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A REVIEW ON TEMPERATURE TRIGGERED OPTHALMIC INSITU GEL

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ABSTRACT

Eye is the most vital 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. The anatomical structure and the protective physiological process of the eye exert a formidable defense against ophthalmic drug delivery, leads to poor precorneal drug loss results in poor ocular by availability and ultimately poor ocular therapy. The 'in situ gel' system has emerged as one of the best novel drug delivery systems; it helps for the sustained and controlled release of the drugs 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 conditions. There are various polymers which under go in situ gel forming and potentially used for various routes of drug administration. There are several applications and advantages of in situ gelling system in today's life. This review mainly focus on introduction to in situ gel, its mechanism, various polymers used and its applications.

KEYWORDS: In situ gel, in situ gelling polymers, temperature sensitive.

INTRODUCTION

The eye is a unique organ, both anatomically and physiologically, containing several widely varied structures with different physiological functions that render the organ highly impervious to foreign substances. The conventional drug delivery such as suspension, ointment, solution show some drawbacks like increase pre-corneal drainage, blurred vision, low bioavailability low residence time. The absorption of drugs in the eye is severely limited by some protective mechanisms that ensure the proper functioning of the eye, and by other concomitant factors like, drainage of the instilled solutions, lachrymation and tear turnover,

metabolism, tear evaporation, non-productive absorption/adsorption, limited corneal area and poor corneal permeability, binding by the lachrymal proteins.

Development of newer, more sensitive diagnostic techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. Conventional ophthalmic formulations like solution, suspension, and ointment have many disadvantages which result into poor bioavailability of drug in the ocular cavity.

The specific aim of designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for the appropriate duration. Ocular disposition and elimination of a therapeutic agent is dependent upon its physicochemical properties as well as the relevant ocular anatomy and physiology. A successful design of a drug delivery system, therefore, requires an integrated knowledge of the drug molecule and the constraints offered by the ocular route of administration. Development of newer, more sensitive diagnostic techniques and novel therapeutic agents are needed to provide ocular delivery systems with high therapeutic efficacy as the conventional systems have some drawbacks which makes them less effective. The various approaches that have been attempted to increase the bioavailability and the duration of the therapeutic action of ocular drugs can be divided into two categories. The first one is based on the use of sustained drug delivery systems, which provide the controlled and continuous delivery of ophthalmic drugs. The second involves maximizing corneal drug absorption and minimizing precorneal drug loss. The development of in situ gel systems has received considerable attention over the past few years owing to the several advantages offered by this polymeric system, such as ease of administration and reduced frequency of administration, improved patient compliance and comfort. In situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange.

ANATOMY AND PHYSIOLOGY OF HUMAN EYE

Owing to its design, human eye represents a gateway to the process called vision.The human eye is comprised of layers and internal structures, each of which performs distinct functions. The eye is composed of two segments.

The anterior segment consists of the

Aqueous humor is a jelly-like substance located¬ in the outer/front chamber of the eye. It is a watery fluid that fills the "anterior chamber of the eye" which is located immediately behind

the cornea and in front of the lens. The aqueous humor is very slightly alkaline salt solution that has a high oxygen tension and about the same osmotic pressure as blood.

Pupil generally appears to be the dark "centre" of the eye, but can be more accurately described as the circular aperture in the centre of the iris through which light passes into the eye.

The iris is a thin circular contractile curtain located in front of the lens but behind the cornea. The iris is a diaphragm of variable size whose function is to adjust the size of the pupil to regulate the amount of light admitted into the eye.

The ciliary muscle is a ring of striated smooth¬ muscles in the eye‟s middle layer that controls accommodation for viewing objects at varying distances and regulates the flow of aqueous humour into schlems canal.

The posterior segment consists

The sclera (white portion of the eye) is the tough¬ white sheath that forms the outer-layer of the ball and can withstand the intra-ocular tension constantly maintained in the eye. The conjunctiva is a thin transparent mucous epithelial barrier, lines the inside of the eyelids.

The conjunctiva is composed of two layers: an outer epithelium and its underlying stroma (substantia propria). The conjunctiva contributes to the formation of the tear film by way of secreting substantial electrolytes, fluid, and mucins.

The cornea is a strong clear bulge located at the front of the eye. It has an important optical function as it refracts light entering the eye which then passes through the pupil and onto the lens (which then focuses the light onto the retina). Non vascular in nature, oxygen and nutrients are transported by aqueous humour and is richly supplied with free nerve endings. Withstand the intra-ocular tension constantly maintained in the eye.

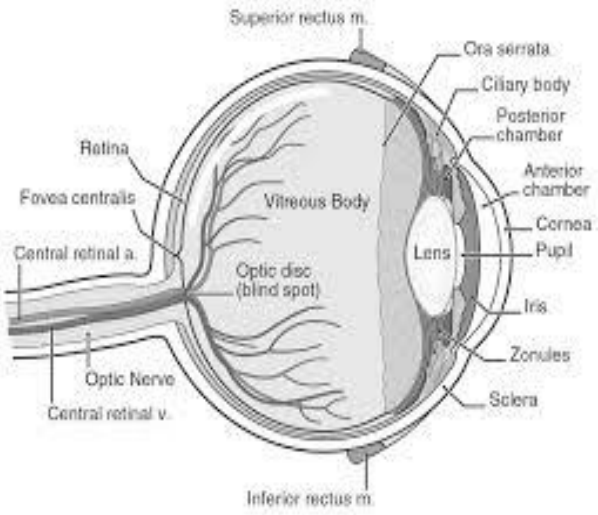
The lens is a transparent structure enclosed in a thin¬ transparent capsule. It is located behind the pupil of the eye and encircled by the ciliary muscles. It helps to refract light travelling through the eye (which first refracted by the cornea). The lens focuses light into an image on the retina. Oxygen and nutrients are transported by aqueous humour as is non vascular. The vitreous humour (also known as the vitreous body) is located in the large area that occupies approximately 80% of each eye in the human body.

The vitreous humour is a perfectly transparent thinjelly-like substance that fills the chamber behind the lens of the eye. Non vascular structure to which oxygen and nutrients are transported by aqueous humour.

The retina is located at the back of the human eye. The retinal "screen" is therefore a light-sensitive structure lining the interior of the eye. It contains photosensitive cells (called rods and cones) and their associated nerve fibers that convert the light they detect into nerve impulses that are then sent onto the brain along the optic nerve.

The choroid layer is located behind the retina and absorbs unused radiation and nourishes the outer portions of the retina. It is a thin, highly vascular (i.e. it contains blood vessels) membrane that is dark brown in colour and contains a pigment that absorbs excess light and so prevents blurred vision.

The optic nerve (a bundle of over 1 million nerve fibers) is responsible for transmitting nerve signals from the eye to the brain.



INSITU GELLING SYSTEMS

This novel drug delivery system promotes the importantly ease and convenience of administration, deliverance of accurate dose as well as to prolong residence time of drug in contact with mucosa, that problems generally encountered in semisolid dosage forms.

In situ-gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition, once administered.

From the early 1970's natural and synthetic polymers began to be investigated for controlled release formulations. The advantages of using biodegradable polymers in clinical applications are apparent. Various natural and synthetic polymers are used for formulation development of in situ forming drug delivery systems.

APPROCHES OF INSITU GELLING SYSTEM

There are three broadly defined mechanisms used for triggering the in situ gel formation of biomaterials:

- Physiological stimuli (e.g., temperature and pH)
- Physical changes in biomaterials (e.g., solvent exchange and swelling),
- Chemical reactions (e.g., enzymatic, chemical photo-initiated polymerization).

IMPORTANCE OF INSITU GELLING SYSTEM

- It helps for the controlled and sustained release of the drug by its special 'Sol Gel transition'.
- It helps for the reduced frequency of drugadministration of the drug in the body.
- Low dose of the drug is required and there will be no drug accumulation and no side effects.
- The bioavailability of the drug will be more.
- There will be increased residence time of the drug due to gel formation.
- The in situ gel system decreases wastage of the drug
- Liquid dosage form that can sustain drug release & remain in contact with cornea of eye for extended period of time is ideal.
- Reduced systemic absorption of drug drained through the naso lacrimal duct may result in some undesirable side effects.

TEMPERATURE TRIGGERED OPTHALMIC INSITU GEL

Temperature triggered in situ gel Temperature is the most widely used stimulus in environmentally responsive polymer systems in in-situ gelling formulation. The change of temperature used in easy to control, and also easily applicable both in vitro and in vivo. In this system, gelation is caused due to body temperature and no need of external heat. These hydrogels are liquid at room temperature (20–25°C) and undergo gelation when in contact with body fluids (35– 37°C), due to an increase in temperature. There are three types of temperature induced systems. They are **negatively thermo sensitive type** Eg:

Poly(Nisopropylacrylamide).

Positively thermo sensitive type .Eg: polyacrylic acid.

Thermally reversible type Eg: poloxamer, pluronics, Tetronics.

In this system, thermo responsive or temperature responsive polymers are used that show a drastic and discontinuous change in their physical properties with temperature. These polymers show a miscibility gap at high or low temperature an upper or lower critical solution temperature exists.

POLYMERS USED IN TEMPERATURE TRIGGERED OPTHALMIC GEL

Pluronic F-127

Poloxamers or pluronic (marketed by BASF Corporation) are the series of commercially available difunctional triblock copolymers of non-ionic nature. They comprise of a central block of relatively hydrophobic polypropylene oxide surrounded on both sides by the blocks of relatively hydrophilic poly ethylene oxide.

Due to the PEO/PPO ration of 2:1, when these molecules are immersed into the aqueous solvents, they form micellar structures above critical micellar concentration. They are regarded as PEOPPO-PEO copolymers. Chemically they are Oxirane, methyl-, polymer with oxirane or α-Hydro-ωhydroxypoly(oxyethylene)a poly(oxypropylene)b poly(oxyethylene)a block copolymer. The pluronic triblock copolymers are available in various grades differing in molecular weights and physical forms. Depending upon the physical designation for the grades are assigned, as F for flakes, P for paste, L for liquid. Pluronics or Poloxamers also undergo in situ gelation by temperature change.

They are triblock copolymers consisting of poly(oxyethylene) and poly(oxypropylene) units that undergo changes in solubility with change in environment temperature. Pluronic™ F127. A 25-40% aqueous solution of this material will gel at about body temperature, and drug release from such a gel occurs over a period of up to one week. Pluronic F-127 was used as an in situ gel forming polymer together with mucoadhesive polymers such as Carbopol 934 and hydroxy propyl methyl cellulose to ensure long residence time at the application site. Controlled release of drug was achieved in-vitro indicating antimycotic efficacy of developed formulation for a longer period of time.

HPMC

Cellulose is consists of glucan chain which has repeating β-(1, 4)-D-glucopyranose unit. Some natural polymers like HPMC, MC and EC these exhibit temperature sensitive sol-gel phase transition. Cellulose material will increases its viscosity when temperature is decreases while its derivatives like HPMC, MC, will also increase its viscosity when temperature is increased. MC is a natural polymer composed of native cellulose with alternate methyl substitution group on its chain. At low temperature (300 C) solution is in liquid form and when temperature is increases (40-500 C) and gelation36 occurred.

EVALUATION AND CHARACTERIZATIONS OF IN SITU GEL SYSTEM

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 cm) 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 byconcentration 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. 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

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 per International Conference on Harmonization (ICH) states Guidelines. Samples are analyzed every month for clarity, pH, gelling capacity, drug content, rheological evaluation, and in vitro dissolution.

APPLICATIONS OF INSITU GELS

Oral drug delivery system

The pH-sensitive hydro gels have a potential use in sitespecific delivery of drugs to specific regions of the GI tract. Hydro gels built of varying proportions of cross linked PEG and PAA derivatives allowed in preparing silicone microspheres, which produce prednisolone in the gastric medium or showed gastro protective property.

Cross-linked dextran hydro gels with a faster swelling under high pH conditions, whereas other polysaccharides such as amidaded pectin's, inulin and guar gum were investigated in order to improve a potential colon-specific drug delivery system.

The formulations of gellan and sodium alginate both contain a complexed calcium ion that undergoes a process of gelation by releasing of these ions in the acidic environment of the stomach. Ocular drug delivery system In ocular delivery system natural polymers like alginic acid, inulin, & xyloglucan, inulin are most commonly used. For local ophthalmic delivery system different compounds such as autonomic drugs, anti-inflammatory agent & antimicrobial agent, are used to release intra ocular tension in glaucoma. Conventional delivery system often result in poor availability & therapeutic response due to high tear fluid turn over & dynamics leads rapid elimination of the drug from the eye so, the overcome the bioavailability problem ophthalmic in-situ gel were developed. To improve the bioavailability viscosity enhancers such as Carboxy Methyl Cellulose, Hydroxy Propyl Methyl Cellulose, Carbomers, Poly Vinyl alcohol used to improve the viscosity of formulation in order to prolong the precorneal residence time & increases the bioavailability, easy to manufacture.

Penetration enhancer such as preservatives, chelating agent, surfactants are used to develop corneal drug penetration.

Nasal drug delivery system

In nasal in-situ gel system xanthan gum and gallan gum are used as in-situ gel forming polymers Momethasone furoate used to evaluate for its efficacy for the treatment of allergic rhinitis. Animal study is used to conduct allergic rhinitis model & effect of in-situ gel on antigen induced nasal symptoms in sensitizes rats was observed. In-situ gel was found to inhibit the increase in nasal symptoms are compared to marketed preparation nosonex (Momethasone furoate suspension 0.05%).

Rectal and vaginal drug delivery system

The rectal route may be used to deliver many types of drugs that are formulated as liquid, semisolid (ointments, creams and foams) and solid dosage forms (suppositories). Acetaminophen an anti inflammatory drug formulated as rectal in situ gel by using polycarbophil and poloxamer F188 and poloxamer 407 as synthetic polymer forming in situ gelling liquid suppository which is considered as an synthetic polymers forming in situ gelling liquid suppository which is considered as an effective method shows enhance bioavailability.

Injectable drug delivery system

In this drug delivery system are also formulated as in situ gels which obtained over the last decade due to its uses as there is no surgical procedure is required and also patient compliance. Mostly synthetic polymers and block copolymers are used in the formulation of Injectable in situ gel. One example of inflammatory drug is Bupivacaine which is formulated as a injectable in situ gel using poly(D,L-lactide), poly (D,L-lactide coglycolide) and PLGA as polymer shows prolong action drug in gel conditions. Dermal and transedermal drug delivery Pluronic F127 in thermally reversible gel was evaluated as vehicle for the percutaneous administration of Indomethacin. In-vivo studies suggest that 20% w/w aqueous gel may be it is used as practical base for topical administration of the drug. The combination of iontophoresis and chemical enhancers resulted in synergistic enhancement of insulin permeation.

CONCLUSION

The development of in situ stimuli activated gel-forming systems for ophthalmic drug delivery provides simplest and best gel-forming systems and have been proved advantageous over other conventional dosage forms. These advantages include sustained and prolonged release of drug (like hydrogel), good stability, biocompatibility, ease of instillation (like solution), etc. It is an ideal system that maintains effective level of drug for the longer duration following a single application and offers the primary requirement of a successful controlled release product. Use of biodegradable and water soluble polymers for the in situ gel formulations can make them more acceptable and excellent drug delivery systems with minimum chances of irritation, and hence improved patient compliance.

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