Development and Evaluation of in-situ gel.

Ms.Tai Pandurang Yele

M. Pharmacy Student
Dattakala College of pharmacy swami chincholi

***Abstract*: The ophthalmic in-situ gels now days manage a palpable sustained drug delivery in various ophthalmic diseases. The formulation of in-situ gels for eye which carries the advantages like easy for administration, decreases frequency of dose and better patient compliance. The formation of in-situ gels depends on phase change system or sol-gel transition system. The formulation approaches like temperature intonation, pH change and presence of ions from which the drug gets released during a sustained and controlled manner are used for in-situ gels. Various polymers that are used for the formulation of in-situ gels include chitosan, Pluronic F-127, poly-caprolactone, gellan gum, algin , xyloglucan, pectin etc.The development of thermo-sensitive in-situ gels for in-vitro evaluation of ophthalmic delivery systems of Acular (KT), supported methylcellulose (MC) together with hydroxypropylmethyl cellulose (HPMC). The gel temperature of 1% MC solution was observed at 60°C. It was found that 6% oral rehydration salt without dextrose (ORS) was capable to decrease the gel temperature below physiological temperature. HPMC was added to extend viscosity and drug release time. The results indicated an outsized increase in viscosity at 37°C with addition of HPMC whch provided sustained release of the drug over a 4h period. From in-vitro release studies, it might be concluded that the developed systems were thus a far better alternative to standard eye drops.**

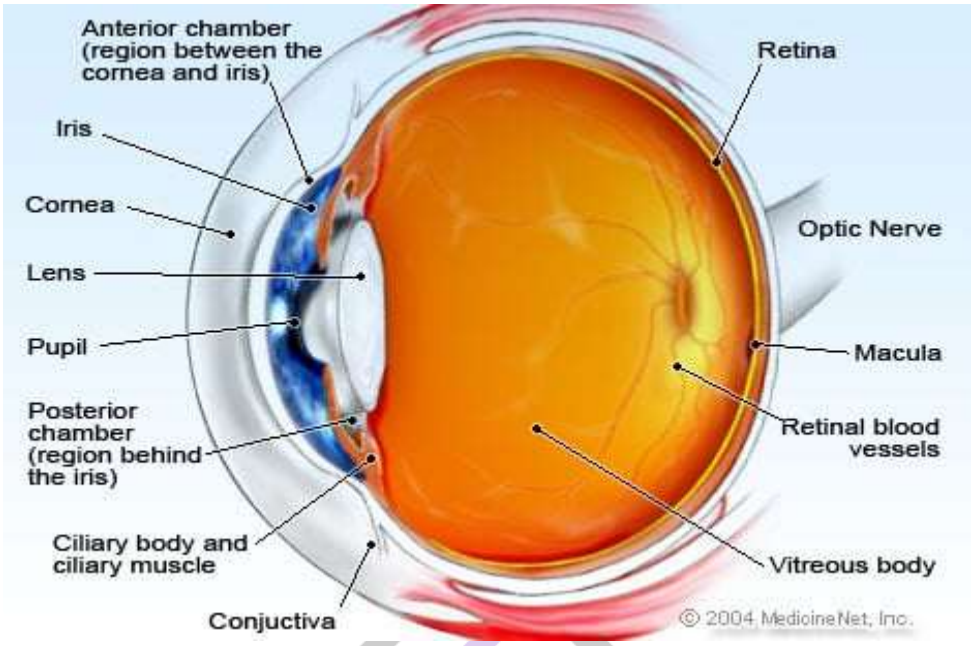
***Keywords*: ketorolac tromethamine (KT), Methylcellulose, Hydroxypropylmethylcellulose, In-situ gel, ORS**

INTRODUCTION

The conventional liquid ophthalmic formulations ar washed out from the precorneal space like a shot upon instillation owing to constant secretion, nasolacrimal voidance and short precorneal duration of the answer .Ophthalmic drug delivery is one among the difficult endeavors facing the pharmaceutical human nowadays. The structural and practical aspects of the attention render this organ extremely moth-resistant to foreign substances. Big challenge to the formulator is to beat the protecting barriers of the attention while not inflicting permanent tissue harm. most important downside encountered with topical administration is that the is that the loss caused by nasolacrimal voidance and high tear fluid turnover that results in solely 100% drug concentrations out there at the positioning of actions Within the last decade, larger attention has been centered on development of controlled and sustained drug delivery systems. Several patents for his or her use in varied medicine applications together with drug delivery are according Eye appears a perfect, simply accessible organ for topical treatment. But the attention is actually well protected against absorption of xenobiotics, 1st by the eyelids and tear-flow then by the tissue layer that forms the physical-biological barrier. Poor bioavailability of medicine from ocular dose forms is especially thanks to the tear production, non-productive absorption, transient duration, and solidness of membrane epithelial tissue. Most ocular treatments like eye drops and suspensions incorporate the topical administration of ophthalmic medication to the tissues round the ocular cavity. These dose forms ar simple to introduce however have the inherent disadvantage that the bulk of the medication in them is straight away diluted. Intensive analysis has been carried in planning of chemical compound drug delivery systems

DEVELOPMENT-

The development of unchanged gel systems has received considerable attention over the past few years and increasing range of unchanged gel forming systems are investigated and within the tear film as before long because the eye drop resolution is instilled into the cul-de-sac and is chop-chop drained removed from cavity by constant tear flow and lacrimo-nasal drain. For this reason, targeted solutions associate degreed frequent dosing square measure needed for the instillation to realize an adequate level of therapeutic impact. among the new categories of drug delivery systems, ophthalmic unchanged gels, which supply several benefits over standard dose forms, like exaggerated ocular residence, chance of emotional medication at a slow and constant rate, correct dosing, exclusion of preservatives and exaggerated period of time four, five Barriers to Ocular Delivery Systems Blood-ocular barriers: the attention is protected against the xenobiotics within the blood stream by blood-ocular barriers. These barriers have 2 parts: blood-aqueous barrier and blood-retina barrier shown in figure one and table A. The anterior blood-eye barrier consists of the epithelium cells within the structure (The middle layer of the attention below the sclerotic coat. It consists of the iris, membrane, and choroid). This barrier prevents the access of plasma simple protein into the aqueous humour, and conjointly limits the access of deliquescent medication from plasma into the aqueous humour. The posterior barrier between blood stream and eye retinal pigment epithelial tissue (RPE) and also the tight walls of retinal capillaries. don't like retinal capillaries the vasculature of the choroid coat has intensive blood flow and leaky walls. Medication simply gain access to the choroidal extravascular house, however thenceforth distribution into the membrane is restricted by the RPE and retinal endothelia.



Dig no.1 Barriers to Ocular Delivery Systems

Table A: BARRIERS FOR THE OCULAR DELIVERY

	Conjunctiva	Cornea	Sclera
Surface area	17.65 ± 2.12 cm2	1.04 ± 0.12	16 – 17
Thickness	-	0.57 mm	0.4 -0.5 mm
Structural Composition	Mucus membrane • Epithelium • Vasculature	• Epithelium • Bowman's membrane • Stomata	• Water • Proteoglycans • Monopolysaccharids

Drug loss from the Ocular Surface: After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of the eye. Even though the lacrimal turnover rate is only about 1µl/min the excess volume of the instilled fluid is flown to the naso-lacrimal duct rapidly in a couple of minutes. Another source of nonproductive drug removal is its systemic absorption instead of ocular absorption. Systemic absorption may take place either directly from the conjunctival sac via local blood capillaries or after the solution flow to the nasal cavity.

Lacrimal fluid-eye barriers: Corneal epithelium limits drug absorption from the lacrimal fluid into the eye. The corneal epithelial cells form tight junctions that limit the paracellular drug permeation. Therefore, lipophilic drugs have typically at least an order of magnitude higher permeability in the cornea than the hydrophilic drugs. In general, the conjunctiva is leakier epithelium than the cornea and its surface area is also nearly 20 times greater than that of the cornea. Various approaches use to prepare in-situ Gel: There are different approaches reported for in-situ gels. An in-situ gelling system should be a low viscous, free flowing liquid to allow reproducible administration to the eye as drops, and the gel formed following phase transition should be strong enough to with stand the shear forces in the cul-de-sac and demonstrated long residence times in the eye. In order to increase the effectiveness of the drug a dosage form should be chosen which increases the contact time of the drug in the eye. This may then prolonged the residence time of the gel formed in-situ along with its ability to release drugs in sustained manner which assist in enhancing the bioavailability, reduce systemic absorption and reduce the need for frequent administration leading to improved patient compliance. Depending upon the method employed to cause sol to gel phase transition on the ocular surface; various approaches for the preparation of in-situ gel are recognized and given in table 2

Table B: VARIOUS APPROACHES FOR THE PREPARATION OF IN-SITU GEL

External stimuli	Mechanism	Examples of polymer
Temperature Dependent system	Formulation is liquid at room temperature(20-25°C) which undergoes gelation in contact with body fluid (35-37°C	Poloxamer/Pluronics, Cellulose derivative
pH triggered system	Phase transition occur due to rise in pH from 4.2 to 7.4	Pseudolatexes, Carbomer(Acrylic acid) Cellulose acetate phthalate latex
Ion activated system	Formulation undergoes liquid-gel transition under influence of an increase in ionic strength	Chitosan, Gallen gum/ Gelrite, Alginate

• **Temperature dependent systems**: Temperature sensitive in-situ gels 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 gels formation for ophthalmic drug delivery. Three main strategies exist in designing of thermo-responsive sol-gel polymeric system. For convenience, temperature sensitive in-situ gels are classified into negatively thermo-sensitive, positively thermo-sensitive, and thermally reversible gels. Negative temperature-sensitive in-situ gels have a lower critical solution temperature and contract upon heating above the LCST. Polymers with low critical temperature (LCST) transition between ambient and physiologic temperature are used for this purpose. Formulation is liquid at room temperature (20-25°C) which undergoes gelation in contact with body fluid (35-37°C). Temperature increases degradation of polymer chains which leads to formation of hydrophobic domains & transition of an aqueous liquid to in-situ gel .

• **pH dependent systems:** 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 in-situ gel 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. Sol to gel transition when pH rises from 4.2 to 7.4; at higher pH polymer forms hydrogen bonds with mucin which leads to formation of in-situ gel The formulation with pH-triggered in-situ gel is therapeutically efficacious, stable, non-irritant and provides sustained release of the drug for longer period of time than conventional eye drops. Pseudolatexes Carbomer (Acrylic acid) Cellulose acetate phthalate latex (CAP- Latex) Polyox are some of the examples of polymer used in pH-triggered in-situ gels.

• **Ion Activated Systems:** Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion sensitive polymers. Alginate (Kelton) is used as the gelling agent in combination with HPMC (Methocel E50Lv) which acted as a viscosity-enhancing agent. Gelrite gellan gum, a novel ophthalmic vehicle that gels in the presence of mono or divalent cations, present in the lachrymal fluid can be used alone and in combinations with sodium alginate as the gelling agent.

Evaluation of in- situ Gel:

a. Clarity: The clarity of the formulations before and after gelling can be determined by visual examination of the formulations under light alternatively against white and black backgrounds

b. 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.

c. Ocular irritation studies: 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 is placed into the lower cul-de-sac with observation of the various criteria made at a designed requiredtime interval of 1hr, 24hrs, 48 hrs, 72hrs, and 1week after administration and rabbits are observed periodically for redness, swelling, watering of the eye

d. 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.

e. In vivo Scintigraphy Studies: Gamma scintigraphy is a well-established technique for in vivo evaluation of ophthalmic retention time. Although the rabbit is the commonly recommended animal model for ophthalmic formulations evaluation, human volunteers are preferred for this study due to physiological differences between rabbits and humans, especially the blinking rate.

f. Accelerated Stability Studies: Formulated gel preparations are kept at different temperature conditions like 25°C to 28°C ambient temperature (temperature in the working area), 4±1°C (refrigerated temperature) and 37±2°C (temperature in the incubator) for 6 week. The following parameters of the gel such as colour, consistency, drug content and degradation rate constant (K) are studied. To assess the shelf life, the samples are subjected to stability studies. Selected sterilized formulations are stored at 4±1°C (refrigerated temperature), 37±1°C (ambient temperature) and45±1°C (extreme temperature) for a period of 3 months and analyzed at intervals of 7, 14, 28, 42, 60 and 90 days. The formulations are evaluated at periodic intervals for drug content (by UV Spectrophotometer), clarity, pH, sol-gel transition, rheology, in-vitro drug release and sterility 41.

g. Texture analysis: The consistency, firmness and cohesiveness of in-situ gel is 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 36. Texture analysis provides information on mechanical properties of samples, namely hardness, compressibility and adhesiveness. These properties can be directly correlated with sensory parameters in vivo and, therefore, are valuable in the development of a product with desirable attributes that contribute to patient acceptability and compliance. A formulation designed for ophthalmic use should be, for example, easily removed from the package, present a good spreadability on the corneal surface and adhere to the mucous layer without disintegrating, in order to prolong retention time.

h. In vitro drug release studies: In-vitro diffusion is generally evaluated by fabricated open flow through assembly (specially designed glass cylinder open at both ends) and semi-permeable cellophane membrane/dialysis membrane. Cellophane membrane, previously soaked overnight in simulated tear fluid is mounted by tied and sandwiched between the donor and receiver compartment. The 0.5 ml aliquot of donor solution is placed on top of cellophane membrane. Aliquots of medium (3.0 ml) are withdrawn at selected time intervals and replaced by 3.0 ml of freshly prepared simulated tear fluid through sampling port for analysis. The samples are diluted suitably and analyzed by UV spectrophotometer at specified wavelength.

i. Ex vivo drug release studies: Goat corneas are used to study the permeation across the corneal membrane. The cornea is carefully removed along with a 5-6 mm of surrounding scleral tissue and washed with cold saline. The washed corneas are kept in cold freshly prepared solution of tear buffer of pH 7.4. The study is carried out by using Franz diffusion cell in such a way that corneum side is continuously remained in an intimate contact with formulation in the donor compartment. The receptor compartment is filled with STF pH 7.4 at 34o C ± 0.5o C. The receptor medium is stirred on a magnetic stirred. The samples are withdrawn at different time intervals and analyzed for drug content. Receptor phase is replenished with an equal volume of STF (pH 7.4) at each time interval.

CONCLUSIONS:

Ophthalmic drug delivery system is burgeoning field in which most of the researchers are taking challenges to combat various problems related to ophthalmic drug delivery. The primary requirement of a successful controlled release product focuses on increasing patient compliance which the in-situ gels offer. The use of polymeric in-situ gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Use of biodegradable and water soluble polymers for the in-situ gels formulations can make them more acceptable and excellent drug delivery systems.

References:

[1] Rathore K and Nema R: Review on Ocular inserts. International Journal Pharmaceutical Technology and Research 2009; 1:164-169.
[2] Patel D, Patel M and Patel N: Preparation and evaluation of ocular inserts containing brimonidine tartrate. International Journal of Pharmaceutics and Research 2009; 1:19-22.
[3] Indu P, Manjit S and Meenakshi K: Formulation and evaluation of ophthalmic preparations of acetazolamide. International Journal of Pharmaceutics 2000; 199:119-127.
[4] Pandit D, Bharathi A and Singh S: Long acting ophthalmic formulation of indomethacin: Evaluation of alginate gel systems. Indian Journal of Pharmaceutical Sciences 2007; 69: 37-40.
[5] Manas B, Sanchita D, Dipankar C and Lakshmi K: In-Situ Gels for Ocular Delivery. Science Pharm. 2011; 79:352-358.