SYNOPTIC REVIEW ON OPHTHALMIC IN-SITU GEL SYSTEM

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ABSTRACT
Ophthalmic drug delivery is one of the most fascinating and difficult endeavours facing pharmaceutical scientists. The main issue encountered by pharmaceutical scientists is rapid precorneal elimination of the drug, resulting in poor bioavailability and therapeutic response due to high tear fluid turnover and dynamics. These benefits, including ease of administration, decreased frequency of administration, improved patient compliance, and comfort, have sparked interest in in situ forming polymeric delivery systems. The development of gels, which allow for the sustained and controlled release of drugs, is dependent on variables including temperature variation, pH changes, the presence of ions, and ultraviolet radiation. In situ-forming gels are liquid when applied, go through a phase change in the ocular cul de sac to become visco-elastic gel, and respond to environmental changes as a result. A significant number of novel temperature, pH, and ion induced in situ-forming systems have been reported in the recent years for sustained ophthalmic drug delivery. Each system has unique benefits and drawbacks. The selection of a specific gel is based on its inherent qualities and intended therapeutic use. In situ gels are now employed as delivery systems for drugs that have both local and systemic effects. The fundamentals of the in situ gel system are discussed in this review. Such devices are easier to produce from a manufacturing standpoint, which reduces investment and manufacturing costs.

Index terms: In-Situ Gel, Poor bioavailability, Controlled release, Sustained release, Ophthalmic

INTRODUCTION
Nowadays peoples in the world especially in the developing countries are suffering from severe eye diseases, resulting in visual impairment and blindness. Technological advancement has yielded various aids like television, computers and smart phones, video games which are being extensively used by young generation and is resulting in to various ophthalmic diseases. Industrialization in developed and developing countries is pathetically deteriorating the environmental conditions by air pollution which is responsible for various epidemic eye infections. The most common method of ocular chemotherapy is topical medication application due to its benefits and safety. The techniques for administering medications through the eyes are divided into two categories: conventional techniques and novel techniques. For the treatment of either external eye diseases like conjunctivitis, blepharitis, and keratitis sicca or internal eye conditions like glaucoma, proliferative vitreoretinopathy, severe retinal rot, and retinitis, medications are typically administered directly to the outer layer of the eye as eye drops. However, due to the conjunctiva's systemic absorption and efficient eye defence mechanisms (such as lachrymal secretion and the blink reflex). Poor bioavailability of the drug for the eye results from a significant portion of it being rapidly cleared from the ocular surface and only a small portion being absorbed into the eye. Eye drops must be used frequently due to the pulse kinetics of the drug in the eye. The primary objective of any ocular drug delivery system are to maintain therapeutic drug concentrations at the target site, reduce dosage frequency, and overcome various dynamic and static ocular barriers. The primary objective of pharmacotherapeutics is to achieve an effective drug concentration at the intended site of action for long enough to elicit the desired response. The achievement of optimal concentration at the site of action is a significant challenge in ocular therapeutics. Tear production, brief residence time, and corneal epithelium impermeability are the main causes of low drug bioavailability from ocular dosage forms[1][2].

One of the most important and intricate tactile organs, the eyes are capable of capturing visual images and relaying them as signs to the mind via the optic nerve. The ophthalmic conveyance of the medication has been one of the challenging tasks for drug researchers because of the unique construction of the eye, which represses the section of the medication atoms into the ideal site. The cul de sace can hold up to about 20–30 µl of tears without spilling without holding 7-9 µl of tears on average. The tear stream

Fig 1.1: Structure of Human Eye
typically 4–9 mm in the parkey and 1 µl/min, respectively. In most cases, the pH of the tear falls between 6.5 and 7.6. Approximately 90 seconds are needed to clear the infused arrangements’ waste (25–50 ml) from the front of the eye. The eye has a somewhat limited volume that it can hold without spilling under normal circumstances. By acting as a barrier for small particles and preventing macromolecular dissemination via the paracellular course, the corneal epithelium acts as a barrier for small particles. A profoundly hydrophilic layer that forms the basis of the epithelium, the stroma, makes up 90% of the cornea. Different layers include the endothelium layer, Descemet's layer, and Bowman's film. Smart polymeric systems have proved to be promising means of delivering the drugs. This system involves sol to gel transition after administration. They are in solution phase before administration but gels under physiological condition. Prolongation of drug residence time in cul-de-sac and increasing their corneal permeability improves the ocular bioavailability of drug. Ocular pathologic disorders are generally described as anterior and posterior segment disorders. The anterior segment disorders include dry eye disease, cataract, allergic conjunctivitis are treated by using topical eye drops. Ocular pathologic conditions involving the posterior segment generally result in vision loss due to damage to the retina. The advantages of in situ gel drug delivery system comes with ease of administration, improved local bioavailability, reduced dose concentration, reduced dosing frequency, improved patient compliance and comfort, simple formulation and manufacturing so less investment and cost. There are various factors such as temperature, pH change, presence of ions, UV irradiation, solvent exchange and from which drug release in a sustained manner[4][5][8].

Fig 1.2: Precorneal and intraocular drug movement from topical dosing

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<tr>
<th>DOSAGE FROM</th>
<th>BENEFIT</th>
<th>CONSTRAINTS</th>
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<tr>
<td>Emulsions</td>
<td>Prolonged release of drug from vehicle</td>
<td>Blurred vision. Patient’s non-compliance. Possible oil entrapment.</td>
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OCULAR BIOAVAILABILITY:
Topical ocular drug delivery is the most popular method of drug delivery in the management of ocular diseases. The ocular bioavailability of medications used intravenously is extremely low. Due to dosage form spillage caused by tear turnover and drug dilution in nasolacrimal drainage, a significant amount of drug is lost. Thus, 1–10% of the drug is reaches to the cornea.

TYPE OF IN-SITU GEL [4][6][7][9][10]

1. Thermo reversible in situ gels
2. pH sensitive in situ gels
3. Ion sensitive in situ gel
4. Electrical signal sensitive hydrogels

Temperature sensitive in situ gel is the oldest, the most extensively studied and common type of stimuli responsive gel. It can be easily and precisely introduced into the eye in liquid form without producing irritation or blurred vision. The gel is formed at precorneal temperature [35°C] to endure the lachrymal fluid dilution without rapid precorneal elimination of instilled drug after administration. Some examples of thermo sensitive in situ gelling polymers-

✓ Poloxamer F27 and carbopol934P;
✓ Pluronic [PF-127 & PF-68] and alginate

The pH sensitive in situ gelling system consist of pH sensitive polymers which are polyelectrolytes contain an acidic (carboxylic or sulfonic) or a basic group (ammonium salts) that either accept or release protons in response to alteration in pH in the surrounding environment. At lower pH (pH 4.4), the formulation exists as a regular solution, however, it undergoes gel formation at pH 7.4, that is the pH of tear fluid. Some examples of pH sensitive in situ gelling polymers-

✓ Carbopol974P and HPMC E4M;
✓ Calcium alginate with HPMC K4M and E50LV

Ion sensitive in situ gelling systems from a crosslinking with cations exists in the tear fluid (Na+, Ca2+, Mg2+), thus forming a gel on the ocular surface, which give rise to an extended contact time . Some examples of ion sensitive in situ gelling polymers-

✓ Gellan gum;
✓ Gellan gum with xanthan gum, carbopol or HPMC
✓ K- Carrageenan
✓ Sodium alginate

MECHANISM OF GELLING SYSTEM
The mechanism of in situ gels is based on following mechanisms:

A. Based on the physical mechanism-
   i. Swelling: The formulation material absorbs water from surrounding environment and swells to desired space.
   ii. Diffusion: This method involves solvent diffusion from polymeric solution into surrounding tissue which results in precipitation or solidification of polymeric matrix.

B. Based on chemical reaction mechanism-
   Various cycles, including temperature, pH, and particle actuated frameworks, can create in-situ gel development. Temperature-set off in-situ gel framework that utilizes temperature delicate polymers that dwell in fluid structure beneath their low basic arrangement temperature (LCST) and gels when the outside temperature comes to or surpasses the LCST . The pH-prompted in-situ gel contains polymers with acidic or basic practical gatherings inside the chain particle and goes through a sol-gel stage change when presented to a low pH to high pH climate. Particle enacted frameworks, otherwise called osmotically started in-situ gel frameworks, happen when a polymer goes through a sol-gel progress because of changes in ionic fixation, which is many times set off by monovalent or divalent cations in tear liquid, especially Na+, Mg2+ and Ca2+.

Furthermore, catalysts cross connecting and photon polymerization have been displayed to create sol-gel stage change.

OVERALL IMPORTANCE OF IN SITU GEL SYSTEM [12]

- It is markedly different following administration, sol gel transition; promote a controlled and sustained release profile.
- The frequency of drug administration can be reduced due to the drug’s prolonged release.
- There is no drug accumulation or side effects due to the precision of dosing and the controlled release of drugs from in situ gels.
- Significant increases in bioavailability and dose reduction of a drug.
- Gel formation increased drug residence time and drug tissue contact.
- In-situ gel systems can deliver accurate and frequent doses when compared to pre-formed gels.
- In-situ gel systems are easier to administer because of their physical form, which improves patient compliance and comfort.
CHARACTERIZATION OF OPHTHALMIC IN SITU GEL.\[^{[11]}\][^[[12]13]\]

- Clarity
- pH
- Drug Content
- Viscosity
- Gelling Capacity
- In vitro Drug Release
- Ex vivo study
- Accelerated Stability Study
- Isotonicity Evaluation
- Sterility Study

ADVANCES IN RESEARCH

Finding effective treatment options that both doctors and patients can readily accept is one of the challenges the pharmaceutical industry faces today. If delivery systems are to offer effective substitutes for pharmaceuticals currently delivered by other routes, they must also contribute to a better therapeutic outcome. One of the difficult drug delivery methods is in situ gel formulations. Different biodegradable polymers are used to create in situ gels, but there are challenges with their fabrication, difficult processing abilities, use of organic solvents in their preparation (especially for synthetic polymer based systems), burst effect, and unpredictable drug release kinetics. Natural polymers meet the criteria for the perfect polymer, but because batch-to-batch reproducibility is challenging, synthetic polymers are used instead. Labile macromolecular therapeutic agents have been created as a result of recent biotechnological advancements; these agents need complex formulations to be administered effectively.

In 2016, it was shown that Soluplus® (polyvinyl caprolactam, polyvinyl acetate, and polyethylene glycol copolymer)-based nanomicelles could improve Lipoic acid (ALA), an antioxidant compound that may be helpful in the treatment of diabetic keratopathy and retinopathy, by increasing its apparent solubility (more than 10-fold than commercially available eye drops). At the temperature of the ocular surface, the thermosensitive properties of the aqueous dispersion of ALA-loaded Soluplus® nanomicelles allowed it to change from a freely flowing liquid system to a weak gel. In situ gelation was useful for extending corneal residence time and improving ALA accumulation into the cornea (ex vivo corneal permeability test). Additionally, ALA-loaded Soluplus® nanomicelles showed stability after being strongly diluted in STF, filtered, freeze-dried, and reconstituted in aqueous media, suggesting that they are a reliable substitute for the current ALA formulations.

In situ gelling formulations with antimicrobial and antifungal compounds, either directly or encapsulated in lipid/polymeric NSs, have been developed in the last ten years for the treatment of infections related to corneal ulcers. As mucoadhesive and viscosity-enhancing agents, various thermo-reversible, ion-sensitive, and/or pH-triggered polymers were frequently used for this purpose, frequently in conjunction with cellulose derivatives like HPMC and MC.

CONCLUSION

As a result, in situ gels provide the key component of a successful controlled release product, which is improving patient compliance. There are several benefits to using polymeric in situ gels for controlled drug release as opposed to traditional dosage forms. The in situ gel dosage forms are very dependable because they provide a prolonged and sustained release of the medication along with good stability and biocompatibility characteristics. Because they can be administered as drops and significantly improve the therapeutic effect, and/or pH-sensitive, and/or pH-triggered polymers were frequently used for this purpose, frequently in conjunction with cellulose derivatives like HPMC and MC.

REFERENCE