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Ocular Insitu Gel: A Review

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ABSTRACT: The in situ gel system has emerged as one of the most effective novel drug delivery system. It helps for sustain and control released of the drug by its special characteristic feature of sol to gel transition. In situ gelling system is a formulation that is in solution form before entering in to the body, but it will change to gel form under various physiological condition. There are several application and advantages of in situ gelling system in today life. This review mainly focus on introduction in introduction to in situ gel, its mechanism,various polymers used and its applications. This review will give us information regarding about in situ gel, approaches, mechanism to gel form and polymer use for gel form.
Keywords: In situ Gel, Approaches,Mechanism to gel form ,polymers

I. INTRODUCTION

The ocular drug delivery system is considered as a crucial and challenging as human eye is an isolated organ where the delivery of drug is quite difficult. The bioavailability of conventional formulation poor and short corneal residence time due to rapid and extensive elimination of drug from corneal lachrymal fluid by solution drainage, lachrymation, and non-productive.The. The eye drop have a poor bioavailability due to their rapid washout during lachrymation in eyes. Most of the system are applied as solution or suspension. The rapid precorneal elimination observed with conventional ocular formulation ends in poor drug bioavailability.so this problem can be overcome by fabricating the drug as a formulation that undergoes instantaneous in situ gel formation upon ophthalmic administration. They undergo gelation after instillation because of physicochemical changes occurring in the eyes.

II. CLASSIFICATION OF OPHTHALMIC DRUG DELIVERY SYSTEMS

A. Conventional delivery system
- eye drops
- ointments and Gels
- Ocuserts and Lacrisert.

B. Drug delivery to anterior segment
- contact lens
- Cal Du sac inserts
- Subconjuctival/ Episcleral implants

C. Drug delivery to posterior segment
- Intravitreal implants (e.g, Duraser Technology system, Novadu Technology, I- ratio TA, NT-501)
- Injectable Particulate Systems (RETAAC, Cortiject, Visudyne)

D. Physical devices
- Iontophoresis
- Micro- electromechanical intra ocular drug delivery devices

E. Vesicular system
- Liposomes
- Niosomes
- Discomes
- Pharmacosomes

F. Controlled delivery systems
- In situ gel systems/ Phase transition systems
- Iontophoresis
- Dendrimer
- Contact lens
- Collagen shield
- Microemulsion
- Nanosuspensions
- Microneedle

G. Particulates
- Nanoparticles
- Microparticles

H. Advanced delivery systems
- Cell encapsulation
- Gene therapy
- Stem cell therapy
- Protein and Peptide therapy

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- Scleral plug therapy
- siRNA therapy
- Oligonucleotide therapy
- Aptamer

III. IMPORTANCE OF IN SITU GELLING SYSTEM

- The major important is the possibilities of administrating accurate and reproducible quantities compared to already form gel.
- In situ forming polymeric delivery system such as ease of administration and reduced frequency of administration improved patient compliance and comfort.
- Poor bioavailability and therapeutic response exhibited by conventional ophthalmic solution due to rapid precorneal elimination of drug may be overcome by use of gel system that is instilled as drops into eye and undergoes a sol-gel transition from instilled dose.
- Liquid dosage form that can sustained drug released and remain in contact with cornea of eye for extended period.
- Reduced systemic absorption of drug drained through the nasolacrimal duct may result in come undesirable side effect

IV. ADVANTAGES:

- Reduced frequency of administration
- Can be administered to unconscious patient
- Ease of administration, comfort
- Improved patient compliance
- Natural polymer have inherent properties' biocompatibility, biodegradability, andbiologically recognizable moieties that support cellular activities.

V. DISADVANTAGES:

- The solution form of the drug is more susceptible for degradation
- It requires high level of fluid
- Chances of stability problem due to chemical degradation
- After placing the drug eating, and drinking may become restricted up too few hours
- The quantity and homogeneity of drug loading into hydro gel may be limited
- Only drug will small dose requirement can be the given

VI. IN SITU GELLING SYSTEM

This novel drug delivery system promotes the importantly ease and convenience of administration, delivery of accurate dose as well as prolong residence time of the drug in contact with mucous,that problems generally encountered in semisolid dosage form. Insitu gel formation occurs due to one or combinations of different stimuli pH change,temperation modulation and ion sensitive. Smart polymeric systems represent promising means of delivering the drug these polymers undergo sol-gel transition,once administered from the natural and synthetic polymers began to be investigated for controlled released formulations. Various natural and synthetic polymers are used for formulation development of in situ forming drug delivery system. The various approaches for in situ gelling system:

♣ Temperature induced in situ gel system
♣ pH induced in situ gel system
♣ Ion activated system

a. Temperature induced in situ gel system:

In drug delivery research temperature sensitive insitu gels are probably the most studied class of environment sensitive polymer system. In this gelling system polymers are liduid at roo temperature (20-25℃)and undergoes gelation at physiological temperature (35-37℃). An ideal temperature triggered gelling polymer solution should remain liduid below its critical solution temperature and upto its upper critical solution temperature and should transform into gel on increase of the surrounding temperature .There is gradual desolvation of the polymers and increase micellar aggregation (enlargement of polymeric network).For the optimum temperature triggered in situ gelling solution , the phase transition temperature should be more than room temperature ,so that it can be easily administered to eye and gelled at precorneal temperature without having any effect of tear fluid dilution even at concentration as low 5%w/v.

b. pH induced in situ gel system:

pH triggered in situ gelling system are solution ,which upon exposure to the pH of thea lachrymal fluid converts into the gel phase e.g such as cellulose acetate phthalate and carbopol .The pH sensitive polymers contains either weakly acidic or basic group along the backbone of the polymer, these either release proton or accept free proton in response to

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change in pH.At specific pH there is electrostatic, hydrophobic interaction and hydrogen bonding takes place , hence leads to inter diffusion and a conformational change in the polymer result in its swelling. Hence sol to gel transition is pH triggered.

c. Ion triggered in situ gelling system:

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

VII. MECHANISM OF IN SITU GELS:

The mechanism of an insitu gel based on following mechanism

I. Based on physical mechanism

a. **Swelling**: In this method of in situ gel formation material absorbs water from surrounding environment and expand to desired space. For example glycerol mono oleate ,which is polar lipid swell in water to form lyotropic liquid crystalline phase structure.It has some bioadhesive properties and can be degraded in vivo by enzymatic action.

b. **Diffusion**: This method involves the diffusion of solvent from polymer solution into surrounding tissue which result in precipitation or solidification of polymer matrix. N-methyl pyrrolidone has been shown to be useful solvent for such system.

II. Based on chemical reaction mechanism

Chemical reactions that result in situ gelation may involve the following processes

a. Enzymatic cross-linking :

Enzymatic cross linking is the most suitable method used in the formation of insitu gelling system .In this method,gel is form by cross linking with the enzymes which are present in body fluid .In situ formation induced by natural enzyme and that are not been investigated widely but appear to possess some advantages over chemical and physiological conditions and no need for possibly destructive chemicals such as monomers and initiator. Hydrogel are employed in intelligent stimuli responsive delivery ststem that can release insulin have been investigated. Modify the number of enzyme also maintain an suitable mechanism for controlling the rate of gel formation .

b. .Polymerization

In photo polymerization method electromagnetic radiation are used duing formation of in situ gelling system. Asolution of reactive macromere or monomers and invader can be injected into a tissue site and the application of electromagnetic radiation used to form gel. The most suitable polymer for photo polymerization are the polymer which undergo dissociation by polymerisable functional group in the presence of photo initiator like acrylate or similar monomers and macromers that are typically long wavelength ultraviolet and visible wavelength are used.Short wavelength ultraviolet are not used often beacause they are limited penetration of tissue and biologically harmful. In this method ,ketone, such as 2,2 dimethoxy-2-phenyl acetophenone ,is used as the initiator for ultraviolet photo-polymerization.

c. Ionic cross linking

In this method ,the ion sensitive polymer is used.Ion sensitive polymers may undergo phase transition in presence of various ions like Na+,K+,and Mg+. Some polysaccharide also are in the class of ion sensitive ones. While k-carrageena forms rigid ,small amount of Ca2+.Gellan gum mainly available as gelrite. It is an anionic polysaccharide, in presence of mono and divalent cation that undergoes in situ gelling system.

VIII. CLASSIFICATION OF INSITU POLYMERIC SYSTEM :

Pectin:

Pectins are a family of carbohydrate , which the polymer backbone mainly includes α(1-4)galacturonic acid residues. Low methoxypectins (degree of esterification < 50%) readily form gels in aqueous solution in the presence of free calcium ions, which crosslink the galacturonic acid chains in a manner represented by egg box model .Although the gelation of pectin will occur in the presence of H+ ions ,

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a source of power ions, generally calcium ions is required to produed the gels that are suitable as vehicles for drug delivery.The main advantages of using pictin for these formulations is that it's water soluble ,so organic solvent are not necessary in the formulation. Divalent cations present in the stomach , carry the transition of pictin to gel state when it is administered orally. calcium ions in the complexed may be is also included in the formation for the induction of pictin gelation

Alginic acid

residues joined by 1,4-glycoszidic linkage. The proportion of each block and the arrangement of block depending on the molecule vary counting on the algal supply.Dilute aqueous solutions of alginates forms firm gels on addition of di-and tri-valent metal ions by cooperative source Alginic acid is a linear block copolymer polysaccharide consisting of β-L-glucuronic acid involving consecutive glucuronic residue in the α -glucuronic acid acid block the aginate chain .alginic acid can be chosen as a vehicle for ophthalmic formulations,sinceexhibit favourable biological properties such as biodegradability and nontoxicity.

Chitosan

Chitosan is a biodegradable ,thermosensitive ,polycationic polymer obtained by alkaline deacetylation of chitin, a natural component of shrimp and crab shell. Chitosan is a biocompatible pH dependent cationic polymer ,which remain dissolve in aqueous solution up to a pH of 6.2.Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to the formation of a hydrated gel like precipitation .The pH gelling cationic polysaccharides solution are transformed into termally sensitive pH dependent gel forming aqueous solutions, without any chemical modification or cross linking by addition of polyol salts bearing a single anionic head such as glycerol ,sorbitol, fructose or glucose phosphate salt to chitosan aqueous solution.

Carbopol

Carbopol is a well know pH dependent polymer,which stay in solution form at acidic pH but form a low viscosity gel at alkaline pH HPMC is used in combination with cabopol to impact the viscisity to carbopol solution ,while reducing the acidity of the solution .Various water soluble polymers such as carbopol system ,hydroxyl propyl methyl cellulose system ,come under the category of pH induced he formulation and in situ precipitating polymeric system.

Gellan gum

Gellan gum is an anionic deacetylated exocellular polysaccharide secreted by Pseudomonas elodea with a tetrasaccharide repeating unit of one α –L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residue .It has the tendency of gelation which is temperature dependent or cations induced .This gelation involves the formation of double helical junction zones followed by aggregation of the double helical segment to form a tree dimentional network by complexation with cation and hydrogen bonding with water. The formulation consist of gellan solution with calcium chloride and sodium citrate complex. When administrered orally ,the calcium ions are released in acidic envionment of stomach leading to gelation of gellan thus forming gel in situ.In situ gelling formulation as vehicle for oral delivery of theophylline.

Pluronic F-127

Poloxamers or pluronic are the series of commercially available difunctional triblock copolymer of non-ionic nature .They comprise of a central block of relatively hydrophobic polypropylene oxide surrounded on both sides by the block of relatively hydrophilic poly ethylene oxide.Due to the PEO/PPO ratio of 2:1 ,when these molecules are immersed into the aqueous solvent ,they form micellar structure above critical micellar concentration .They are regarded as PEOPPO-PEO copolymer. Chemically they are oxirane methyl ,polymer with oxirane or α–Hydro-ω-hydroxypoly(oxypropylene) units that undergo changes in solubility with change in environment temperature .

Xyloglucan

Xyloglucan is a polysaccharide derived from tamarind seed and is composed of a(1-4) β-D-glucan backbone chain ,which has (1-6)-α-D-xylose branch that are partially substituted by(1-2)β-D-galactoxylose, when xyloglucan is partially degraded by β–galactosidase,the resultant product exhibit thermally reversible gelation by the lateral stacking of the rod like chain. The sol- gel transition temperature varies with the degree of galactose elimination. It forms themally reversible gels on warming to body temperature .Its potentially application in oral delivery exploits the proposed slow gelation time that would allow in

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situ gelation in the stomach following the oral administration of chilled xyloglucan solution.

IX. EVALUATIONS:

Clarity and visual appearance

The clarity and visual appearance of the formulation before and after gelling decided by visual examination of formulation under light alternatively against white and black background.

pH

The pH of each of prepared ophthalmic formulations was determined by using pH meter.The pH meter was calibrated before each use with standard pH 4, 7 and 9.2 buffer solution.

Determination of gelation time and gelation temperature

The gelation time was determine by gragually increased the temperature of the formulation, and the time required by the formulations (containing different concentration of the polymers) to form a stiff gel was recorded using a digital stopwatch.

In-vitro gelling capacity

The in vitro gelling capacity was determined by placing freshly prepared solution of insitu gel in a vial containing freashly prepared stimulated tear fluid (pH 7)and equilibrated at 37℃ .The visual assessment of gel formation was carried out .Time required forgelation as well as time taken for the formed gel to dissolved were also noted .Different grade were allowted with the gel integrity ,and rate of formation of gel with respect to time . The grade were given as a no gelation (-), gelation after few minutes, and remaining for 1-2 hours(+),gelation immediate and remain for up to 8 hr(++) ,gelation immegiate and remain extended time(+++)and very stiff(++++).

Viscosity and rheological studies

Brookfield digital viscometer was used for the determination of viscosity and rhehological properties using spindle no.4.The viscosity of gel was measured at different angular velocities at a temperature of 25℃ . A typical run comprised changing of the angular velocity from 5 to 25 rpm.The viscosity measurement were done before (at pH 6.0)and after gelling (at STF pH7.4).

Isotonicity evaluation

Isotonicity is important characteristic of the ophthalmic preparation .Isotonicity has to be maintained to prevent tissue damage or irritation to cornea .Ophthalmic formulation were subjected to isotonicity testing to evaluate their isotonic(osmotic pressure same as body fluid)and hypotonic (osmotic pressure is greater than body fluid) and hypertonic (osmotic pressure less than body fluid).The tonicity of insitu gel was determined by hemolytic method .In this method prepared formulation were mixed with few drop of blood and observed under microscope at 45x and observe the effect of formulation on red blood cells(RBC) sucj as, swelling bursting and cremation. Finally compared the shape of formulation mixed blood cell with isotonic ,hypotonic, hypertonic.

Drug content

The drug content estimation was carried out by diluting 1 ml of prepared formulation in 100 ml of distilled water and analyzed using UV-visible spectrophotometer at 285nm.

In vitro dissolution study

The in vitro released of drug from the prepared formulation was studied using a modified diffusion testing apparatus . The freshly prepared simulated tear fluid was used as a diffusion medium . Semi permeable membrane , previously soaked in the diffusion medium for overnight , was tied to one end of a specially designed glass cylinder (open at both end) having inner diameter of 3.4 cm. Two milliliter of formulation was accurately pipette out the glass cylinder known as donor chamber. The cylinder was suspended in a beaker (Acceptor chamber) containing 100 ml of diffusion medium so that membrane just touches the surface of the medium .Acceeptor chamber was maintained at a temperature of 37±2℃ with a stirring rate of 50 rpm using magnetic stirrer. About 1 ml of sample was withdrawn at a time interval of 1 hour and replaced with an equal volume of fresh diffusion medium . The aliquots were diluted with the diffusion medium and analyzed at 285 nm using UV spectrophotometer.

Ocular irritancy

Ocular Irritation study was performed on optimized formulation in four albino rabbits(male) , each weighing about 2 to 3 kg , and 0.1 ml of the optimized sterile drug

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formulation was instilled in were monitored periodically for redness , swelling , watering of Eye.

X. CONCLUSION :

Ocular drug delivery system is burgeoning field in which most of the researcher are taking challenges to combat various problem associated to this delivery. Steady advancement in the understanding of the principles and processes governing ocular drug obsorption and disposion and and continuing technological advanced have surely brought some improvement in the efficacy of ophthalmic delivery system .The primary requirement successful controlled released product focuses on increase patient compliance which the insitu gel offers.Furether use of biodegradable and water soluble polymers for the insitu gel formulation can make them more acceptable and excellent drug delivery SYSTEM .Moreover,insitu gels have ease of commercialization which adds advantages from industrial point of view.

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