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Review Article

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## Review article on in-situ of ocular drug delivery system

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Article History	Abstract
Received on: 02-12-2021 Revised On : 21-12-2021 Accepted on : 18-01-2022	Ocular drug delivery is the most challenging and interesting field in the pharmaceutical industry and pharmaceutical scientist. Blindness and vision impairment are the most problematic global health problem. In ophthalmic in-situ gels, various polymers are used. Generally, hydrogels are used. These polymers will increase the viscosity of the solution. In the physiology of the eye, this organ is impermeable to foreign particles. Novel drug delivery systems focus to overcome the biological barrier which can obstruct efficient ocular drug delivery. The conventional ophthalmic formulation shows a short pre-corneal residence time and poor bioavailability. Many attempts have been made towards the development of stable sustained-release in-situ gels. In this review, we specify a brief note about in-situ gels, various approaches for in-situ gelling systems, different types of polymers used in in-situ gels, their mechanisms of gel formation, and evaluation of polymeric in-situ gel.
<b>Keywords:</b> Ocular drug delivery, In-situgels, cul-de-sac, pH induced in-situgel system	
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### Introduction

The eye is the ORGAN OF SIGHT. It is located in the orbital cavity and supplied by the optic nerve (2nd cranial nerve). It is an isolated, complex, unique organ in our human body. It had been considered as the WINDOW TO HUMAN SOUL [1]. The human eye is divided into two segments; [1]. Anterior segment [2]. Posterior segment. The ophthalmic delivery of the drug has been one of the most challenging tasks for pharmaceutical scientists. The ocular drug delivery system is considered as crucially as challengingly like human eye. Moreover, conventional ophthalmic

Formulations exhibits a short pre-corneal residence time, poor bioavailability (due rapid elimination of drug from pre-corneal lachrymal fluid). IN-SITU GEL [In-situ- In position] system; It is formulated as liquid preparation to be suitable into EYE, which upon exposure to the physiological environmental changes to gel result in-situ. This system is one of the believing approaches to improve the retention time of drug on ocular surface. After instillation the aqueous solution containing stimuli response. Polymer such as PH – sensitivity polymer, thermo sensitivity polymer, ion sensitivity polymer, the mucoadhesive gels are formed on eye surface [2]. So here ocular retention time and ocular bioavailability of ophthalmic drugs are improved. Eye drops accounts for more than 90% of ocular preparation on market. These are used to treat external ocular infection. The ocular bio availability of

drug can be improved by the prolonging their residence time in the CLU-DE-SAC (deadend barrier/one side opened) and by increased their corneal permeability.

#### Drawback

Retaining of optimal concentration of drug at desired site. Non productivity absorption. Impermeability of drug to cornea. Induced lachrymation and tears turn over.

#### Anatomy of Eye

The eye has 3 layers of tissues in the walls [1]; Outer fibrous layer; sclera & cornea. Middle most layer (uveal tract); choroid, ciliary body & iris. Inner nervous tissue; retina.

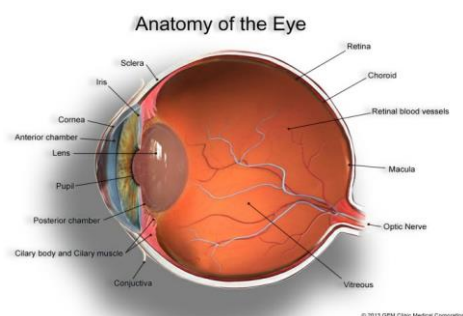


Fig. 1; Anatomy of the eye

**Sclera (white of eye);** outermost layer of the posterior. It has firm fibrous membrane that maintain shape of eye.

**Cornea;** Light rays pass through the cornea reach the retina. It is convex anteriorly and involved in refracting light.

**Choroid;** lines the posterior 5-6th of inner surface of sclera. Rich in blood vessels.

**Ciliary body;** it is anterior prolongation of choroid consist ciliary muscle and secretory epithelial cells. It acts like sphincter. These supplied by parasympathetic branches of oculomotor nerve (3rd cranial nerves).

**Iris;** It is a visible coloured ring at the front of eye. Centre of aperture called the pupil. Iris is supplied by the parasympathetic (constricts the pupil) and sympathetic nerve (dilates). The color dependent based on the number of pigment cells.

**AIBINOS;** It has no pigment example, people with blue eyes, browns eyes.

**Retina;** Inner most lining of the eye. Delicate in structure. The light sensitive layer consist of sensory receptor cells. **1. RODS 2. CONES.** Near the centre of posterior part is the macula lutea (yellow spot). In the centre of yellow spot a little depression called **FOVEA CENTRALIS.** It consist only cones. The small area of retina where the optic nerve leaves the eye called optic disc/blind spot. It has no light because of sensitive cells.

**Lens;** Highly elastic circular biconvex body. Its thickness is controlled by the ciliary muscle through the suspensory ligaments. Increases thickness and thicker lens becomes to allow focusing.

**Aqueous fluid;** both anterior and posterior chamber by iris contain aqueous fluid.

**Canal of schlemm;** aqueous fluid circulates in front of lens through pupil into the anterior chamber and returns to venous circulation through the scleral venous sinus in angle between iris and cornea.

**Vitreous body;** Behind the lens and filling the posterior segment of eyeball is vitreous body [2]. It is soft, colourless, transparent, jelly like substance composed of 99% water, salts, mucoprotein. The eye keeps its shape because of intraocular pressure exerted by vitreous body and aqueous fluid. **Optic nerve (2nd cranial nerve);** Fibers of optic nerve originates in retina and they converge to form the optic nerve meet the nerve from the other eye at the optic chiasma, situated in front of above the pituitary gland.

#### Classification of ocular drug delivery system;

1. **Conventional delivery systems;** Eye drops, Ointments and Gels, Ocuserts and Lacrisert.
2. **Drug delivery to anterior segment;** Contact lens, Cal du sac inserts Subconjunctival/ Episcleral implant.
3. **Drug delivery to posterior segment;** Intravitreal implants, Injectable Particulate Systems
4. **Vesicular system;** Liposomes, Niosomes.
5. **Controlled delivery system;** Phase transition systems Contact lens, Collagen shield, Microemulsion, Nanosuspensions, Microneedle.
6. **Particulates;** Nanoparticles, Microparticles.

**Classification of In-Situ Gelling Polymers;** Polymers used for formulating in situ gelling systems can be classified on the basis of their origin or mechanism of gelation. According to their origin, in situ gelling systems can be divided into two types;

1. **Natural:** chitosan, alginate, xyloglucan, gellan gum, sodium hyaluronate, pectin.
2. **Synthetic/semi synthetic:** hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), cellulose acetate.

**Ocular absorption of the drug;** very common method to ocular drug delivery system is topical administration of ophthalmic dosage formulation drops into the lower

cul-de-sac [11]. Eye drops overflow quickly due to the eye blinking reflex, and the precorneal region returns to maintain resident volume of around 7 $\mu$ l [5]. The human conjunctiva shows 2-30 times more permeable for drugs than cornea and also loss of drug by route is a major path for drug clearance are used.

**Ocular Sustained Drug Delivery Systems:** In the novel drug delivery system various approaches like, use of mucoadhesive polymers, polymer coated Nanoparticles and Liposomal formulations These delivery systems delay the elimination of active ingredient from eye and also improve corneal penetration of drug molecule.

I. **Liposomes:** Liposomes are biocompatible and biodegradable. lipid vesicles made up of natural lipids and about 25–10 000 nm in diameter<sup>7</sup>. Desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility and thus increases the probability of ocular drug absorption. Evaluated soft contact lenses coated with ciprofloxacin entrapped in liposomes.

II. **Niosomes:** Niosomes are non-ionic surfactant vesicles that have potential applications in the delivery of hydrophobic or amphiphilic drugs. Niosomes are developed as they are chemically stable as compared to liposomes.

III. **Implants:** For chronic ocular diseases like cytomegalovirus (CMV) retinitis, implants are effective drug delivery system. Earlier non-bio degradable polymers were used but they needed surgical procedures for insertion and removal<sup>6</sup>. Presently biodegradable polymers such as Poly Lactic Acid (PLA) are safe and effective to deliver drugs in the vitreous cavity and show no toxic signs.

IV. **Dendrimers:** Dendrimers are large and complex molecules with well-defined chemical structure. Dendrimers can successfully use for different routes of drug administration and have reported to have better watersolubility, bioavailability and biocompatibility. The residence time was longer for the solutions containing dendrimers.

V. **Micro emulsion:** Micro emulsion is dispersion of water and oil stabilized using surfactant and co-surfactant to reduce interfacial tension and usually characterized by small droplet size<sup>100</sup> nm, higher thermodynamic stability and clear appearance. Optimization of these components results in significant improvement in solubility of the drug molecule e.g. Indomethacin, Chloramphenicol for eye diseases.

VI. **Nanosuspensions:** Nanosuspensions have emerged as the efficient delivery of hydrophobic drugs because they enhanced not only the rate and extent of ophthalmic drug absorption but also the intensity of drug action with significant extended duration of drug effect. For commercial preparation of nano suspensions, techniques like media milling and high-pressure homogenization have been used.

**MECHANISM OF INSITU GELS;** the mechanism of in situ gels is based on following

Mechanisms: Based on physical mechanism,

1. **Swelling:** In this method of In situ gel formation material absorbs water from surrounding environment and expand to desired space<sup>4</sup>. For example glycerol mono- oleate, which is polar lipid swells in water to form lyotropic liquid crystalline phase structures. It has some bioadhesive properties and can be degraded in vivo by enzymatic action
2. **Diffusion:** This method involves the diffusion of solvent from polymer solution into surrounding tissue which results in precipitation or solidification of polymer matrix. N- methyl pyrrolidone (NMP) has been shown to be useful solvent for such system.
3. Based on chemical reaction mechanism Chemical reactions that results in situ gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes.

**Routes of ocular drug administration;**

1. **Topical administration;** Most commonly used routes for treatment of anterior segment complications.
2. **Intra-vitreal administration;** Recent advancement in surgical procedures, larger retention time and higher vitreous concentration of drug<sup>3</sup>. Patient noncompliance, pain and discomfort are major obstacles to clinical application. Removal of implants requires a skillful surgical procedure.
3. **Scleral administration;** Due to large surface area. Recently it become a potential vector for posterior segment drug delivery. It has different ways scleral plugs, implants.
4. **Systemic administration;** Due to presence of blood retinal barrier it has limited success to delivery the drug vitreo-renal tissue.

**Advantages of in-situ gels;**

1. Prolonged drug release.
2. Less blurred vision as compared to ointment.

3. Improved local bioavailability due to increased precorneal residence time and absorption.
4. Easy administration.
5. Due to increased residence time frequent instillation is not required.

#### Evaluation parameters;

1. **Texture analysis;** Firmness, consistency and cohesiveness of in-situ gel is determined by using texture profile analyzer which indicates gel strength and ease of application.
2. **sol-gel transition temperature and gelling time;** This evaluation test is carried out for the formulations which are formulated by using thermo sensitive polymer [7]. Gelling time can be defined as time required for first detection of gelation as mentioned above.
3. **Gel strength;** Evaluation of gel strength rheometer is used. The changes in load from gel to empty space can be measured as a function of depth of immersion of probe below the gel surface [10]. On male albino rabbits. The formulation is placed in lower cul-de-sac and irritancy is tested at time interval of 1hr, 2hr, 48hr, 72hr, and 1 week after administration.
4. **Gelling capacity;** the in situ gel is mixed with simulated tear fluid. Gelation is assessed visually by noting time taken for gelation.
5. **Evaluation;** Ophthalmic preparations isotonicity is maintained prevent tissue damage or irritation of eye. The formulation is mixed with few drops of blood & observed under microscope at 45x magnification and compared with standard marketing formulations.
6. **Texture analysis;** Texture profile analyzer the consistency, firmness and cohesiveness of in situ gel can be analyzed. These studies may indicate gel strength and ease in administration.

#### Conclusion

This review we gave introduction to ophthalmic in situ gels. The various type of polymers which used for gelling are seen. The sol is converted into the gel by various situations. The ocular drug absorption is by corneal or noncorneal permeation. The various types of drug releases, different kinds of administration of drug, evaluation parameters, and advantages are also covered in this review.

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