A Review on Triggered Gel for Ocular Drug Delivery

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ABSTRACT
The conventional ocular drug delivery system like eye drops, ointments, suspensions etc, encounters the drawback like increased pre-corneal elimination, less bioavailability, blurred vision and needs more number of applications for instillation of drug, etc. To overcome these problems a novel drug delivery system has been discovered i.e. In-Situ Gelling system, which is liquid but when instilled into the eye it undergoes phase transition from sol to gel. The triggering factors that favour the phase transition are change in to pH, temperature modulation, presence of ions. The formulation will be evaluated for pH of gel, Gelling capacity, Drug content, Rheological studies, In-vitro drug release and texture analysis. This formulation will be proved beneficial as it increase the bioavailability of the drug, increase the contact time, reduces number of application.

Key words: In-Situ Gelling system, Triggered gel.

INTRODUCTION
Eye is vital as well as delicate organ of the body and delivering drug into eye is most complicated task as it offers the numerous protective mechanisms that are present in the eye to shield it from various foreign particles. Secondly, delivering drug into ocular cavity results in poor bioavailability and therapeutic response because of high tear fluid turnover and rapid pre-corneal elimination of the drug. An alternative and novel approach has been designed to overcome the problems of conventional dosage form. This novel approach is called as gelling system. Gelling system, which is liquid but when instilled into the eye it undergoes phase transition from sol to gel. This consists of polymer that exhibit sol-to-gel phase transitions and the triggering factors that favours formation of gel are temperature modulation, pH change, presence of ions and ultraviolet irradiation from which the drug gets released in a sustained and controlled manner. Gel forming drug delivery is a type of mucoadhesive drug delivery system. gels are administered by oral, ocular, rectal, vaginal, injectable and intra-peritoneal routes. Both natural and synthetic polymers can be used for the production of gels. There are various polymers that are used for the formulation of gels include gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly(DL-lactic acid), poly(DL-lactide-co-glycolide) Carbopol, Cellulose acetophalate latex and poly-caprolactone. The solvents like water, dimethylsulphoxide, N-methyl pyrrolidone, triacetin and 2-pyrrolidone are choosed for these formulations depends on the solubility of polymer used.

Advantages of gels [8-13]
1. Prolonged drug release
2. More bioavailability
3. Prolong contact time
4. Less blurred vision as compared to ointment
5. Reduced number of application
6. Better patient compliance

Approaches for gelling system
The various approaches for gelling system are:-
1. pH triggered gels
2. Temperature modulated gels
3. Ion activated gels

1. pH triggered gels:-
In this system, gelling of the solution is triggered by a change in pH. At pH 4.4 the formulation is a free-running solution which undergoes coagulation when the pH is raised by the tear fluid to pH 7.4. The pH change of about 2.8 units after instillation of the formulation (pH4.4) into the tear film leads to an almost instantaneous transformation of the highly fluid latex into a viscous gel .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 polymers which shows pH induced gelation are cellulose acetate phthalate (CAP) latex, carbomer and its derivatives polyvinylacetal diethylaminoacetate (AEA), polymethacrylic acid (PMMA), polyethylene glycol (PEG), pseudolatexes etc. \[14,15\]

2. Temperature modulated gels:

In this system, gelling of the solution is triggered by change in temperature, thus sustaining the drug release. 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. 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 polymers which show temperature induced gelation are poloxamers or pluronics, cellulose derivatives [methyl cellulose, HPMC, ethyl hydroxyl ethyl cellulose (EHEC)] and xyloglucan etc. \[14, 15,16\]

3. Ion activated gels:

In this system, gelling of the solution instilled is triggered by change in the ionic strength. The aqueous polymer solution forms a clear gel in the presence of the mono or divalent cations typically found in the tear fluids. The electrolyte of the tear fluid and especially Na+, Ca2+ and Mg2+ cations are particularly suited to initiate gelation of the polymer when instilled as a liquid solution in the conjunctival cul-de-sac. The polymer which shows osmotically induced gelation are gelrite or gellan gum, hyaluronic acid and alginates etc. \[14, \],15,16\]

Barriers for ocular Drug delivery System

1. Drug loss from the ocular surface
2. Lacrymal fluid-eye barriers
3. Blood-ocular barrier

Drug loss from the ocular surface \[17, 18, 20\]

After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of the eye. Routes of drug kinetics refer to following processes:

1) Transcorneal permeation from the lacrimal fluid into the anterior chamber,
2) Non-corneal drug permeation across the conjunctiva and sclera into the anterior uvea,
3) Drug distribution from the blood stream via blood-aqueous barrier into the anterior chamber,
4) Elimination of drug from the anterior chamber by the aqueous humor turnover to the trabecular meshwork and Schlemm's canal.
5) Drug elimination from the aqueous humor into the systemic circulation across the blood-aqueous barrier.
6) Drug distribution from the blood into the posterior eye across the blood-retina barrier, intravitreal drug administration.
7) Drug elimination from the vitreous via posterior route across the blood-retina barrier, and
8) Drug elimination from the vitreous via anterior route to the posterior chamber.

The source that causes non-productive drug removal is its systemic absorption instead of ocular absorption. Systemic absorption may take place through two ways, firstly directly from the conjunctival sac via local blood capillaries or it can take place after the solution flow to the nasal cavity. Drug absorption through the systemic circulation decreases the drug concentration in lacrymal fluid extensively. The constant release of drug from solid delivery system to the tear fluid may lead only to ocular bioavailability of about 10%, because the local systemic absorption clears most of the drug.

Lachrymal fluid-eye barriers \[17, 18, 19\]

Drug absorption from the lacrymal fluid into the eye is limited by corneal epithelium. Mature epithelial cells forms corneal barrier. From the limbal region they migrate towards the center of the cornea and to the apical surface. Paracellular drug permeation is limited by the most of apical corneal epithelial cells that forms tight junctions. Despite the tightness of the corneal epithelial layer, transcorneal permeation is the main route of drug entrance from the lacrymal fluid to the aqueous humor. The conjunctiva is more leaky epithelium than the cornea and its surface area is also nearly 20 times greater than that of the cornea. Since conjunctiva is fairly permeable to the hydrophilic and large molecules therefore, drug absorption across the bulbar conjunctiva has gained increasing attention. For larger bio-organic compounds such as proteins and peptides it may serve as a route of absorption. Cornea and conjunctiva in both these membranes principles of passive diffusion have been investigated, but the role of active transporters is only lightly studied.

Blood-ocular barriers \[17, 19, 20\]

Blood-ocular barriers protect the eye from xenobiotics in the blood stream. Blood-ocular
barriers have two parts: blood-aqueous barrier and blood-retina barrier. The anterior blood-eye barrier is composed of the endothelial cells in the cornea. The access of plasma albumin into the aqueous humor is prevented by this barrier, the access of hydrophilic drugs from plasma into the aqueous humor is also limited. The integrity of this barrier can be disrupted by inflammation which causes the unlimited drug distribution to the anterior chamber. A retinal pigment epithelium (RPE) and the tight wall of retinal capillaries comprise the posterior barrier between blood stream and eye. Unlike retinal capillaries the vasculature of the choroid has extensive blood flow and leaky walls. Drugs easily gain access to the choroidal extravascular space but thereafter the RPE and retinal endothelia limits its distribution into the retina. Despite its high blood flow the choroidal blood flow constitutes only a minor fraction of the entire blood flow in the body. Therefore, without specific targeting systems only a minute fraction of the intravenous or oral drug dose gains access to the retina and choroid. Unlike blood brain barrier, the blood-eye barriers have not been characterized in terms of drug transporter and metabolic enzyme expression.

Routes of ocular drug delivery

The selection of the route of administration depends primarily on the target tissue. The various routes of drug delivery into the ocular tissues are:

a. **Topical route**
Topical ocular drug administration is accomplished by eye drops, but they have only a short contact time on the eye surface. The contact, and thereby duration of drug action, can be prolonged by formulation design (e.g. gels, gellifying formulations, ointments, and inserts).

b. **Subconjunctival administration**
Subconjunctival injections have been used to deliver drugs at increased levels to the uvea.

c. **Intravitreal administration**
The access of drug straight into the vitreous and retina can be achieved by administrating drug directly into the vitreous. The delivery from the vitreous to the choroid is more complicated due to the hindrance by the RPE (Retinal Pigment Epithelium) barrier. Small molecules are able to diffuse rapidly in the vitreous but the mobility of large molecules, particularly positively charged, is restricted.

**MECHANISM OF GELLING SYSTEM IN OCULAR DRUG DELIVERY**

1. **Temperature induced in situ gelling system**
In this type of gelling system, formulation shows gellation due to the change in temperature i.e. from (20° – 25°C) to (35° – 37°C). The 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.

2. **pH induced in situ gelling system**
In this type of gelling system, sol to gel formation takes when pH of the formulation is raised from 4.2 to 7.4 (pH of the eye). When pH is raised the polymer forms hydrogen bonds with mucin which leads to formation of hydrogel networks.

3. **Ion activated in situ gelling system**
In this type of gelling system, sol to gel phase transition takes place under the influence of increased ionic strength. Formation of gel takes because of complexation with polyvalent cations (like Ca+2) in lachrymal fluid.

**Mechanism of ocular drug absorption**

A. **Corneal permeation**
The precorneal space permeates the drugs across the corneal membrane. Thus, the mixing and the kinetic behavior of drug disposition in tears have a direct bearing on efficiency of drug absorption into the inner eye. The productive absorption of most ophthalmic drugs results from diffusion process across corneal membrane. The efficiency of absorption process is a function of rate and extent at which the transport processes occur. Consequently, depending on the physicochemical properties of a diffusing drug, the resistance offered by the individual layers varies greatly. Epithelium, being lipoidal, represents a diffusion barrier offering high resistance to ionic or other aqueous soluble or polar species. In contrast, compounds with relatively low polarity encounter a greater diffusional resistance in the hydrophilic stroma layer.

B. **Non-corneal permeation**
Mechanism of drug permeation in the sclera is likely to be diffusion across the intercellular aqueous media in the case of structurally similar corneal stroma. Therefore the possibility of partitioning mechanism cannot be eliminated. Like cornea, the conjunctiva is composed of an
epithelial layer covering an underlying stroma; the conjunctival epithelium offers substantially less resistance than the corneal epithelium.

**APPLICATION OF In Situ GELLING SYSTEM**

1. **In Situ gelling system for ocular delivery**

Eye drops, eye gels, eye ointments are the conventional ocular drug delivery system but they suffer poor bioavailability due to tear production, transient residence time, impermeability of corneal epithelium, binding to the lachrymal proteins and problem like blurring of vision. The use of the new gel system which is instilled as drops into the eye and undergo a sol-gel transition in the cul de sac can overcome the problem of poor bioavailability and therapeutic response exhibited by conventional ophthalmic solutions due to rapid precorneal elimination of the drug.\[27\] The various natural and synthetic polymers such as polymers such as gellan gum, alginic acid, xyloglucan, cellulose acetate phthalate(CAP) latex, carbopol, polymethacrilic acid(PMMA), polyethylene glycol (PEG), pseudolatexes, chitosan, pluronics, tetronics etc are used. Local ophthalmic drug delivery system has been used for the delivery of antimicrobial agents, anti-inflammatory agents and autonomic drugs used to relieve intraocular tension in glaucoma.\[27, 28\]

2. **In Situ gelling system for parenteral delivery**

Implants, microspheres and liposomes are controlled parenteral systems that are used in drug delivery. These suffer from limitations such as implants need surgical implantation, microspheres for parenteral delivery have complex manufacturing process and on other hand liposomes have high production cost and drug leakage is a problem. Injectable gel forming drug delivery system represents an attractive alternative to microspheres and implants as parenteral depot systems and has following advantages over conventional parenteral system.\[29, 30\]

- **Less invasive technique:** The application is less invasive and less painful compared to implants.
- **Direct delivery to a target area:** This helps in achieving higher drug concentration at the desired site of action to minimize systemic side effects.
- **Biodegradable and biocompatible:** Injectable system is made of biodegradable polymers and biocompatible solvents and therefore do not require removal.
- **Economic factors:** Operating expenses for the production of forming applications are marginal, thus lowering investment and manufacturing costs.\[29\]

3. **In Situ gelling system for nasal delivery**

For nasal delivery of the gels polymers such as gallan gum and xanthan gum are used as gel forming polymers. The efficacy of Momethasone furoate was evaluated for the treatment of allergic rhinitis Animal study were conducted using allergic rhinitis model & effect of in-situ gel on antigen induced nasal symptoms in sensitizes rats was observed. When compared to marketed preparation nosonex (Momethasone furoate suspension 0.05%), the In-situ gel was found to inhibit the increase in nasal symptoms.\[27, 28\]

4. **In Situ gelling system for rectal delivery**

Many types of drugs that are formulated as liquid, semisolid (ointments, creams and foams) and solid dosage forms (suppositories) are delivered through rectal route. Conventional form such as suppositories can often cause discomfort during insertion. Suppositories sometimes are unable to sufficiently retained at a specific position in the rectum, sometimes they can migrate up-wards to the colon that makes them possible for drug to undergo the first-pass effect. Choi et al. developed novel gel ling liquid suppositories with gelation temperature at 30–36°C. Poloxamer 407 and/or poloxamer 188 were used to confer the temperature-sensitive gelation property.\[31, 32\]

5. **In Situ gelling system for vaginal delivery**

The vagina, an important organ of reproductive tract, also serves as a potential route for drug administration. Formulations based on a thermo-plastic graft copolymer that undergo gelation have been developed to provide the prolonged release of active ingredients such as nonoxynol- 9, progestins, estrogens, peptides and proteins.\[33\] Chang et al.\[34\] have recently reported a mucoadhesive thermo-sensitive gel (combination of poloxamers and polycarbophil), which exhibited, increased and prolonged antifungal activity of clotrimazole in comparison with conventional PEG-based formulation.
6. In Situ gelling system for oral delivery

The pH-sensitive hydrogels have a potential use in site-specific delivery of drugs to specific regions of the GI tract. Hydrogels made of varying proportions of PAA derivatives and crosslinked PEG allowed preparing silicone microspheres, which released prednisolone in the gastric medium or showed gastro protective property. Cross-linked dextran hydrogels with a faster swelling under high pH conditions, likewise other polysaccharides such as amidated pectins, guar gum and insulin were investigated in order to develop a potential colon-specific drug delivery system. [35, 36]

Evaluation parameters for gels [37, 38, 39]

1. Clarity :-
Clarity was evaluated by visual observation against a black and white background.

2. Determination of pH:-
As pH is an important parameter to evaluate for ophthalmic preparations. The pH was checked using pH meter.

3. Viscosity and rheology:-
Viscosity of the formulation was evaluated by Brookfield Synchoelectric Viscometer. Viscosity is determined at different speeds (10, 20, 50, 70, 100 rpm). The formulation should have 5 to 1000 mpa viscosity before gelling and 50 to 50,000mpa viscosity after gelling.

4. Determination of gelling capacity:-
Gelling capacity is evaluated by mixing the stimulated tear fluid with the formulation. A visual assessment of gel formulation is carried out. Time required for gelling as well as time required for formed gel to dissolve is also noted.

5. In vitro drug release :-
In vitro drug release can be carried out using cellophane membrane, modified USP XXII dissolution apparatus, Circular teflon cup, Franz diffusion cell, Dialysis tube.
The formulation is kept in the donor compartment and freshly stimulated tear fluid in receptor compartment. Between the donor and receptor compartment dialysis member is placed (0.22 um pore size). The whole assembly is placed on thermostatically controlled magnetic stirrer. Temperature of the medium was maintained at 37°C±.5°C. 1ml of sample is withdrawn at predetermined time interval of 1 hour for 6 hours and same volume of fresh medium is replaced.

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