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REVIEW ARTICLE

In-Situ Gel Formation for Ocular Drug Delivery System an Overview

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ABSTRACT

Ophthalmic *In-situ* gels are viscous polymer-based liquids that exhibit sol-to-gel phase transition on the ocular surface due to change in a specific physicochemical parameter like ionic strength, pH or temperature Gel dosage forms are successfully used as drug delivery systems considering their ability to prolong the drug release. To prolong the precorneal resident time and improve ocular bioavailability of the drug various polymers system were studied as *in situ* gelling vehicle for ophthalmic drug delivery system. The *In situ* formulation exhibited well, viscosity, drug content and sustained drug release. Conventional liquid ophthalmic formulations demonstrate low bioavailability because of a constant lacrimal drainage in the eye. The normal drainage of an instilled drug dose commences immediately upon instillation and is essentially completed within 5 min. typically ophthalmic bioavailability of only 1–10% is achieved due to the short precorneal residence time of ophthalmic solutions. Each system has its own advantages and drawbacks. The choice of a particular hydrogeldepends on its intrinsic properties and envisaged therapeutic use. This review includes various temperature, pH, and ion induced in situ-forming polymeric systems used to achieve prolonged contact time of drugs with the cornea and increase their bioavailability. Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. The conventional ocular drug delivery systems like solutions, suspensions, and ointments show drawbacks such as increased precorneal elimination, high variability in efficiency, and blurred vision respectively.

KEY WORDS: In-*situ* gels, pH, eye, viscosity, precorneal elimination

INTRODUCTION

CONVENTIONAL DOSAGE FORM:

1. VISCOUS SOLUTIONS: [10]

In order to prolong precorneal residence time and to improve bioavailability, attempts were made to increase the viscosity of the formulation. The viscosity enhancers used were hydrophilic polymers such as cellulose, polyalcohol and polyacrylic acid. Sodium carboxy methyl cellulose is one of the most important mucoadhesion polymers having good adhesive strength8. The effects of polyacrylic acid and polyacrylamide based hydrogels are tested on miotic response of pilocarpine. Carbomer were used in liquid and semisolid formulations as suspending or viscosity increasing agents. Formulations including creams, gels and ointments were used as ophthalmic products9. Polycarbophil is water insoluble cross linked polyacrylic acid helps in the retention of the drug delivery system in the eye due to the formation of hydrogel bonds and mucoadhesive strength. Hyaluronic acid offers a biocompatible and biodegradable matrix for fabrication of ocular sustained release dosage forms. Films and microspheres were also prepared from hyaluronic acid. Polysaccharide such as xanthan gum was found to increase the viscosity10. Today, hydrophilic polymers continue to be used in formulation of numerous ophthalmic products for bioadhesion rather than viscosity enhancement. Viscosity vehicles increases the contact time and no marked sustaining effect is seen.

2. GELS: [10]

Gel formation is an extreme case of viscosity enhancement through the use of viscosity enhancers. So the dosing frequency can be decreased to once a day11. Cellulose acetate phthalate dispersion constituted a micro-reservoir system of high viscosity. Poloxamer 407 is used as an ophthalmic vehicle for pilocarpine delivery and found that the gel formation enhances the activity of pilocarpine. Timolol maleate form thermo gelling drug delivery system composed of cellulose ether ethylhydroxylethylcellulose13. The effect of flurbiprofen, a non steroidal anti inflammatory drug, formulated in carbopol 940 and pluronic F 127 hydrogels were compared in ocular hypertension. Gelrite is a polysaccharide (gellen gum), which forms a clear gel in the presence of mono or divalent cation. The high viscosity of the gel, however, results in blurring of vision and malted eyelids which substantially reduce patient acceptability. Sterilization is another drawback for large-scale production.

3. EYE DROPS: [12]

Eye drops are saline-containing drops used as a

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route to administer medication in the eye. Depending on the condition being treated, they may contain steroids, antihistamines, sympathomimetics, beta receptor blckers, parasympathomimetics, parasympatholytics, prostaglandins, non-steroidal anti-inflammatory drugs (NSAIDs) or topical anesthetics. Eye drops sometimes do not have medications in them and are only lubricating and tear-replacing solutions. Eye drops have less of a risk of side effects than do oral medicines, and such risk can be minimized by occluding the lacrimal punctum, (i.e. pressing on the inner corner of the eye) for a short while after instilling drops.

Figure-1: use of eye drop

4. OINTMENT: [11]

An ointment is a homogeneous, viscous, semi-solid preparation, most commonly a greasy, thick oil (oil 80% - water 20%) with a high viscosity, that is intended for external application to the skin or mucous membranes. They are used as emollients or for the application of active ingredients to the skin for protective, therapeutic, or prophylactic purposes and where a degree of occlusion is desired.Ointments are used topically on a variety of body surfaces. These include the skin and the mucous membranes of the eye (an *eye ointment*), vagina, anus, and nose. An ointment may or may not be medicated. Ointments are usually very moisturizing, and good for dry skin. They have a low risk of sensitization due to having few ingredients beyond the base oil or fat, and low irritation risk. There is typically little variability between brands of generics and namebrand drugs. They are often disliked by patients due to greasiness.

Figure-2: use of ointment

LIMITATION OF CONVENTIONAL DOSAGE FORM:

1. The conventional liquid ophthalmic formulation is eliminated from the precorneal area immediately upon instillation because of lacrimal secretion and nasolacrimal drainage [2].

2. only a small fraction of the drug being ocularly absorbed. only 10% drug Concentrations available at the site of actions[3].

3. *In vivo* resident experiments showed the drug resident time and the total resident amount in rabbit's conjunctivae sac were 2. L6 to 5.0 folds less in conventional than *in situ* gel [2].

4. Some conventional ophthalmic preparation such as gels, ointment, and viscous preparation were reported to blurred vision.

5. These preparations have no bioadhesive property.

IN SITU FORMING GELS: [10]

The progress has been made in gel technology for the development of droppable gel. They are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form visco-elastic gel and this provides a response to environmental changes19. Three methods have been employed to cause phase transition in the eye surface. These are change in pH, change in temperature and ion activation.

pH:

In this method, gelling of the solution is triggered by a change in the pH. CAP latex cross linked polyacrylic acid and its derivatives such as carbomers are used. They are low viscosity polymeric dispersion in water which undergoes spontaneous coagulation and gelation after instillation in the conjunctival cul-de-sac.

TEMPERATURE:

In this method gelling of the solution is triggered by change in the temperature.Sustained drug delivery can be achieved by the use of a polymer that changes from solution to gel at the temperature of the eye. But disadvantage of this is characterized by very high polymer concentration 21. Methyl cellulose and smart hydrogels are the examples.

IONIC STRENGTH:

In this method, gelling of the solution instilled is triggered by change in the ionic strength. For example, Gelrite is a polysaccharide, low acetyl gellan gum, which forms a clear gel in the presence of mono or divalent cations. The concentration of sodium in human tears is 2.6

g/l is particularly suitable to cause gelation of the material when topically installed into the conjunctival sac.

ADVANTAGES OF *IN-SITU* OCULAR DRUG DELIVERY SYSTEMS: [10]

1. Increased accurate dosing. To overcome the side effects of pulsed dosing produced by conventional systems.
2. To provide sustained and controlled drug delivery.
3. To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.
4. To provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.
5. To circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.
6. To provide comfort, better compliance to the patient and to improve therapeutic performance of drug.
7. To provide better housing of delivery system.

APPROACHES OF *IN SITU* GEL DRUG DELIVERY:

There are four 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).

***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. 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 faccilated 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 (1, 3). Negative temperature-sensitive hydrogels have alower critical solution temperature (LCST) and contract upon heating above the LCST. Polymers with low critical temperature (LCST) transition between ambient and physiologic temperature is used for this purpose. One of the most extensively investigated polymers that exhibit useful LCST transition is poly(Nisopropylacrylamide) (PNIPAAm). PNIPAAm is a water soluble polymer at its low LCST, but hydrophobic above LCST, which result on precipitation of PNIPAAm from the solution at the LCST. Pluronics are poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) (PEO-PPOPEO) triblock co-polymer that are fluid at low temperature, but forms thermo responsible gel when heated as a consequences of a disorder-order transition in micelle packing which makes these polymers suitable for *in situ* gelation. A positive temperaturesensitive hydrogel has an upper critical solution temperature (UCST), such hydrogel contracts upon cooling below the UCST. Polymer networks of poly(acrylic acid) (PAA) and polyacrylamide (PAAm) or poly(acrylamide-co-butyl methacrylate) have positive temperature dependence of swelling. The most commonly used thermoreversible gels are these prepared from poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide) (Pluronics®, Tetronics®, poloxamer). Polymer solution is a freeflowing liquid at ambient temperature and gels at body temperature. Cappello et al.developed novel “protein polymers” ProLastins, which undergo an irreversible sol gel transition. When injected as a solution into the body, the material forms a firm, stable gel within minutes. It remains at the site of injection providing absorption times from less than one week to many months. Such a system would be easy to administer into desired body cavity.

pH TRIGGERED SYSTEMS:

Another formation of *in situ* gel based on physiologic stimuli is formation of gel is induced by pH changes. 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. The most of anionic pH-sensitive polymers are based on PAA (Carbopol®, carbomer) or its derivatives. Likewise polyvinylacetal diethylaminoacetate (AEA) solutions with a low viscosity at pH 4 form hydrogel at neutral pH condition. Drug formulated in liquid solutions have several limitations , including limited bioavailability and propensity to be easily removed by tear fluid.Kumar and Himmelstein sought to minimize this factors and maximize this drug delivery by making a poly (acrylic acid) (PAA) solution that would be gel at pH 7.4.The author found that at concentrations high enough to cause

gelation, however, the low pH of PAA solution would cause damage to surface of eye before being neutralized by the lacrimal fluid. This problem was solved by partially by combining PAA with HPMC, a viscous enhancing polymer, which resulted in pH responsive polymer mixtures that was sol at pH 4 and gel at pH 7.4. Mixtures of poly(methacrylic acid) (PMA) and poly (ethylene glycol) (PEG) also has been used as a pH sensitive system to achieve gelation.

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. One such substance is myverol 18-99 (glycerol mono-oleate), which is polar **Nirmal H.B. et al** /Int.J. PharmTech Res.2010,2(2) **1400** 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.

DIFFUSION:

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. Nmethyl pyrrolidone (NMP) has been shown to be useful solvent for such system.

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.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+. Gelation of the low-methoxy pectins can be caused by divalent cations, especially Ca2+. Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations e. g. Ca2+ due to the interaction with guluronic acid block in alginate chains.

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. Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion. Adjusting the amount of enzyme also provides a convenient mechanism for controlling the rate of gel formation, which allows the mixtures to be be injected before gel formation.

PHOTO-POLYMERISATION:

Photo-polymerisation is commonly used for *in situ* formation of biomaterials. A solution of monomers or reactive macromer and initiator can be injected into a tissues site and the application of electromagnetic radiation used to form gel.Acrylate or similar polymerizable functional groups are typically used as the polymerizable groups on the individual monomeers amd macromers because they rapidly undergo photo polymerisation in the presence of suitable photoinitiator. Typically long wavelength ultraviolet and visible wavelengths are used.Short wavelength ultraviolet is not used often because it has limited penetration of tissue and biologically harmful. A ketone, such as 2,2 dimethoxy-2-phenyl acetophenone, is often used as the initiator for ultraviolet photo- polymerization,where as camphorquinone and ethyl eosin initiators are often used in visible light systems. These systems can be designed readily to be degraded by chemical or enzymatic processes or can be designed for long term persistence in vivo. Photopolymerizable systems when introduced to the desired site via injection get photocured *in situ* with the help of fiber optic cables and then release the drug for prolonged period of time. The photo-reactions provide rapid polymerization rates at physiological temperature. Furthermore, the systems are easily placed in complex shaped volumes leading to an implant formation. A photopolymerizable, biodegradable hydrogel as a tissue contacting material and controlled release carrier is reported by Sawhney et al.

IN SITU FORMING POLYMERIC SYSTEMS FOR OCULAR DELIVERY: [13]

For in situ gels based ocular delivery, natural polymers such as gellan gum, alginic acid and xyloglucan are most commonly used polymers. Local ophthalmic drug delivery has been used for various compounds such as antimicrobial agents, antiinflammatory agents and autonomic drugs used to relieve intraocular tension in

glaucoma. Conventional delivery systems often result in poor bioavailability and therapeutic response because high tear fluids turn over and dynamics cause rapid elimination of the drug from the eyes. So, to overcome bioavailability problems, ophthalmic in situ gels were developed. Aqueous solution of gellan dropped into the eye undergoes transition into the gel state due to the temperature and ionic condition (Ca++) in the tear fluid. Much of the interest in the pharmaceutical application of gellan gum has concentrated on its application for ophthalmic drug delivery. Drug release from these in situ gels is prolonged due to longer precorneal contact times of the viscous gels compared with conventional eye drops. 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 di- and trivalent metal ions by a cooperative process involving consecutive glucuronic residues in the α-L-glucuronic acid blocks of the alginate chain. Alginic acid can be chosen as a vehicle for ophthalmic formulations, since it exhibits favorable biological properties such as biodegradability and nontoxicity. A prolonged precorneal residence of formulations containing alginic acid was looked for, not only based on its ability to gel in the eye, but also because of its mucoadhesive properties. Miyazaki et al. attempted to formulate in situ gels for ocular delivery using xyloglucan (1.5% w/w) as the natural polymer.These in situ forming polymeric systems were observed to show a significant mitotic response for a period of 4h when instilled into lower cul-de-sac of rabbit eye. Various water soluble polymers such as carbopol system-hydroxypropylmethylcellulose system, poly (methacrylic acid)-poly (ethylene glycol) come under the category of pH-induced in situ precipitating polymeric systems. 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. Based on this concept, the formulation and evaluation of an ophthalmic delivery system for indomethacin for the treatment of uveitis was carried out. A sustained release of indomethacin was observed for a period of 8 h in vitro thus considering this system as an excellent candidate for ocular delivery.

EVALUATION AND CHARACTERIZATION OF IN-*SITU* GELS SYSTEMS:

In situ gels may be evaluated and characterized for the following parameters.

VISCOSITY AND RHEOLOGY:

This is an important parameter for the in situ gels, to be evaluated. Viscosity and rheological properties of in situ forming drug delivery systems may be assesses using 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.

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.

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.

FOURIER TRANSFORMS 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. Thermo-gravimetric 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.

TEXTURE ANALYSIS:

The firmness, consistency and cohesiveness of hydrogels 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.

***In vivo* Studies:** [9]

Male rabbits weighing between 2.5-3.0 kg were used in the study. The studies were carried out with the guidelines of Council for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India. Left eye of each rabbit was used for test while the right eye was served as control. The formulations (50 µl) were instilled into the conjunctival sac of the test eye of the rabbits of different groups. After dosing, the lids were held together for few seconds in order to avoid loss of the dosage form.

Drugs that may be used in *In situ* technology for ocular delivery [19] S

1. Naphazoline HCL TI-ALLERGIC
2. Ofloxacin
3. Chloramphenicol
4. Gentamycin NTIBIOTICS
5. Dexamethasone
6. Prednisolone
7. Tobramycin WITH STEROID
8. Brimonidine Tartrate
9. Pilocarpine
10. Pilocarpine Nitrate ophthalmic solution 2% w/v 5ml
11. Timolol GENTS FOR GLAUCOMA
12. Ketorolac tromethamineANTI-INFLAMMATORY - NSAID
13. Clotrimazole
14. Econazole
15. Lignocaine HCL
16. Proparacaine HCl CAL ANESTHETICS
17. Atropine sulfate
18. Cyclopentolate
19. Phenylephrine Hcl
20. Tropicamidel.No. GENERIC NAME (with strength) TRADE
21. Prednisolone
22. Triamcinolone Acetonide

CONCLUSION

The development of ophthalmic drug delivery systems is easy because we can easily target the eye to treat ocular diseases and complicated at the same time because the eye has specific characteristics, which make the development of ocular drug delivery systems extremely difficult. The most widely developed drug delivery system is represented by the polymeric hydrogels. Hydrogels generally offer a moderate improvement of ocular drug bioavailability despite their favorable bioadhesive properties. One of the disadvantages is that hydrogel may result in blurred vision as well as foreign body sensation to patients. In situ activated gel-forming systems seem to be preferred as they can be administered in drop form and create significantly less problems with vision. Moreover, they provide good sustained release properties. Over the last decades, an impressive number of novel temperature, pH, and ion induced in-situ forming solutions have been described in the literature. Each system has its own advantages and drawbacks. The choice of a particular hydrogeldepends on its intrinsic properties and envisaged therapeutic use.

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