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Review Article

Recent Developments and Strategies of Ocular Insitu Drug Delivery System: A Review

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ABSTRACT

Ocular drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist for past 10-20 years. As an isolated organ, eye is very difficult to study from a drug delivery point of view. Despite these limitations, improvements have been made with the objective of maintaining the drug for an extended period. Recently, controlled and sustained drug delivery has become the standard in modern Pharmaceutical design and an intensive research have been undertaken in achieving much better drug product effectiveness, reliability and safety. The formation of ocular in-situ gels depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation, from which the drug gets released in a sustained and controlled manner. Various biodegradable polymers that are used for the formulation of in situ gels include gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly(DLlactic acid), poly(DL-lactide-co-glycolide) and poly-caprolactone. The in situ gel forming polymeric formulations offer several advantages like sustained and prolonged action in comparison to conventional drug delivery systems. From a manufacturing point of view, the production of such devices is less complex and thus lowers the investment and manufacturing cost.

Keywords: In-Situ, Hydrogels, biodegradable polymers, controlled release, Novel ocular drug delivery system.

INTRODUCTION

The eye is a sensory organ that converts light to an electric signal that is treated and interpreted by the brain. Briefly, the eye ball is covered by three layers: an outer fibrous protective layer (sclera and cornea), a middle vascular layer(choroid),and an inner nervous layer (retina). The cornea is a clear, transparent, thin avascular tissue that is composed of five layers: epithelium, bowmans's layer, stroma, Descemet's membrane and endothelium[1-5](fig.1). Eyes can get infections from bacteria, fungi or viruses. Eye infections can occur in different parts of the eye and can affect just one eye or both. Common eye infections are Conjunctivitis, Corneal ulcers & Endophthalmitis.

Conjunctivitis Conjunctivitis is swelling (inflammation) or infection of the membrane lining the eyelids (conjunctiva).It is characterized by cellular infiltration and exudation. Staphylococcus aureus is the most common cause of bacterial conjunctivitis and blepharo-conjunctivitis. Many other organisms like Haemophilus influenza, Streptococcus pneumoniae also cause conjunctivitis. Conjunctivitis can be classified as

- Infective – Acute, Sub acute & Chronic
- Allergic conjunctivitis.

Corneal ulcers / Keratitis Inflammation of cornea (Keratitis) is characterized by corneal edema, cellular infiltration & ciliary congestion. Being the most anterior part of eyeball, cornea is exposed to atmosphere & hence prone to get infected easily. Bacterial corneal ulcers are the most commonly caused by virulent organism. Common bacteria associated with corneal ulceration are Staphylococcus aureus, Pseudomonas pyocyanea, E.coli, Proteus etc.

Endophthalmitis is severe form of intraocular inflammation (purulent uveitis) involving ocular cavities & inner coats of eyeball. Causative organisms include Streptococci, E.coli, Pseudomonas, etc. Accordingly, the armamentarium of available antimicrobials used in the prevention and treatment of these infections includes antivirals, antifungals, and antibacterials. Among the most common ocular infections and in more than 80% of cases, the infections are caused by Staphylococcus aureus, Streptococcus pneumoniae, or Pseudomonas aeruginosa Standard initial treatment consists of frequent instillation of eye drops with a broad-spectrum antibiotic.

The bioavailability of conventional ophthalmic solutions is very poor due to efficient protective mechanisms of the eye, blinking, reflex lachrymation and drainage which remove rapidly various foreign substances including drug from the surface of the eye. Frequent instillation of drug solution is necessary to maintain a therapeutic drug level in the tear or at the site of action but the frequent use of highly concentrated solution may induce toxic side effects due to systemic absorption of drug through nasolachrymal drainage.

Various problems encountered in poor bioavailability of the eye installed drugs are

- Binding by the lachrymal proteins
- Drainage of the instilled solutions
- Lachrimation and tear turnover
- Limited corneal area and poor corneal
- Metabolism

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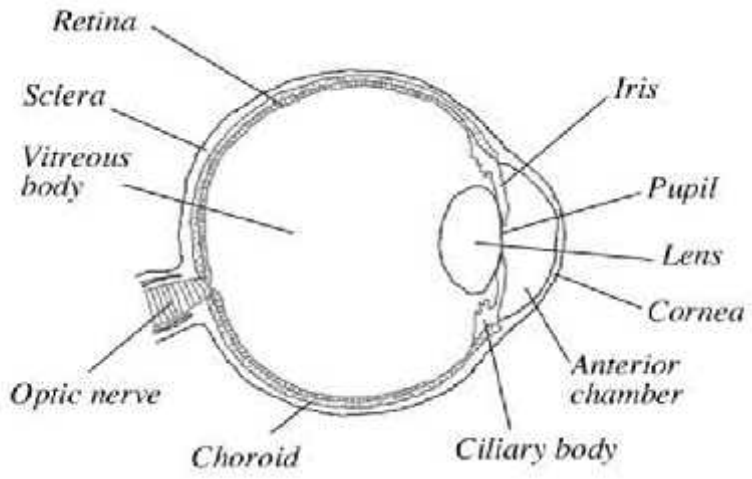

Fig:1 Anatomy Of Human Eye

• Non-productive absorption/adsorption
• Tear evaporation and permeability[7](fig.2)

To enhance the amount of the active substances reaching the target tissue or exerting a local effect in the cul de sac, Numerous strategies were developed to increase thec (fig.3) by prolonging the contact time between the drug and cornea/ conjunctival epithelium such as muco adhesive polymers, hydro gel insitu gelling system, colloidal system like nanoparticles, microspheres, vesicular system, dendrimers, solid dosage forms ocular inserts, iontophorosis and many recent developments[8].

The current review was reported on the insitu gels and depending upon the method employed to cause sol to gel phase transition on the ocular surface, the following types of systems are recognized

- pH-triggered systems: cellulose acetate phthalate(CAP) latex, carbopol, polymethacrilic acid(PMMA), polyethylene glycol (PEG), pseudolatexes.
- Temperature dependent systems: chitosan, pluronics, tetronics, xyloglucans, hydroxypropylmethyl cellulose or hypromellose (HPMC).
- Ion-activated systems (osmotically induced gelation): gelrite, gellan, hyaluronic acid, alginates.
- UV induced gelation
- Solvent exchange induced gelation[7].

In this regard many polymers are very useful. which undergo reversible sol to gel phase transition in response to physiological stimuli. In situ gels are conveniently dropped as a solution into the conjunctival sac, where they undergo a transition into a gel with its favorable residence time[9].

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[10].

This review attempts to discuss the newer developments and strategies for this drug delivery including physiological factors, physiochemical factors and formulation factors to be considered in the development of in-situ drug delivery system.

Approaches of In Situ Gel Drug Delivery: There are 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 and photo-initiated polymerization)[10]

In Situ Formation Based on Physiological Stimuli: Thermally trigged system: Temperature-sensitive hydrogels are probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research[11]. The use of biomaterial whose transitions from sol-gel is triggered by increase in temperature is an attractive way to approach in-situ formation. The ideal critical temperature range for such system is ambient and physiologic temperature, such that clinical manipulation is fascinated and no external source of heat other than that of body is required for trigger gelation. A useful system should be tailorable to account for small differences in local temperature, such as might be encountered in appendages at the surface of skin or in the oral cavity. Three main strategies are exists in engineering of thermoresponsive sol-gel polymeric system. For convenience, temperature-sensitive hydrogels are classified into negatively thermosensitive, positively thermosensitive, and thermally reversible gels.

pH triggered systems: Another formation of in situ gel based on physiologic stimuli is formation of gel is induced by pH change[11]. All the pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH .The polymers with a large number of ionizable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups[12]. The most of anionic pH-sensitive polymers are based on PAA (Carbopol®, carbomer) or its derivatives[13]. Likewise polyvinylacetal diethylaminoacetate (AEA) solutions with a low viscosity at pH 4 form hydrogel at neutral pH condition[14].

In Situ Formation Based on Physical Mechanism

Swelling: In situ formation may also occur when material absorbs water from surrounding environment and expand to occur desired space[15]. One such substance is myverol 18-99 (glycerol mono-oleate), which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures.It has some Bioadhesive properties and can be degraded invivo by enzymatic action[16].

Diffusion: This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-methyl pyrrolidone (NMP) has been shown to be useful solvent for such system[17].

In Situ Formation Based on Chemical Reactions: Chemical reactions that results in situ gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes.

Ionic Crosslinking: Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion-sensitive ones[18]. While k-carrageenan forms rigid, brittle gels in reply of small amount of K+, i-carrageenan forms elastic gels mainly in the presence of Ca2+. Gellan gum commercially available as Gelrite is an anionic polysaccharide that undergoes in situ gelling in the presence of mono- and divalent cations, including Ca2+, Mg2+, K+ and Na+.

Enzymatic Cross-Linking: In situ formation catalysed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators.

Drugs Used Under Ocular Preparations: Common topical antibacterials used in the treatment of ocular infectious diseases include sulfonamides, aminoglycosides, polymyxin-based combinations, Fluoroquinolones. The fluoroquinolones represent an expanding class of broad-spectrum antibacterials which cover a host of Gram-negative and anaerobic species responsible for ocular infections. These antibacterials have gained popularity in the ophthalmology field since they have been shown to be equivalent to combination therapy in the treatment of many ocular infections. Fluoroquinolones are also effective against a variety of Gram-positive organisms, including Streptococcal and Staphylococcal species; however, resistance is emerging among some of these organisms. [19-21]The classification (Table.2) and mechanism of action of fluoroquinolones are given below.

Classifications of ocular polymeric systems:

Pectin: Pectins are a family of polysaccharides, in which the polymer backbone mainly comprises α-(1-4)-Dgalacturonic 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 described by egg-box model . Although the gelation of pectin will occur in the presence of H + ions, a source of divalent ions, generally calcium ions is required to produce the gels that are suitable as vehicles for drug delivery[22].

Xyloglucan: Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1-4)-β-D-glucan backbone chain, which has (1-6)-α-D xylose branches that are partially substituted by (1-2)-β-D-galactoxylose[23]. When xyloglucan is partially degraded by β- galactosidase, the resultant product exhibits thermally reversible gelation by the lateral stacking of the rod like chains . The sol-gel transition temperature varies with the degree of galactose elimination. It forms thermally reversible gels on warming to body temperature.

Gellangum: Gellan gum (commercially available as Gelrite TM or Kelcogel TM) is an anionic deacetylated exocellular polysaccharide secreted by Pseudomonas

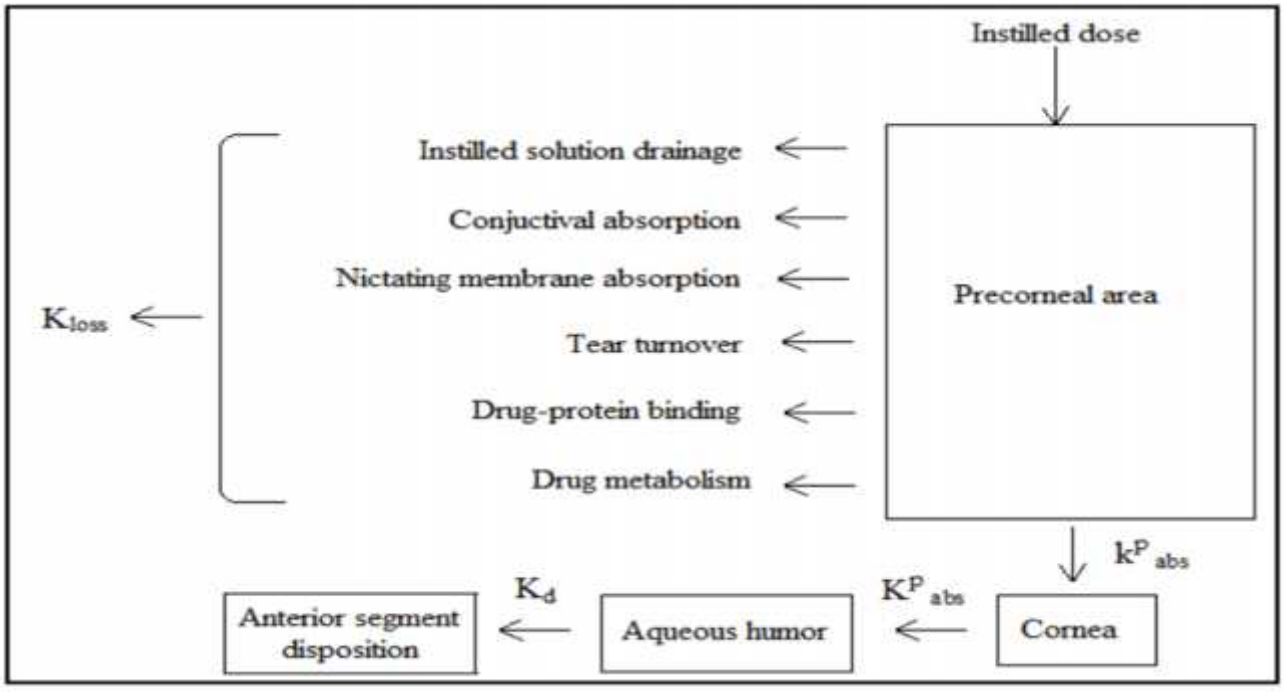

Fig.2 Various problems encountered in poor bioavailability of the eye installed drugs

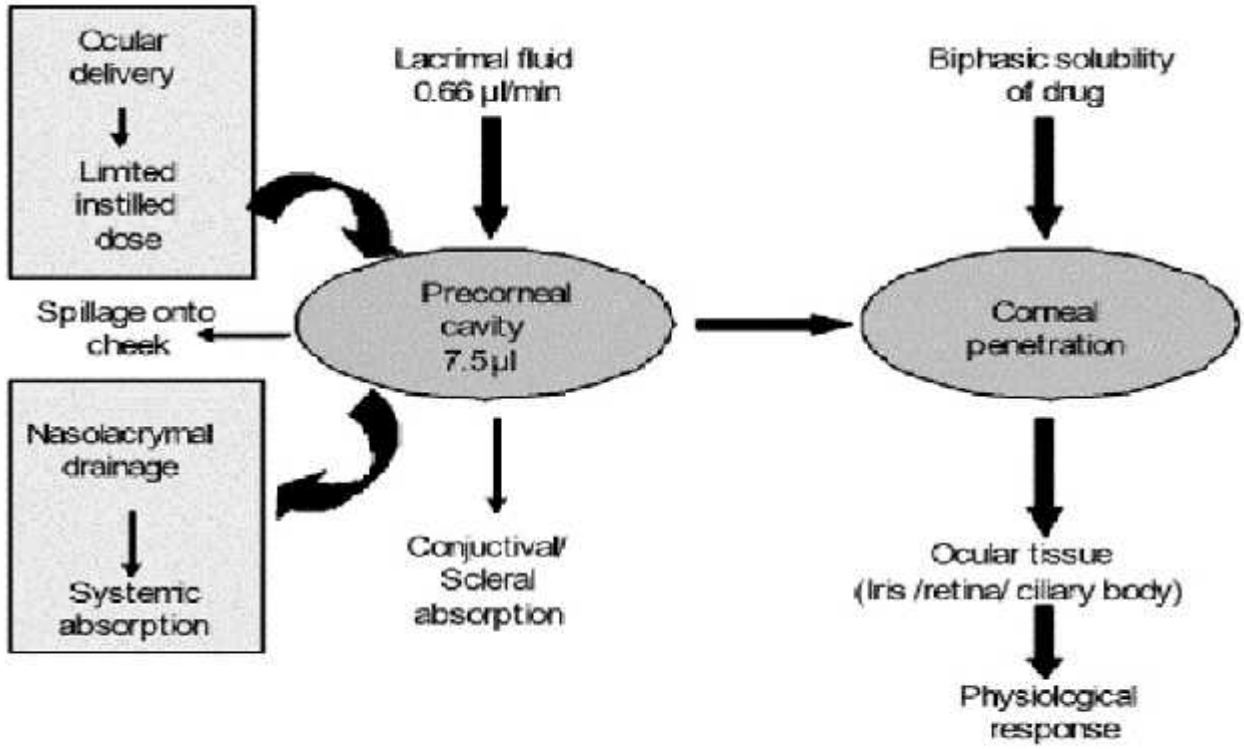

Fig:3 Bioavailability and absorption in ocular drug delivery

Stimuli sensitivity of hydrogels

External stimuli	Mechanism	Examples
Temperature	Formulation is liquid at room temperature (20° – 25° c) which undergoes gelation with contact to body fluids (35° – 37°c) temperature increases the degradation of polymer chain which leads to formation of hydrophobic domains and transition of an aqueous liquid to hydrogel network	Poloxamer/pluronics Co-polymers of polyethylene oxide peo Co-polymers of polypropylene oxide ppo Polyester Xyloglucan Cellulose derivatives
Ionic interactions	Formulation undergoes liquid-gel transition under influence of an increase in ionic strength Gel formation takes place because of complexation with polyvalent cations (like ca+2) in lacrimal fluid	Chitosan Gallen gum Alginates
Ph-change	Sol to gel transition when ph raised from 4.2 – 7.4 (eye ph) At higher ph polymer forms hydrogen bonds with mucin which leads to formation of hydrogel networks	Pseudolatexes Acrylates (carbopols) Cellulose acetate phthalate (cap) Polyox

elodea with a tetrasaccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues [24]. It has the tendency of gelation which is temperature dependent or cations induced.

Alginic acid: Alginic acid is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic linkages . The proportion of each block and the arrangement of blocks along the molecule vary depending on the algal source. Dilute aqueous solutions of alginates form firm gels on addition of diand trivalent metal ions by a cooperative process involving consecutive glucuronic residues in the α-Lglucuronic acid blocks of the alginate chain [25].

Xanthum gum: Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium Xanthomonas campestris. The primary structure of this naturally produced cellulose

Commonly used fluoroquinolones in ophthalmic delivery

Antibiotic generation	Example	Activity
1 st generation	Nalidixic acid	Have limited activity against gram negative & gram positive organism.
2 nd generation	Oxolinic acid Cinoxacin	Improvement in gram negative coverage including antipseudomonal activity.
	Pipemic acid	Shows limited activity against gram positive organism.
3 rd generation	Norfloxacin Ciprofloxacin Levofloxacin Ofloxacin	Having antipseudomonal activity against gram negative bacilli.
4 th generation	Moxifloxacin	Having dual mechanism of action in gram positive bacteria in addition reducing efflux from the bacterial cell and improved spectrum of activity.

Examples of marketed ocular formulations

S.no	Drug used in the formulation	Example of drug with generic name	Company
1	Lanatoprost	Lumigan	Allergan
2	Travoprost	Travatan	Alcon
3	Prostaglandins	Xalatan	Pfizer
4	Timolol	Timoptic xe	Merck
5	Epinephrine	Propine	Allergan

derivative contains a cellulosic backbone (β-D-glucose residues) and a trisaccharide side chain of β-D-mannose-β-D-glucuronicacid-α-D-mannose attached with alternate glucose residues of the main chain. The anionic character of this polymer is due to the presence of both glucuronicacid and pyruvic acid groups in the side chain[26].

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 remains dissolved in aqueous solutions up to a pH of 6.2[27]. Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to the formation of a hydrated gel like precipitate. The pH gelling cationic polysaccharides solution are transformed into thermally 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 salts to chitosan aqueous solution[28].

Carbopol: Carbopol is a well known pH dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH. HPMC is used in combination with carbopol to impart the viscosity to carbopol solution, while reducing the acidity of the solution. Various water soluble polymers such as carbopol system- hydroxy propyl methyl cellulose system, poly (methacrylic acid)-poly (ethylene glycol) come under the category of pH-induced in-situ precipitating polymeric systems[29].

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[30]. 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[31]. Pluronic F-127 was used as an in situ gel forming polymer together with mucoadhesive polymers such as Carbopol 934 and hydroxylpropylmethylcellulose 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[32].

Synthetic polymers: Synthetic polymers are popular choice mainly for parenteral preparations. The trend in drug delivery technology has been towards biodegradable polymers, requiring no follow up surgical removal, once the drug supply is depleted. Aliphatic polyesters such as poly (lactic acid), poly (glycolic acid), poly (lactide-coglycolide), poly (decalactone), poly ε-caprolactone have been the subject of the most extensive recent investigations. Synthetic polymers are popular choice mainly for parenteral preparations. The trend in drug delivery technology has been towards biodegradable polymers, requiring no follow up surgical removal, once the drug supply is depleted. Aliphatic polyesters such as poly (lactic acid), poly (glycolic acid), poly (lactide-coglycolide), poly (decalactone), poly ε-caprolactone have been the subject of the most extensive recent investigations[27].

A.In situ hydrogels: Hydrogels are polymeric networks that absorb large quantities of water while remaining insoluble in aqueous solutions due to chemical or physical crosslinking of individual polymer chains. They resemble natural living tissue more than any other class of synthetic biomaterials due to their high water content; furthermore,

the high water content of the materials contributes to their biocompatibility[10].

B. Smart hydrogels: Smart hydrogels, or stimuli-sensitive hydrogels, are very different from inert hydrogels in that they can sense changes in environmental properties such as pH and temperature and respond by increasing or decreasing their degree of swelling. The volume-changing behavior of smart hydrogels is particularly useful in drug delivery applications as drug release can be triggered upon environmental changes.

Evaluations of ocular drug delivery system

The prepared ocular formulations were evaluated for clarity, pH measurement, gelling capacity, drug content, rheological study, in vitro diffusion study, isotonicity, antibacterial activity, in vivo ocular testing in rabbits and accelerated stability studies. The pH of insitu gel solution was found to be 7.4 for all the formulations. The formulation should have an optimum viscosity that will allow for easy instillation into the eye as a liquid (drops), which would undergo a rapid sol-to-gel transition (triggered by pH, temperature or ion exchange). Marketed products of ocular insitu formulations are also included(table.3).

Physical Parameters: The formulated insitu gel solution is tested for clarity, pH, gelling capacity, and drug content estimation.

Appearance and Determination of Ph: The appearance of the formulation was observed which included clarity, color of solution visually and pH was measured using pH meter.

Drug Content: The drug content was determined by taking 1ml of the formulation and diluting it to 100 ml with distilled water. Aliquot of 5 ml was withdrawn and further diluted to 25 ml with distilled water. Drug concentration was determined at by using UV is spectrophotometer form the standard graph of r2=0.99.

Spreadability: For the determination of Spreadability, excess of sample was applied in between two glass slides and was compressed to uniform thickness by placing 1000g weight for 5 min. weight (50 g) was added to the pan. The time in which the upper glass slide moves over to the lower plate was taken as measure of Spreadability.

S= ML/T

Where, M = weight tide to upper slide, L = length moved on the glass slide, T = time taken.

Sterility test: All ophthalmic preparations should be sterile, therefore the test for sterility is very important evaluation parameter. 2 ml of the formulation from test container was removed with a sterile pipette or with a sterile syringe or a needle. The test formulation was aseptically transferred to fluid thioglycolate medium (20 ml) and soya bean-casein digest medium (20 ml) separately. 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 soya bean-casein digest medium.

Measurement of Gel Strength: A sample of 50 gm of gel was placed in a 100 ml graduated cylinder and gelled in a thermostat at 370c. The apparatus for measuring gel strength was allowed to penetrate in ocular gel. The gels strength, which means the viscosity of the gels at physiological temperature, was determined by the time (seconds), the apparatus took to sink 5cm down through the prepared gel[33].

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[34,35].

Rheological studies: The viscosity measurements can be calculated using Brookfield viscometer, Cone and Plate viscometer. The insitu gel formulations were placed in the sampler tube. From the literature it was evident that, the formulation before gelling should have a viscosity of 5 to 1000 mPas. And after ion gel activation by the eye, will have a viscosity of from about 50- 50,000 mPas10, 13. The samples are analyzed both at room temperature at 25°C and thermostated at 37°C ± 0.5°C by a circulating bath connected to the viscometer adaptor prior to each measurement. The angular velocity of the spindle was increased 20, 30, 50, 60, 100, 200 and the viscosity of the formulation is measured. All the formulations exhibited Newtonian and pseudoplastic flow characteristics before and after gelling in the simulated tear fluid respectively[36,37].

In vitro drug release studies: In vitro release study of insitu gel solution was carried out by using Franz diffusion cell. The formulation placed in donor compartment and freshly prepared simulated tear fluid in receptor compartment. Between donor and receptor compartment dialysis membrane is placed (0.22µm pore size). The whole assembly was placed on the thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37°C ± 0.5°C. 1ml of sample is withdrawn at predetermined time interval of 1hr for 6 hrs and same volume of fresh medium is replaced. The withdrawn samples are diluted to 10ml in a volumetric flask with respective solvent and analyzed by UV spectrophotometer at respective nm using reagent blank. The drug content calculated using the equation generated from standard calibration curve. The % cumulative drug release (%CDR) calculated. The data obtained is further subjected to curve fitting for drug release data. The best fit model is checked for Krosmeyers Peppas and Fickinian diffusion mechanism for their kinetics[34].

Texture analysis: The consistency, firmness and cohesiveness of insitu gel are 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[38].

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[39].

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): Differential Scanning calorimetry is conducted to observe if there are any changes in thermograms as compared with pure active ingredients used for gelation[38].

Antibacterial activity: 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 antibiotic. To carryout microbiological assay serial dilution method is employed[40].

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[41,42].

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[39]. Statistical analysis The results obtained from the experiments of mucoadhesive strength and release studies were analysed statistically using multivariate tests. A statistically significant difference was conducted by using various SPSS software and difference was considered to be significant at $P<0.05$.

CONCLUSION

In conclusion, the primary requirement of a successful controlled release product focuses on increasing patient compliance which the in situ gels offer. Exploitation of polymeric in- situ gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the in situ gel dosage forms very reliable. Use of biodegradable and water soluble polymers for the in situ gel formulations can make them more acceptable and excellent drug delivery systems.

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