetamol has been reported. The formulation consisted of gellansolution with calcium chloride and sodium citrate complex. When administered orally, the calcium ions are released in acidic environment of stomach leading to gelation of gellan thus forming a gel in situ.[13]

d) In situ forming drug delivery system for nasal administration

Gellan gum and Xanthan gum were used as in situ gel forming polymers. Animal studieswere conducted using an allergic rhinitis model and the effect of in situ gel on antigen induced nasal symptoms in sensitised rats was observed.[13]

e) In situ forming drug delivery system for rectal and vaginal administration

In situ gels also possess a potential application for drug delivery by rectal and vaginal route.Miyazaki et al. investigated the use of xyloglucan based thermo reversible gels for rectal drug delivery of Indomethacin. Administration of Indomethacin loaded xyloglucan based systems to rabbits indicated broad drug absorption peak and a longer drug residence time as compared to that resulting after the administration of commercial suppository.[13]

Evaluation and Characterization of In-Situ Ophthalmic Gel

1] Physical parameter[14,15]

The formulated In-situ solution is tested for clarity, pH, gelling capacity, appearance.

a] Gelling capacity

Gelling capacity of prepared formulation can be determine 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.

b] Viscosity[15]

Viscosity can be calculated by using Brookfield viscometer, cone and plate viscometer. The In-situ gel formulation was placed in sampler tube. The samples are analyzed 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.

c] Clarity /Appearance[16]

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

2] In-vitro drug release studies[17]

In vitro drug release study of In-situ gel solution should be 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 compartment 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 analyzed by UV spectrophotometer at respective nm using blank reagent.

3] Drug content[18]

Is calculated using equation generated from standard calibration curve. The % cumulative drug release is calculated. The 1 ml of formulation was dissolved in 100ml of artificial tear fluid. The whole system was stirred on magnetic stirrer for 4-5 hr. From this solution the sample should be withdrawn and analyzed for UV for Drug content.

4] Texture analysis[18]

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 withmucus surface.

5] Isotonicity evaluation[19]

Isotonicity is important characteristics of the ophthalmic preparation. Isotonicity has to be maintained to prevent tissue damage or irritation of eyes. Formulation is mixed with few drops of blood and observed under microscope at 42x magnification and compared with standard marketed ophthalmic preparation.

6] Interaction study[19]

It 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 Press Pellet method 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.

7] Antibacterial/Antibiotic activity[19]

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.

8] The Draize irritancy test[20] It 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

eyes is normally 25µl m placed into the lower cul- de-sac with observation of the various criteria made at a designed required time interval of 1 hr, 24hrs, 45 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.

9] Accelerated stability studies[20]

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 analyzed every month for clarity, pH, gelling ability, drug content etc.

10] Assay[21]

An accurate amount of drug was dissolved in diffusion media of desired pH, and theabsorbance of the resulting solutions was determined at nm. Drug content was calculated to estimate the percentage recovery of the loaded drug.

11] Sol-gel Transition Temperature and Gelling time[22]

For in situ gel forming systems incorporating thermo reversible 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.

12] Gel-strength[22]

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.

13] Viscosity and Rheology[23]

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) 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 should encounter during their administration by the patient, especially during parenteral and ocular administration.

CONCLUSION

In-situ gelling systems have been proved advantageous over other conventional dosage forms. These advantages include sustained and prolonged release of drug, good stability, biocompatibility, ease of instillation, etc. Polymers used in in-situ gelling systems also play an important role. Various natural, synthetic, semi synthetic polymers are being used by the pharmaceutical researchers for controlled release of drug. These polymers are very useful in the formulation of in-situ gel systems. Moreover,in situ gels have ease of commercialization which adds advantage from industrial point of view.

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