ejpmr, 2021,8(6), 593-597

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A SHORT REVIEW ON IN- SITU GEL FORMULATION FOR OCULAR DRUG DELIVERY: ITS PREPARATION AND EVALUATION

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Article Received on 20/04/2021 **Article Revised on 10/05/2021** **Article Accepted on 30/05/2021**

ABSTRACT

Conventional ocular drug delivery systems like eye drops, ointments, suspensions has varied disadvantages of lachrymation, blurred vision and most vital speedy precorneal elimination, therefore so as to beat these drawbacks varied novel approaches were developed. in place ocular gel is one in every of the recent advancement in ocular drug delivery system. in place ocular gel system comprise delivery vehicle composed of polymers (natural, semi artificial or synthetic) that incorporates a special property of sol-gel conversion once influenced by some biological input like pH scale, temperature and ions. The developed formulation was therapeutically efficacious, stable, non bother and provided sustained unleash of the drug. This review tries to debate the newer Developments and techniques for this drug delivery together with physiological factors, physiochemical factors and formulation factors to be thought-about within the Development of unchanged drug delivery system.

KEYWORDS: In – situ ocular gel, temperature dependent system, pH sensitive system, ion-activated system, polymers, cul- de- sac, etc.

INTRODUCTION

The eye is very fragile and significant organ of the human body. It is necessary to treat eye in effective as well as convenient way. "The ocular function and accurate vision of eyes are performed by the visual cells and transparent tissues due to tight cellular membrane and barriers which control the fluid and solvent".[1] The foreign material from the eye removed by the tear flow and blinking reflex which help in maintaining a good environment. Thetear flow and barriers hindrance lead to drainage of drug from the eye when instilled into eye which leads to poor bioavailability of drug and reducing the desired therapeutic effect of the drug. But one of the advantage of ocular route is that drug enter to the systemic circulation by eliminating hepatic first pass metabolism.[2] Conventional ocular drug delivery has eye drops as widely used formulation. Eye drop can be manufactured easily and can show better compliance but the major problem is poor bioavailability, which arises due to:

- Instilled solution drainage
- Lacrimation
- Non-productive absorption
- Tear evaporation and permeability
- Limited corneal area and poor corneal metabolism.[3]

Few other conventional ocular formulations developed to enhance ophthalmic bioavailability are suspensions, ointments and aqueous gels have drawbacks are:

- Poor patient compliance,
- Blurred vision,
- Self-insertion difficulties
- Premature release of drug, and
- Instability.[3-5]

To overcome these problems of retention of drug concentration at optimum level at the site of action within the eye various novel approaches were studied. In Ocular Drug Delivery System in situ Ocular gel is one of the novel approach. These system contains delivery vehicle made up of polymers with a property of sol – gel transition when influenced by biological stimulus.[6]

These frameworks are more satisfactory for patients. They are regulated into eye as an answer and go through a quick gelation when in contact with the eye. Studies have shown that the precorneal home season of some in situ gelling for a few hours. Various polymeric mixes have been effectively utilized for creation.[7] Contingent upon the strategy utilized to make sol gel Stage change on the eye surface, the accompanying three sorts of Frameworks are perceived. PH triggered framework, temperature dependent framework and ion activated

framework including Alginate and gallan gum and carbopol/ pluronic.

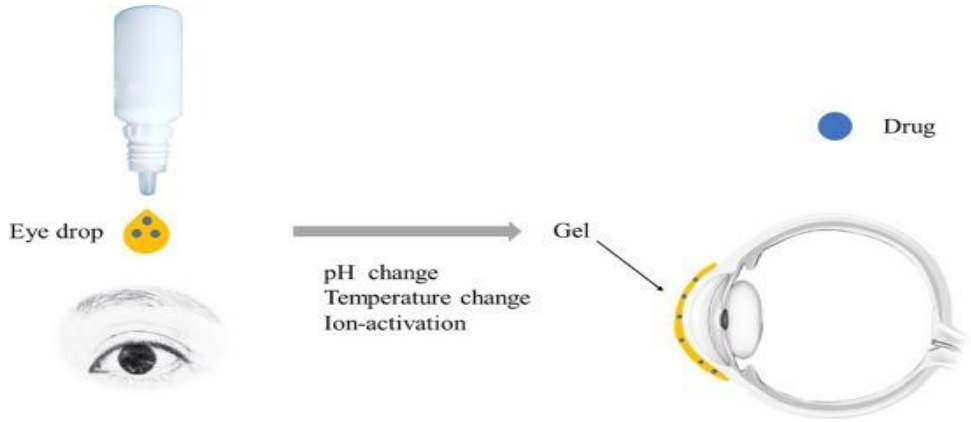

Fig: Showing in- situ Ocular gelling system.

Benefits Of In – Situ Ocular Gels

The few benefits of in situ ocular drug delivery over conventional systems are as:

- Administration is easy
- Ease of fabrication
- Reduce frequency of dosing
- Sustained and controlled drug release due to formation of gel network
- Enhancement of drug bioavailability by increasing the precorneal contact time
- Better patient compliance and comfort
- Improvement in therapeutic performance of drug
- Prolonged retentivity at site of action.[8-10]

The principle advantage of this formulation is the possibility of administering accurate and reproducible quantities, in contrast to already gelled formulations and moreover promoting precorneal retention.[11]

Approaches To In – Situ Gelation

In situ gel framework shows stage change from sol to gel after getting biologicalstimulus. Three types of biological stimulus are presented by ocular route viz Temperature, pH and ions that are present in the lachrymal fluid.[6]

Temperature sensitive in- situ gel

Also known as temperature triggered in situ gel.In this System at a particular temperature sol gel advances happen, And this temperature is called as 'lower critical solution Temperature (LCST).The main reason (assumed) for the Sol to gel conversion is the difference in the solubility at Different temperature. At the point when the temperature is beneath LCST, the hydrogen bonding between the hydrophilic Group on polymeric surface and water particle favors Enhanced disintegration of polymer chain and the framework remain in the form of solution. But when the system is placed in temperature greater than LCST, the hydrogen Bond corrupts. Thus the hydrophobic interaction is increased, there by facilitating sol-gel transformation.[12]

The polymers that shows temperature actuated Gelation are Poloxamer or pluronics, cellulose subsidiaries (methyl cellulose, HPMC, EGEC) and xyloglucan.

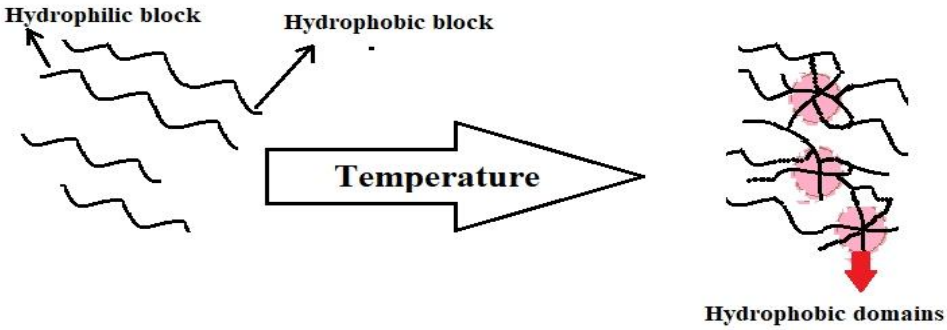

Fig: Showing mechanism for temperature sensitive system.

pH triggered in- situ gel

pH is viewed as the significant natural boundary present at visual site and quickly shapes gel development after getting bio- stimulus. At pH 4.4 the formulation is a free – running solution which goes through coagulation when the pH is raised by the tear liquid to pH 7.4.Thus the pH change is about 2.8 units after instillation of the formulation (at pH 4.4) into the tear film leads to almost instantaneous transformation of the highly fluid latex into viscous gel.[8]

The polymers that show pH induced/ triggered Gelation Are Chitosan, Carbopol, and HPMC etc. The pH Sensitivity of these polymers is because of the presence of ionisable groups present on the polymer surface that display a sharp change in the level of ionization and water solubility at specific pH (pKa).[13]

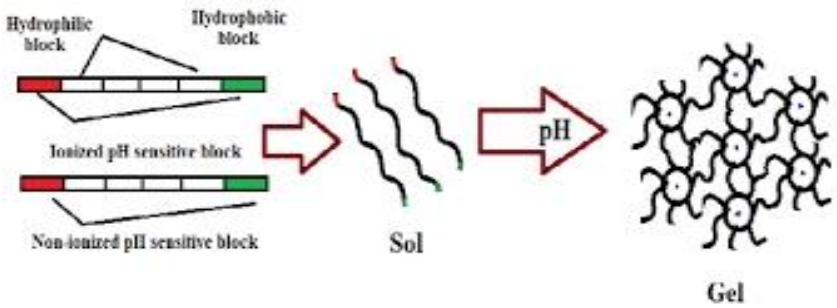

Fig: Showing mechanism of pH triggered system.

Ion Activated in- situ gelation

Also known as ion sensitive gelling system.Gelation is the process wherein Gelation of the solution imparted is set off by the adjustment of ionic strength. It is assumed that the osmotic gradient across the surface of the gel is responsible for the gelation. The aqueous polymer solution frames a clear gel within the sight of mono or divalent cations ordinarily found in the tear liquids.The initiation of Gelation process of the polymeris stimulated by electrolyte of the tear fluid especially Na+, Ca2+ and Mg2+ cations when liquid solution is instilled in the conjunctival cul-de-sac.[14]

The polymers that show ion sensitive Gelation are Gellan Gum, Alginates and Carrageenan.

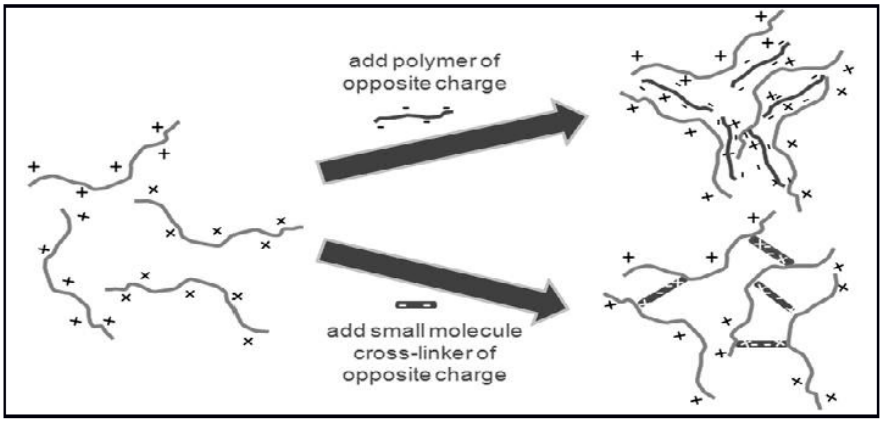

Fig: Showing mechanism of ion activated in- situ system.

Table 1: List of Ocular in- situ gels approved for the market.

Name of the Product	Polymer	Type of In- Situ gelling system
Timoptic-XE® (Timolol maleate ophthalmic gel forming solution)	Gellan gum	Ion-induced
Pilopine HS® (pilocarpine hydrochloride ophthalmic gel)	Carbopol 940	pH-triggered
AzaSite (azithromycin ophthalmic solution)	Poloxamer 407	Temperature-triggered
Timoptol-LA (Timolol maleate)	Gellan gum	Ion-activated

Evaluation Of In- Situ Ocular Gels

Clarity

The clarity of formulated solutions can be determined by visual inspection against black and white background.[15,16]

Viscosity and Rheology

The viscosity and rheological properties of the polymeric formulations, either in solution or in a gel made with artificial tissue liquid (contingent on the route of administration\'s) were determined with various viscometers. The viscosity of these formulations should be such that it should be patient complient.[17,18]

pH of Gel

pH can be determined formulation is taken in beaker & 1ml NaOH added drop wise with continuous stirring pH is checked by using pH meter.[19]

Isotonicity Evaluation

Isotonicity is maintained to prevent tissue damage or irritation of eye. For testing Formulations are mixed with few drops of blood & observed under microscope at 45x

magnification &compared with standard marketed ophthalmic formulation.[20]

Ocular irritancy studies

"Ocular irritation Studies were performed on male albino rabbits weighing 1-2 kg. The modified Draize Technique was designed for the ocular irritation Potential of the ophthalmic product. According To Draize test, the eye drops (100µl) was normally placed in the lower cul-de-sac and Irritancy was tested at the time interval of 1hr, 24hrs, 48hrs, 72hrs, and 1 week after Administration. The rabbits were observed periodically for redness, swelling and watering Of the eye".[21]

Sterility testing

For sterility direct inoculation method was used. 2 ml of liquid from test container was removed with a sterile pipette or with a sterile syringe or a needle. The test liquid was aseptically transferred to fluid thioglycolate medium (20 ml) and soyabean-casein digest medium (20 ml) separately. The liquid was mixed with the media. The inoculated media were incubated for not less than 14 days at 30°C to 35°C in the case of fluid thioglycolate medium and 20°C to 25°C in the case of soyabean-casein digest medium.

Accelerated stability studies

Accelerated temperature stability studies, are generally conducted at 40 °C, 50 °C and 60 °C, as well as at room temperature andFreezing temperature. The samples were stored at different storageConditions of elevated temperature such as 40oc and room temperature at RH of 75%. The sampleswere withdrawn at weekly intervalsAnd estimated for the drug content spectrophotometerically at 272nm using UV-visible spectrophotometer under fluorescent light.

Fourier transform infra- red spectroscopy and thermal analysis

During gelation process, the nature of interacting forces can be evaluated using this technique by employing potassium bromide pellet method. Thermogravimetric analysis can be conducted for in situ forming polymeric systems to quantitate the percentage of water in hydrogel. Differential scanning calorimetry is used to observe if there are any changes in thermograms as compared with the pure ingredients used thus indicating the interactions.[22]

In- Vitro drug release studies

The in situ gel formulations to be administered by ocular routes, the drug release studies are carried out by using the plastic dialysis cell.[23] The cell is made up of two half cells, donor compartment and a receptor compartment. Both half cells are separatedwith the help of cellulose membrane. The sol form oftheformulation is placed in the donor compartment.The assembled cell is then shaken horizontally in anincubator. The total volume of the receptor solutioncan be removed at intervals and replaced with the freshmedia. This receptor solution is analyzed for the drug release using analytical technique.[24]

Antimicrobial Activity

Antimicrobial efficacy studies are carried out to ascertain the biological activity of sol-gel-system against microorganisms. This is determined in agar diffusion medium employing 'Cup Plate Techniques'. The microbial growth of bacteria is measured of antibiotic & compared with that produced by known conc. Of standard preparation of antibiotic & carried out the microbial assay serial dilution method is employed.

CONCLUSION

In situ ocular gel system is the new novel approach toward ocular drug delivery. Better patient compliance, enhancement of drug bioavailability, prolonged retentivity at the site of action and controlled release of drug are the advantages on in situ ocular gel over conventional ocular drug delivery system. The created formulations are a suitable option in contrast to ordinary eye drops by temperance of its steadiness To upgrade bioavailability through its more extended precorneal residence Time and capacity to sustain burrowed discharge. Likewise ease of Administration and decreased frequency of administration resulting in better patient compliance. Thus in situ ocular gels are found to a viable alternative to conventional eye drops.

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