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A Novel Approach of Ophthalmic Drug Delivery: *In Situ* gel

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ABSTRACT

Eye is the most vital organ of body. The usual ophthalmic dosage forms are account for 90% of currently accessible ophthalmic formulations. The major trouble encountered is quick precorneal drug loss. To improve ophthalmic drug bioavailability, there are considerable efforts directed toward newer drug delivery systems for ophthalmic administration. Newer research in ophthalmic drug delivery systems is directed towards an amalgamation of several drug delivery technologies, that includes to build up systems which is not only extend the contact time of the vehicle at the ocular surface, but which at the same time slow down the removal of the drug. There are various new dosage forms like in situ gel, collagen shield, minidisc, ocular film, ocusert, nanosuspension, nanoparticulate system, liposomes, niosomes, dendrimers, ocular iontophoresis etc. 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.

Keywords: *In situ gel, Novel ocular drug delivery system, pH-triggered in situ system, Ion-activated in situ system, Temperature sensitive in situ system, Sol to gel.*

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. The stroma is the only hydrophilic layer. The eye is generally divided into two parts: the anterior and the posterior segments. The anterior segment includes the cornea, sclera, ciliary body, and the lens; these structures delimit a cavity: the anterior chamber filled with the aqueous humor. The posterior segment includes all the structures between the lens and the optic nerve that delimit a cavity: the vitreous filled with an aqueous gel (the vitreous humor). The eye possesses efficient protective mechanisms like reflex blinking, lachrymation, and drainage, while lid closure protects the eye from external aggression. Tears permanently wash the surface of the eye and exert an anti-infectious activity through the lysozyme and immunoglobulin's they contain. Finally, the lachrymal fluid is drained down the nasolacrimal pathways. All these protective mechanisms are responsible for therapist and extensive procorneal loss of topically applied ophthalmic drugs [1-2]. *In situ* is a Latin word which means 'In its original place or in position'. There are many mechanisms which triggers the formulation of *in situ* gels such as solvent exchange, ultra violet irradiation, ionic cross linkage, temperature modification, pH change and ionization. Studies are performed through various routes like oral, rectal, ocular, injectable, vaginal, nasal, parental and intraperitoneal. With the increased demand in techniques and recent developments in the field of polymer sciences various stimuli sensitive hydrogels like pH and temperature sensitive hydrogels are developed, which are used as chemotherapeutic agents to tumour regions. Prolonged and sustained release of the drug, reproducible, excellent stability, biocompatible and accurate quantities of administration makes the *in situ* gel system more reliable. *In situ* gel formulation applied for targeted delivery via ophthalmic, rectal, vaginal, nasal mucosa avoids the hepatic first-pass metabolism, especially for the proteins and peptides [3]. The development of *in situ* gel systems has received considerable attention over the past few years. *In situ* gel forming drug delivery systems are principle, capable of releasing drug in a sustained manner maintaining relatively constant plasma profiles. These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. These have a characteristic property of temperature dependent, pH dependent and cat ion induced gelation [4].

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Overview of Anatomy and Physiology of Human Eye:

The eye is vital organ of human body. The cornea, lens, and vitreous body are transparent media with no blood vessels. Oxygen and nutrients are transported to these nonvascular tissues by the aqueous humors. The aqueous humors has a high oxygen tension and about the same osmotic pressure as blood. The cornea also derives part of its oxygen need from the atmosphere and is richly supplied with free nerve endings. The transparent cornea is continued posterior into opaque white sclera, which consists of tough fibrous tissue. Both cornea and sclera withstand the intra-ocular tension constantly maintained in the eye. The eye is constantly cleansed and lubricated by the lachrymal apparatus, which consists of four structures: Lachrymal glands, lachrymal canals, lachrymal sac, naso-lachrymal duct. The lachrymal fluid secreted by the lachrymal glands is emptied on the surface of the conjunctiva of the upper eyelid at a turnover rate of 16% per min. It washes over the eyeball and is swept up by the blinking action of the eyelids. Thus the eyeball is continually irrigated by a gentle stream of lachrymal fluid that prevents it from becoming dry and inflamed. The lachrymal fluid in humans has a normal volume of 7µl and is an isotonic aqueous solution of bicarbonate and sodium chloride (pH 7.4) that serves to dilute irritants or to wash the foreign bodies out of the conjunctival sac. It contains lysozyme, whose bactericidal activity reduces the bacterial count in the conjunctival sac. The rate of blinking varies widely from one personto another, with an average of approximately 20 blinking movements per min. During each blink movement the eyelids are closed for a short period of about 0.3 sec [5].

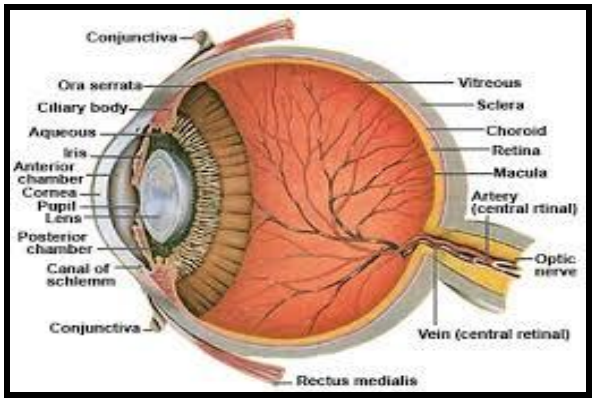

Fig. 1: Anatomy of Human Eye

Fate of the Formulation Administered Through Ocular Route:

At first sight, the eye seems an ideal, easily accessible target organ for topical treatment. However, the eye is, in fact, well protected against absorption of foreign materials, first by eyelids and tear-flow and then by the cornea, which forms the physical-biological barrier. When any foreign material or medication is introduced on the surface of the eye, the tear-flow immediately increases and washes it away in a relatively short time. Under normal conditions, the eye can accommodate only a very small volume without overflowing. This anatomy, physiology and biochemistry of the eye are responsible for the low bioavailability of drug. The challenge is to overcome these protective barriers of the eye without causing permanent tissue damage [6].

Advantages: [7]

1. Flexibility in dosing / accurate dosing.
2. Sustained and controlled drug delivery possible.
3. Increased ocular bioavailability of drug (by increased corneal contact time).
4. Ability to circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.
5. Needle-free drug application, self medication possible, better patient compliance.
6. Avoidance of hepatic first pass metabolism and thus potential for dose reduction compared to oral delivery.

Limitations: [7]

1. Interference with vision.
2. Difficulty in placement and removal.
3. Limited permeability of cornea resulting into low absorption of drugs.
4. Entry of drug to the lachrymal duct may cause unwanted systemic side effects.
5. The elimination of the drug through the eye blinking and tear flow may lead to short duration of the therapeutic effect resulting in a frequent dosing regimen.

Various ocular delivery systems include the eye drops, ointments, gels, ocuserts, lacriserts [8], etc. The newly developed particulate and vesicular systems like nanoparticles, microparticles [9], microspheres, liposomes [10], niosomes [11], dendrimers [12], nanoemulsions, implants, etc. were also investigated and were found to be useful in delivering the drug for a longer extent and were found to be helpful in reaching the systemic circulation too.

There are various physiological constraints which severely limit the extent of absorption of an ophthalmic drug. Among the factors that limit ocular absorption is the relatively impermeable corneal barrier. The cornea consists of three membranes, the epithelium, the endothelium and inner stroma (highly hydrophillic), which are the main absorptive barriers.

The conjunctiva is a thin, vascularized mucus membrane that lines the inner surface of the eyelids and covers the anterior part of the sclera up to the cornea. Conjunctival uptake of a topically applied drug from tear fluid is typically greater than corneal uptake because of the relative leakiness of the membrane, rich blood flow and large surface area [13].

Classification of *in situ* gelling system: [14]

1. pH sensitive *in situ* gelling system
2. Temperature sensitive *in situ* gelling system
3. Ion sensitive *in situ* gelling system

1. pH sensitive in situ gelling system:

In this system, gelling of the solution is triggered by change in pH, when pH is raised from 5-7.4 [15]. At higher pH, polymer forms hydrogen bond with mucin, which leads to hydrogel formation. Cellulose acetate phthalate latex, Carbopol, Polyacrylic Acid, Polyethylene Glycol are pH dependent polymers.

Mechanism for pH sensitive gelling System:

All pH sensitive polymers contain pendant acidic or basic groups that can either accept or release protons in response to changes in environmental pH. In case of weakly acidic group, swelling of hydrogel increases as the external pH increases, while decreases in case of weakly basic groups [16].

2. Temperature sensitive in situ gelling system:

These are liquid solutions at room temperature (25-27oC) and undergo gelation when in contact with body fluid (35-37oC) due to change in temperature. Temperature sensitive gels are three types; positive temperature sensitive gel, negative temperature sensitive gel, thermally reversible gel. Negative temperature sensitive gel has Lower Critical Solution Temperature (LCST), such gel contracts on heating above LCST25 [17]. Positive temperature sensitive gel has an Upper Critical Solution Temperature (UCST) such gel contracts on cooling below UCST.

Mechanism:

The sol-gel phase transition occurs upon increasing temperature is due to three mechanisms: Desolvation of the polymer, increased micellar aggregation and increased entanglement of polymeric network [18]. When temperature increases polymeric chain degraded, leads to the formation of hydrophobic domain and phase transition (liquid to hydrogel) occurred [19].

3. Ion Sensitive Gelling System:

Gelation is triggered by the presence of cat ions (Na+, Mg++, Ca++) in the tear fluid. These can be achieved by polymers like sodium alginate, gellan gum.

Gelation is occurred by ionic interaction of polymer and divalent ions of tear fluid. When anionic polymers come in contact with cationic ions, it converts to form gel [20].

Evaluations of *in situ* gel system:

The prepared *in situ* gel 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 *in situ* 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).

Physical parameters:

The formulated *in situ* gel solution is tested for clarity, pH, gelling capacity, and drug content estimation.

Gelling capacity:

The gelling capacity of the prepared formulation is deter mined 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 [21].

Swelling studies:

Swelling studies are conducted with a cell, equipped with thermo jacket to maintain a constant temperature .The cell contains artificial tear fluid. (composition – 0.67g Nacl , 0.20g NaHCO3, 0.008g Cacl2.2H2o & distilled water q.s to 100g). Swelling medium equilibrating at 370c one milliliter of formulated solution is placed in dialysis bag & put into the swelling medium. At specific time interval the bag is removed from the medium & weight is recorded. The swelling of the polymer gel as a function of time is determined by using the following relationship. % St = (Wt – W0) 100/W0 Where, St = Swelling at time't'. W0=Initial weight of gelling solution. Wt=Final weight of gel [22].

High performance liquid chromatography:

The HPLC system is used in reversed phase mode. Analysis is performed on a Nova pack C18 packed column (150 mm length X 3.9 mm i.d) [23].

Fourier transformer infra red:

The possibility of drug excipient interaction is investigated by FTIR studies. The FTIR graph of pure drug & combination of drug with excipient are recorded by using KBR pellets [23].

Thermal analysis:

Thermo gravimetric analysis can be conducted for in situ forming polymeric system to quantitative the percentage of water in hydrogel. Different scanning calorimetry is used to observed, if there are many changes in thermograms as compared with pure ingredients used thus indicating the interaction [24].

Rheological studies:

The viscosity measurements can be calculated using Broo kfield viscometer, Cone and Plate viscometer. The in situ 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 [20, 21]. And after ion gel-activation by the eye, will have a viscosity of from about 50-50,000mPas. The samples are analyzed both at room temperature at 25°C and thermostatic 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.

***In vitro* drug release studies:**

In vitro release study of *in situ* 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 [25].

Texture analysis:

The consistency, firmness and cohesiveness of *in situ* 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 [26].

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 [30].

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 [27].

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 [28].

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 10 µl placed into the lower cul-de-sac 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 [28, 29].

Accelerated stability studies:

Formulations are placed in ambient color vials and sealed with aluminum 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 [30].

Statistical analysis:

The results obtained from the experiments of mucoadhesive strength and release studies were analyzed statistically using multivariate tests. A statistically significant difference was conducted by using various SPSS software and difference was considered to be significant at $P<0.05$ [30].

Stabilities Studies:

Stability studies were carried out on optimized formulation according to ICH guidelines. Stability is defined as the extent, to which a product retains with in specified limits and throughout its period of storage and use i.e., shelf life. Stability studies were carried out on optimized formulations according to International Conference on Harmonization (ICH) guidelines. A sufficient quantity of formulations in previously sterilized vials was stored in desiccato+-rs containing a saturated solution of sodium chloride, which gives a relative humidity of 75±5 %. The desiccators were placed in a hot air oven maintained at a temperature 40°C±0.5°C and at room temperature. Samples were withdrawn at 7 days interval for 42 Days. The logarithms of percent drug remaining were calculated and plotted against time in days [31].

Commercial formulation of in situ polymeric system:

A. Timoptic-XE:

It is a Timolol Maleate ophthalmic gel formulation of Merck and Co. Inc., supplied as a sterile, isotonic, buffered, aqueous gel forming solution of Timolol Maleate. This formulation is available in two dosage strengths 0.25% and 0.5% in market. The pH of the solution is approximately 7.0, and the osmolarity is 260-330mOsm. Each ml of Timoptic-XE 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Inactive ingredients include gellan gum, tromethamine, mannitol, and water for injection and the preservative used is benzododecinium bromide 0.012%. Timoptic-XE, when applied topically on the eye, reduces the elevated, as well as normal intraocular pressure, whether or not accompanied by glaucoma [32].

B. Regel:depot-technology:

Regel is one of the Macromed's proprietary drug delivery system and based on triblock copolymer, composed of poly (lactide-co-glycolide)-poly (ethylene glycol)-poly (lactide-co-glycolide). It is a family of thermally reversible gelling polymers developed for parenteral delivery that offers a range of gelation temperature, degradation rates and release characteristics as a function of molecular weight, degree of hydrophobicity and polymer concentration. Following injection, the physical properties of polymer undergo a reversible phase change resulting in formation of a water insoluble, biodegradable gel depot. Oncogel is a frozen formulation of paclitaxel in Regel. It is a free flowing liquid below room temperature which upon injection forms a gel *in situ* in response to body temperature. HGHD-1 is a novel injectable depot formulation of human growth hormone (HGH) utilizing Macromed's Regel drug delivery system for treatment of patients with HGH deficiency [33].

C. Cytoryn:

This is one of the Macromed's products, which is a novel, peritumoral, injectable depot formulation of interleukin-2 (IL-2) for cancer immunotherapy using Regel drug delivery system. It is a free flowing liquid below room temperature that instantly forms a gel depot upon injection from which the drug is released in a controlled manner. Cytoryn enhances the immunological response by safely delivering four times the maximum tolerated dose allowed by conventional IL-2 therapy. Cytoryn also activates the systemic antitumor immunity. Regel system stabilizes and releases IL-2 in its bioactive form. The release of drugs is controlled by the rate of diffusion from and degradation of the depot [34].

CONCLUSION

Ophthalmic drug delivery system is burgeoning field in which most of the researchers are taking challenges to combat various problems related to this delivery. Steady advancement in the understanding of principles and processes governing ocular drug absorption and disposition and continuing technological advances have surely brought some improvements in the efficacy of ophthalmic delivery systems. 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. *In situ* activated gel-forming systems seem to be favored as they can be administered in drop form and produce appreciably less inconvenience with vision. Moreover, the provide better sustained release properties than drops.

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