Nishtha Ugave *et al*, International Journal of Pharmaceutical Sciences and Medicine (IJPSM), Vol.9 Issue. 2, February- 2024, pg. 23-28

ISSN: 2519-9889
Impact Factor: 5.9

A REVIEW ON OCCULAR IN-SITU GELS

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DOI: 10.47760/ijpsm.2024.v09i02.004

ABSTRACT: The present study of ophthalmic in-situ gels are now days proved a sustained drug delivery in various eye diseases. The formulation of in-situ gels for eye which carries the advantages like easy for administration, reduces frequency of dose and improves patient compliance. The formation of in-situ gels depends on phase transition system or sol-gel transition system. The formulation approaches like temperature intonation, pH change and presence of ions from which the drug gets released in a sustained and controlled manner are utilised for in-situ gels. Various polymers that are used for the formulation of in-situ gels
KEYWORDS: In-situ gel, polymers, ophthalmic drug delivery, Temperature, pH

1.0 INTRODUCTION

Ophthalmic drug delivery is one of the challenging endeavours facing the pharmaceutical scientist today. The structural and functional aspects of the eye render this organ highly impervious to foreign substances. A significant challenge to the formulator is to overcome the protective barriers of the eye without causing permanent tissue damage. The major problem encountered with topical administration is the rapid precorneal loss caused by nasolacrimal drainage and high tear fluid turnover which leads to only 10% drug concentrations available at the site of actions[1]. The major problems in conventional liquid ophthalmic formulations are washing out of drug from the precorneal area immediately upon instillation because of constant lachrymal secretion, nasolacrimal drainage and short precorneal residence time of the solution. To increase precorneal residence time and ocular bioavailability, different ophthalmic delivery system such as viscous solutions, ointments, gels, suspensions or polymeric inserts are used. But because of blurred vision or lack of patient compliance, these formulations have not been widely accepted. This problem can be overcome by using in situ gel forming ocular drug delivery system, prepared from polymer, exhibit sol-to-gel phase transition due to a change in a specific physio-chemical parameterpH, temperature, ion-sensitive[2]. In ocular delivery of medicaments, the physiological constraints imparted by the protective mechanisms of the eye lead to drainage from the eye, resulting in a short duration of the therapeutic effect. When a conventional eye drops is applied into the eye, the blinking action and effective tear drainage of the eye result in at least a 10-fold reduction in the drug concentration within 4–20 min. We can improve the ocular therapy by improving the precorneal residence time of drugs. In order to slow down drug elimination and to prolong the

ISSN: 2519-9889
Impact Factor: 5.9

resident time on the ocular surface, several new preparations have been developed for ocular use. In situ gel-forming ocular drug delivery systems are one of them. In situ gel exhibits reversible phase transitions (sol–gel–sol) and pseudoplastic behaviour to minimize drainage from blinking. In situ gel is formulated as a liquid dosage form which is suitable to be administered as conventional eye drops which, upon exposure to eye physiological conditions, changes to the gel phase, thus increasing the precorneal residence time of the delivery system and enhancing ocular bioavailability.[3]

In situ gel forming systems are drug delivery systems that are 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 crosslinking 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[4].Both natural as well as synthetic polymers can be used for the fabrication of in situ gels.[5]

2.0 ADVANTAGES OF IN SITU GELS[6]

- 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.

3.0 APPROACHES FOR IN SITU GELLING SYSTEM

Temperature triggered in situ gelling system: In this gelling system polymers are liquid at room temperature (20-25°C) and undergoes gelation at physiological temperature (35-37°C)[7]. An ideal temperature triggered gelling polymer solution should remain liquid below its low critical solution temperature (LCST) and up to its upper critical solution temperature (UCST) and should transform into gel on increase of the surrounding temperature. There is gradual desolvation of the polymer and increased micellar aggregation.[8]

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Impact Factor: 5.9

pH triggered in situ gelling system: pH triggered in situ gelling systems are solutions, which upon exposure to the pH of the lachrymal fluid converts into the gel phase. The pH sensitive polymers contain either weakly acidic or basic groups along the backbone of the polymer, these either release proton or accept free proton in response to change in pH.[9]

Ion triggered in situ gelling system: In ion triggered in situ gelling system solution viscosity increases upon exposure to ionic concentration of the tear fluids 28. It is also called osmotically induced gelation. Ion sensitive polymers are able to crosslink with cations (monovalent, divalent) present in lacrimal fluid on ocular surface and enhance the retention time of drug.[9]

4.0 MECHANISM OF IN SITU GEL

Many mechanisms have been employed to cause reversible sol-gel phase transition, i.e., in situ gel forming system by different environmental conditions. The stimuli that induce various responses to form hydrogels includes: physical stimuli such as change in temperature, electric fields, light, pressure, sound and magnetic fields; chemical stimuli such as change in pH and ion activation from biological fluids; and biological or biochemical stimuli such as change in glucose level. Out of these different environmental conditions only pH, ion activated and temperature stimuli are used for ophthalmic drug delivery.[10]

5.0 POLYMERS USED IN THE FORMULATION OF IN SITU GELS

The most important ingredients in the manufacture of in situ are the polymer. 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 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.[11]

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 gel has the type according to gel formation.[12]

POLYMER	DESCRIPTION
Carbopol	It is a pH sensitive polymer. It is also called as carbomer, acrylic acid polymer.
Poloxamer	It is a temperature sensitive polymer. It is commercially called as Pluronic.
Gellan Gum	It is an ion-sensitive polymer. It is also known as Gelrite.[13]
Sodium Alginate	It is an ion-sensitive polymer. It is also known as algin, alginic acid, sodium salt, E401, Kelcosol,Keltone,Protanal,sodium polymannuronate.[14]

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Chitosan	It is a polycationic polymer, exhibits pseudoplastic and viscoelastic behaviour. It has good antibacterial and bioadhesive property.[15]
Hydroxy Propyl Methyl Cellulose (HPMC)	It is a temperature sensitive polymer. It is also known as Hypromellose, Methocel etc

6.0 EVALUATION OF IN SITU GEL

Gelling capacity: -The gelling capacity of the prepared formulation is determined by placing a drop of the formulation in a vial containing 2.0 ml of freshly prepared simulated tear fluid and visually observed. The time taken for its gelling is noted.[16]

Visual appearance and clarity: - Visual appearance and clarity of prepared in situ formulation is checked for presence of any particulate matter under fluorescent light against a white and black back ground.[17]

pH : - affects both solubility as well as stability of drug in ophthalmic formulations. It should be such that the formulation will remain stable at that pH at the same time there would no irritation to the patient upon administration. It is measured by digital pH meter.[18]

Isotonicity: -It is important characteristics of ophthalmic formulation which has to be maintained to prevent any tissue damage or irritation to the eye. It refers to the osmotic pressure exerted by salts in aqueous solution. Ophthalmic formulation must possess osmotic pressure within the range of 290-310 mosmol/kg. Tonicity is measured by using osmometer.[19]

In vitro drug release studies: In-vitro diffusion is generally evaluated by fabricated open flow through assembly (specially designed glass cylinder open at both ends) and semi-permeable cellophane membrane/dialysis membrane. Cellophane membrane, previously soaked overnight in simulated tear fluid is mounted by tied and sandwiched between the donor and receiver compartment the 0.5 ml aliquot of donor solution is placed on top of cellophane membrane. Aliquots of medium (3.0 ml) are withdrawn at selected time intervals and replaced by 3.0 ml of freshly prepared simulated tear fluid through sampling port for analysis. The samples are diluted suitably and analysed by UV spectrophotometer at specified wavelength.[3]

Rheological studies: Brookfield viscometer is mainly used for determination of Viscosity of ophthalmic in situ gels. Viscosity is measured before and after gelation by increasing angular velocity gradually from 0.5 to 100 rpm.[20]

The consistency, firmness and cohesiveness of in-situ gel is assessed by using texture profile analyzer which mainly indicated gel strength and easiness in administration in vivo. Higher values of adhesiveness of gels are needed to maintain an intimate contact with mucus surface.[21]

Sterility testing: Sterility testing of ophthalmic preparations is very important evaluation parameter. The sterility test is performed according to Indian Pharmacopoeia. Direct

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Impact Factor: 5.9

inoculation method is used; 2 ml of liquid from test container is removed with a sterile pipette or with a sterile syringe or a needle. The test liquid is then aseptically transferred to fluid thioglycolate medium (20 ml) and soyabean-casein digest medium (20 ml) separately. The liquid is mixed with the media. The inoculated media is 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 media.

In vivo Scintigraphy Studies: Gamma scintigraphy is a well-established technique for in vivo evaluation of ophthalmic retention time. Although the rabbit is the commonly recommended animal model for evaluation of ophthalmic formulations, but human volunteers are preferred for this study due to physiological differences between rabbits and humans, especially the blinking rate.[22]

7.0 ACKNOWLEDGEMENT

The author is thankful to the management of Swami Vivekanand College of Pharmacy, Indore. For providing necessary facilities to carry out the research work and heartily thankful to my Co-Guide and guide for providing all the support and encouragement to carry out this studies.

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