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# A REVIEW ON OCULAR IN SITU GEL

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**ABSTRACT:** Ophthalmic drug delivery presents major challenges for pharmaceutical and medicinal sciences. New ocular drug delivery forms are various; they included in situ gelling systems, liposome's, nanoparticles, noisome, nanoemulsions and microemulsions. They are suitable for hydrophilic or lipophilic drugs, have the capacity of targeting a specific site and can be administrated in different routes. With the appropriate excipients, in situ gelling systems are able to increase the precorneal residence time and decrease the loss of drug due to the tear. In situ gelling system is a formulation that is in solution form before entering in to the body, but it will change to gel form under various physiological conditions. The sol to gel transition depends on various factors like temperature, change in pH, solvent exchange, UV radiation, and presence of specific molecules or ions. Pectin, gellan gum, chitosan, alginic aicd, guar gum, carbopal, xyloglucan, xantham gum, HPMC, poloxamer etc are some of natural polymers used for in situ gelling system. This review on ocular in situ gel to enhance the bioavailablity of cyclosporine, prolonged retention time of drug, using various polymers for eyes remain moist for longer time, evaluation.

**KEYWORDS:** Novel ocular drug delivery system, Insitu gels, sustain release of drug, Dry eyes.

1. **Introduction:** The delivery of drug to the posterior segment of the eye for glaucoma, endophthalmitis or uveitis and to the anterior segment has the same issue of poor bioavailability of the drug and barriers. However, intraocular administration might be preferred despite its risk of complication. In addition, compared to the oral route, ocular drug delivery provided equivalent or better bioavailability in the eye. Approaches have been made for the improvement of the bioavailability of the drug, the controlled release and the improvement of the therapeutic effect. The antimicrobial resistance is the ability of bacteria to resist to the effect of an antibiotic administration. This limitation of efficacy is caused by the misuse of antibiotic, the overuse of this group of medicine and the adaptation of the bacteria to the effect. In fact, ophthalmic antibiotic delivery aims to decrease the frequency of administration and dosing by improving the current forms and developing new ones.

 

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New Optical medicine delivery forms are colorful; they included in situ gelling systems, liposome's, nanoparticles, noisome, nanoemulsions and microemulsions. They're suitable for hydrophilic orlipophilic medicines, have the capacity of targeting a specific point and can be conducted in different routes. With the applicable excipients, in situ gelling systems are suitable to increase the precorneal hearthstone time and drop the loss of medicine due to the gash. Different polymers, styles of medication and compositions allow the nanoparticles to respond to a need for mucoadhesion, topical, periocular or intraocular administration, and to gain a stable, effective and non-irritating expression for the case.[1]

## ➢ Advantages of a Ophthalmic Drug Delivery System

- They are easily administered by the nurse.
- They are easily administered by the patient himself.
- They have the quick absorption and effects.
- Increased shelf life.
- Better patient compliance.

## ➢ Disadvantages of a Ophthalmic Drug Delivery System

- The very short time the solution stays at the eye surface.
- It's poor Bioavailability.
- The instability of the dissolved drug.
- The necessity of using preservative.

## ➢ Mechanism Of Ocular Drug Absorption

- Drugs administered by instillation must penetrate the eye and do so primarily through the cornea followed by the non-corneal routes. These non-corneal routes involve drug diffusion across the conjunctiva and sclera and appear to be particularly important for drugs that are poorly absorbed across the cornea.

## ➢ Corneal permeation

- The permeation of drugs across the corneal membrane occurs from the precorneal space.

 

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## ➢ Non-corneal permeation

- Primary mechanism of drug permeation is 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. Although like cornea, the conjunctiva is composed of an epithelial layer covering an underlying stroma, the conjunctival epithelium offers substantially less resistance than does the corneal epithelium.

## ➢ Dry Eyes Syndrome

- Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. In Situ Gel The in situ gel' system has emerged as one of the best novel drug delivery systems, the in situ gelling system helps for the sustained and controlled release of the drugs, improved patient compliance and comfort by its special characteristic feature of 'Sol to Gel' transition. In situ gelling system is a formulation that is in solution form before entering in to the body, but it will change to gel form under various physiological conditions. The sol to gel transition depends on various factors like temperature, change in pH, solvent exchange, UV radiation, and presence of specific molecules or ions. The drug delivery systems having the above mentioned properties 'sol to gel transition' can be widely used for sustained delivery vehicle preparation of bioactive molecules. There are several advantages in 'in situ gelling system' which includes ease of application of dosage, reduced frequency of administration and even protection of drug from change in environmental conditions. Various natural and synthetic polymers undergo in situ gel forming and potentially can be used for oral, ocular, transdermal, buccal, intraperitonial, parenteral, injectable, rectal and vaginal routes. Recent advances in in situ gels have made it possible to exploit the changes in physiological uniqueness in different regions of the Gastrointestinal tract for improved drug absorption as well as patient's convenience and compliance. Pectin, gellan gum, chitosan, alginic acid, guar gum, carbopal, xyloglucan, xantham gum, HPMC, poloxamer etc are some of natural polymers used for in situ gelling system. There are several applications and advantages of in situ gelling system in today's life. This review

 

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mainly focus on introduction to in situ gel, its mechanism, various polymers used and its applications.[2,3]

## ➢ Importance of in situ gelling system

- ➢ It helps for the controlled and sustained release of the drug by its special 'Sol Gel transition.
- ➢ It helps for the reduced frequency of drug administration of the drug in the body.
- ➢ Low dose of the drug is required and there will be no drug accumulation and no side effects.
- ➢ The bioavailability of the drug will be more.
- ➢ There will be increased residence time of the drug due to gel formation.
- ➢ The in situ gel system decreases wastage of the drug.
- ➢ Liquid dosage form that can sustain drug release & remain in contact with cornea of eye for extended period of time is ideal.
- ➢ Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effect.

## ➢ Advantages of in situ gel system

- Controlled and sustained release of the drug.
- Ease of the drug administration.
- It can be administered to unconscious patients.
- More patient compliance and comfort.
- Minimizing the dose frequency and drug toxicity.
- Increased bioavailability.
- Use of natural polymers provide biocompatibility and biodegradation.

**2. POLYMERS USED IN FORMULATION OF IN SITU GEL:** An essential ingredient in the manufacture of any gel is a polymer. Some of the relevant polymer characteristics for in situ gels given below.

- The polymer should be capable of adhering to the mucous membrane.
- It should be well compatible and should not provide any toxic effects
- It should influence the tear
- Good tolerance and optical clarity is more preferred.

 

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- Preferred pseudo plastic behavior of polymer.
- The polymer should be capable of decreasing the viscosity with increase in shear rate.
- It should have pseudo plastic behavior.[4]

➢ **Classification of in situ gel polymers:** Based on their origin, polymers are classified or the mechanism of gelation. According to a source in situ, gelling systems classified into two types.

- **Natural polymers** (E. g., Alginic acid, Carrageenan, chitosan, Guar gum, gellan gum, pectin, sodium hyaluronate, xanthan gum, xyloglucan, etc.)
- **Synthetic or semi-synthetic polymers** (E. g., Cellulose acetate phthalate, hydroxypropyl methylcellulose, methylcellulose, polyacrylic acid, poly (lactic-co-glycolic acid, poloxamers).

➢ **Natural polymers**[5]

- **Alginic acid or sodium alginate** A biodegradable, hydrophilic, non-toxic, linear block copolymer polysaccharide consists of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic linkages. It is used as a vehicle for ophthalmic formulations. Alginate transforms into a stable gel upon exposure to divalent cations (Ca+2, Mg+2) by cross-linking the carboxylate groups, which is not easily eroded by tear fluid.
- **Carrageenan** It is used as a home remedy to cure a cold and cough as gelatine. Depending on the sulfate group number and position classified into three types:
  **a.** Iota carrageenan: It forms an elastic gel in the presence of calcium or potassium ions and completely soluble in hot water.
  **b.** Kappa carrageenan: It forms a 'gel' in the presence of potassium ions and shows similar properties of locust bean gum, like soluble in hot water.
  **c.** Lambda carrageenan: It does not induce gel formation, but it forms highly viscous solutions and is completely soluble in cold water.
- **Chitosan** It is a biodegradable, biocompatible, thermosensitive, pH-dependent, cationic, amino polysaccharide obtained by alkaline deacetylation of chitin. Gelling of chitosan occurs by pH and temperature changes. It has excellent mucoadhesive properties due to the electrostatic interaction between positively charged chitosan and negatively charged mucosal surfaces. At low critical solution temperatures due to extreme hydrophobic interactions, gels formed with electrostatic forces. At upper critical solution temperature, exhibiting polymers are used for the gelation process of chitosan. Due to availability,

 

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non-toxic, inexpensive, etc., this is the second most abundant polysaccharide using after cellulose[6].

- **Guar gum or guaran** It is soluble in water but insoluble in hydrocarbons, fats, ester, alcohols, and ketones. It shows better dispersibility and forms high viscous colloidal solutions with hot and cold water with small amounts. Temperature changes cause a reversible shift in gel formation.
- **Gellan gum** It is commercially known as Gelrite or Kelcogel, and it is a linear, water-soluble, temperature-dependent, extracellular, hetero, anionic polysaccharide; like alginate, this gellan gum form gel in the presence of metal cations (mono or divalent). Monovalent cations such as Na+or K+and divalent cations such as Ca+2 or Mg+2 inducecross-linking gelation. The gelation includes the formation of double-helical junction zones followed by aggregation of the double-helical segment to form 3-D networks by complexation with cations and hydrogen bonding with water. In the preparation of in situ gels, it is one of the most commonly used polymers.
- **Pectin** A family of cationic, linear polysaccharides comprises α-(1, 4)-D galacturonic acid residues. In the presence of H+ions, the gelation of pectin will occur, a source of mono, divalent, and trivalent ions. It is only applicable to water-soluble formulations and not for the organic solvents. Monovalent cations (alkali metal) salts of pectin and pectic acids are soluble in water. But di and trivalent cationic salts are weakly soluble or insoluble in water. When the addition of water to dry powdered pectin, clumps (i.e., semi-dry packets) formed due to its tendency to hydrate and solubilization of cluster's done by mixing with water-soluble carrier. The degree of methylation (DM), defined as the percentage of carbonyl groups esterified with methanol. Based on the degree of esterification, pectins classified into two categories[7].
  **a)** Low methoxy pectins; less than 50% of the carboxyl groups methylate the pectins.
  **b)** High methoxy pectins; more than 50% of the carboxyl groups methylate the pectins.
- **Xyloglucan or tamarind gum** Xyloglucan is an abundant, hemicellulosic polysaccharide due to the non-toxic, biocompatible, and biodegradable nature, potentially using in several delivery systems. It is partially degraded by β-galactosidase and undergoes gelation by the thermoresponsive process. When used in oral delivery shows gelation time up to minutes and allows gelation in the stomach in chilled condition. Like, poloxamer it exhibits gelation on heating/refrigerator temperature or cooling from higher heat. Xyloglucan has the gelling ability in the presence of sugars (40-65%) or alcohols over a wide pH range. Still, in the combination (20% alcohols), the sugars are substantially reduced to form a gel [66-68]. Thiolated chitosan or thiomers Nowadays, thiol groups exhibit much higher adhesive (mucoadhesive) properties than other polymers. Thiomers interact cysteine-rich sub-domains or mucus glycoproteins via cross-linking intra-and inter-disulfide bonds by the simple oxidation process that leads to gel

 

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formation reaching the physiological . These are the most promising multi-functional, cationic, hydrophilic macromolecules, and they also act as permeation enhancers than chitosans. It has positive charges which interact with the cell membranes causing a structural reorganization of tight junction-associated proteins. Apart from this, it also exhibits a robust, cohesive nature. [8]

- **Xanthan gum Xanthan** gum shows good stability at both acidic and alkali conditions and soluble in cold and hot water. It exhibits anionic nature due to the presence of both glucuronic and pyruvic acid groups.

## ➢ Synthetic or semi-synthetic polymers[9]

- **Cellulose acetate phthalate (CAP)** CAP also knows as pseudo latex. It is artificial latex, prepared in an aqueous medium by dispersion of a pre-existing polymer. It is pH sensitive, cross-linked polyacrylic polymers with potentially useful properties for sustained drug delivery to the eye because latex is a free-running solution at a pH of 4.4, which undergoes coagulation tear fluid, raises the pH to pH 7.4. CAP is used to monitor the ocular residence time of an ophthalmic preparation in γ-scintigraphy, and the production doesn't require the use of organic solvents.
- **Hydroxypropyl methylcellulose (HPMC)** This is a biocompatible, thermoreversible, mucoadhesive polymer. It is a type of cellulose ether due to high swellability, thermal gelation properties, and used as hydrophilic matrices and used for oral drug delivery systems. HPMC used in combination with carbopol, enhancing the solution's viscosity while reducing the solution's acidity. HPMC goes for gelation at higher temperatures due to the interaction between hydrophobic components of the polymer. It was playing an active role in aqueous solution formation for topical treatment of the eye. It proved to be essential to formulate vaginal mucoadhesive film with CR of S-nitroso glutathione and effects on the gelling behavior. [11]
- **Methylcellulose (MC)** It is also a cellulose derivative, used as in situ gelling polymer. Several cellulose derivatives stay on liquid at low temperatures and become gel upon heating. For example, MC and HPMC's aqueous solution undergoes a phase transition into gels between 40-50 °C and 75-90 °C, respectively. However, MC and HPMC's phase transition temperature is higher than the physiological temperature but lowered by making chemical and physical changes in the polymers. Hydrophobic interaction among molecules with methoxy groups causes gelation of HPMC and MC solutions. Polymer-polymer contact occurs between macromolecules due to hydration at a lesser temperature. The hydration is lost gradually on increasing the heat consequential in lower viscosity. At the transition where enough dehydration of the polymers takes place, they start associating, and the thickness starts rising, showing a network structure formation. At

 

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low temperature (30 °C) solution is in liquid form, and when the temperature increased (40-50 °C) and gelation occurred.[12]

- **Polyacrylic acid (PAA)** PAA is commercially known to be carbopol. It is widely used in ophthalmology for enhancing pre-corneal retention. It can exhibit excellent mucoadhesive properties to compare with other cellulose derivatives. Comparing different grads such as carbopol 910, 934, 940, 941, etc. concluded that 940 showed superior one [13].
- **Poly (lactic-co-glycolic acid) or PLGA** It is a biocompatible and biodegradable polymer. It is a synthetic copolymer of polylactic acid (PLA) and polyglycolic acid (PGA). These systems are applied to controlled drug delivery and are available as implants, microparticles, and in situ implants in the market. PLGA is one of the most capable polymers used to fabricate drug delivery and tissue engineering applications because of its long clinical experience.[14]
- **Poloxamers:** Poloxamers are commercially known as pluronic and used in thermosensitive in situ gels. It has excellent thermal setting properties and increases drug residence time. It is a water-soluble tri-block copolymer and consists of two polyethylene oxide (PEO) and polypropylene oxide (PPO). Pluronic F127 is the most commonly used poloxamer polymer in pharmaceuticals due to its colorless and transparent gels forming character. It consists of PEO (70%) and PPO (30%). A copolymer pluronic F127-g-poly (acrylic acid) was used as in situ gelling vehicles to prolong the residence time and better bioavailability of the ocular drugs.
- **Poloxamines** Poloxamines are commonly known as tetronics. These are biocompatible, tetra functional block copolymers of ethylene and propylene oxide. Four arms of PEO-PPO form X-shaped poloxamines, linked by an ethylenediamine group, and seem crucial for the osteoinductive capability of tetronics. It exploited until now for rendering temperature and pH-responsive micelles and gels dually. There is no other polymer reported to be osteoinductive itself. Hydrophilic one is more cytocompatible than hydrophobic and shows better compatibility as their molecular weight increases.
- **Poly (N-isopropyl acrylamide) or PNIPAAm** It is a thermosensitive polymer with a reversible phase transition at 32-35 °C; it is closer to the human body temperature reach therapeutic targets.

## 3. METHOD OF PREPARATION OF IN SITU GEL:[15]

- **Temperature induced in situ gel system**

  Some polymers and hydrogels are temperature responsive will transform from sol to gel is inducedby increase in temperature. The body temperature is sufficient to trigger sol to gel conversion noexternal temperature is required to trigger sol to gel conversion. The system which is set shouldtolerate small changes in temperature. Temperature sensitive

 

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hydrogels are classified in threecategories negatively thermo sensitive, positively thermo sensitive and thermally reversible gels.Some hydrogels are negative temperature sensitive (Insoluble upon heating) and they have lower critical solution temperature and if heated at above lower critical solution temperature it willcontract. Gelling of these solutions is enhanced by change in temperature which will furthersustain the drug release. Due to change in temperature there is change in hydration state which willcause volume phase transition where intra and intermolecular hydrogen bonding of the polymer molecule favored compared to solualisation by water. This condition can be achieved by usingdrug polymer which is in solution form at room temperature and transform into gel at bodytemperature. Some polymers are soluble upon heating known as upper critical solutiontemperature. The change in hydration state causes volume phase transition which leads to inter andintra molecular hydrogen bonding of polymer which leads insolubility of that compound e.g poloxamer- it is a thermosetting polymer, when concentration of poloxamer is increased the contact time and elasticity of the drug is increased and sol to gel conversion is decreased.

- **pH induced in situ gel systems**

  In this case transition of sol to gel triggered by change in pH. The polymers which shows Ph dependent transition and has acidic or basic groups which upon change of pH either accept or release proton. Weakly acidic (anionic) group shows swelling with reference to increase in pH where as weakly basic (cationic) groups at decreased pH14 .The anionic pH sensitive polymers e.g carbopol, carbomer and its derivatives. At pH 4.4 the formulation is in solution form but when it is instilled in eye its pH is changes from 4.4 to 7.4 due to change in pH the formulation is from sol to gel. e.g cross-linked polyacrylic, derivatives of carbomer etc.

- **In situ formation based on physical mechanism[16]**

**a)Swelling**

In situ conversion of sol to gel some time may also occur when material absorb water on the surface from surrounding and expand to get desired space. e.g myverol 18-99, it is polar lipid which form pyotropic liquid crystalline structure after swelling in water.

**b) Diffusion**

In the method of diffusion the solvent is diffused from polymer solution in to the surrounding tissue which leads to precipitation or solidification of polymer matrix. e.g N methyl pyrolidone used as solvent for such system.

**c) In situ formation based on chemical reaction**

The chemical reactions which include in gelation may involve precipitation of in organic solids from supersaturated ionic solutions, enzymatic process and photo initiated processes.

 

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### d) Ion induced In situ gel systems

Sometimes polymers may convert from sol to gel in presence of various ions. Some polysaccharides come under ion sensitive polymers. It is assumed that the rate of gelation is depend on osmotic gradient across gel surface. The osmolality of the solution may influence the sol to gel transition in eye. In tear fluid generally mono or divalent cations are present which form clear gel of aqueous polymer solution8. Gellan gum is an anionic polysaccharide that undergoes gelling in presence of mono and divalent cation. The Na,Ca,Mg ions which are present in the tear fluid generally initiate the sol to gel transition. In presence of divalent cation(Ca) alginic acid undergo gelation.

## 4. EVALUATIONS OF INSITU GEL SYSTEM[17]

Evaluation parameters for insitu gel formulations includes 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 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** Physical parameters to be tested for insitu gel solution are clarity, pH, gelling capacity, and drug content estimation.
- **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 observe.
- **Rheological studies** The viscosity measurements can be calculated using Brookfield viscometer, Cone and Plate viscometer. In-situ gel formulation is placed in sample tube. Formulation should have viscosity of 5-1000 m Pas, before gelling & after formation of gel should have viscosity from about 50-50,000 m Pas.
- **In vitro drug release studies** In vitro release study of insitu gel solution is carried out by using Franz diffusion cell. The best fit model is check for Krosmeyers Peppas and Fickinian diffusion mechanism for their kinetics.
- **Texture analysis** The consistency, firmness and cohesiveness of insitu 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. [18]
- **Isotonicity evaluation** Isotonicity is important characteristic of the ophthalmic preparations. Isotonicity has to be maintained to prevent tissue damage or irritation of

 

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eye. All ophthalmic preparations are subjected to isotonicity testing, since they exhibited good release characteristics and gelling capacity and the requisite viscosity.

- **Drug-polymer interaction study and thermal analysis** Interaction study should 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 thermo grams as compared with pure active ingredients used for gelation.
- **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.[19]
- **Ocular irritancy test** The Draize irritancy test should 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 placed into the lower culdesac 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 [20].

## 5. CONCLUSION:

Development of ophthalmic drug delivery system has proved to be beneficial as compared to the conventional drug delivery. Likewise it is also challenging enough to establish successful ophthalmic drug delivery systems. However, the persistent attempts towards advancement the understanding of principles and processes governing ocular drug absorption and disposition have led to the improvements in the efficacy of ophthalmic delivery systems. The use of biocompatible, biodegradable, and water-soluble polymers for the in situ gel formulation can make excellent and excellent drug delivery systems. In recent years, researchers have drawn interest, providing a lot of scope to advanced drug delivery techniques. One such novel approach is development of in-situ ocular gels. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the in situ gel dosage forms very reliable. The evaluation of in-situ gels can be carried out based on the parameters like gelling capacity, rheological studies, in-vitro drug release studies, drug-polymer interaction study, thermal analysis, antibacterial activity and ocular irritancy test.

 

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Impact Factor: 5.721

# REFERENCES

**[1].** Pignatello R; Flurbiprofen-loaded acrylate polymer nano suspensions for ophthalmic application; Biomaterials; 2002; 23: 3247- 3255.

**[2].** Wen-Di Ma, Hui Xu, Chao Wang, Shu-Fang Nie, Wei-San Pan; Pluronic F127-gpoly (acrylic acid) copolymers as in situ gelling vehicle for ophthalmic drug delivery system, International Journal of Pharmaceutics; 2008; 350: 247-256.

**[3].** Kaur P, Garg T, Rath G, Goyal AK. In situ nasal gel drug delivery: A novel approach for brain targeting through the mucosal membrane. Artif Cells Nanomed Biotechnol 2016;44:1167-76.

**[4].** Hsiue GH, Chang RW, Wang CH, Lee SH. Development of in situ thermosensitive drug vehicles for glaucoma therapy. Biomaterials 2003;24:2423-30.

**[5].** Madan M, Bajaj A, Lewis S, Udupa N, Baig JA. In situ forming polymeric drug delivery systems. Indian J Pharm Sci 2009;71:242-51.

**[6].** Kute JU, Darekar AB, Saudagar RB. A review: an in-situ gel-novel approach for nasal delivery. World J Pharm Pharm Sci 2013;3:187-203.

**[7].** Ravindra Reddy K, Ravi Shankar Yadav M, Sabitha Reddy P; Preparation and evaluation of Aceclofenac ophthalmic In situ gels; Journal of Chemical, Biological and Physical Sciences. 2011; 1(2): 289-298.

**[8].** Katariya dhirajkumar champalal, Poddar Sushilkumar S; Current status of ophthalmic insitu forming hydrogel. International Journal of Pharma and Bio Sciences. 2012; 3(3): 372- 388.

**[9].** Gariepy ER, Leroux GC; In situ-forming hydrogels-review of temperature sensitive systems; European Journal of Pharmaceutics and Bio pharmaceutics; 2004; 58: 409–426. 18. Masteikova R, Chalupova Z, Sklubalova Z; Stimuli-sensitive hydrogels in controlled and sustained drug delivery; Medicina; 2003; 39:

**[10].** Harish NM, Prabhu P, Charyulu RN, Gulzar MA, Subrahmanyam EV. Formulation and evaluation of in situ gels containing clotrimazole for oral candidiasis. Indian J Pharm Sci 2009;71:421-7.

**[11].** Khan S, Patil K, Bobade N, Yeole P, Gaikwad R. Formulation of intranasal mucoadhesive temperature-mediated in situ gel containing ropinirole and evaluation of brain targeting efficiency in rats. J Drug Target 2010;18:223-34.

**[12].** Saini R, Saini S, Singh G, Banerjee A, Railmajra DS. In situ gels-a new trends in ophthalmic drug delivery systems. Int J Pharm Sci Res 2015;6:386-90.

**[13].** Tao T, Zhao Y, Yue P, Dong WX, Chen QH. Preparation of huperzine A nasal in situ gel and evaluation of its brain targeting following intranasal administration. Acta Pharm Sin. 2006;41:1104–1110.

**[14].** Srividya B, Cardoza RM, Amin PD. Sustained ophthalmic delivery of ofloxacin from a pH triggered in situ gelling system. J Control Release. 2001;69:379–88.

**[15].** Vijaya C., Goud K.S. Ion-activated in situ gelling ophthalmic delivery systems of azithromycin. Indian J. Pharm. Sci. 2011;73(6):615–620.

**[16].** Johan C, Katarina E, Roger P, Katarina J. Rheological evaluation of gelrite in situ gel for opthalmic use. Eur J Pharm Sci. 1998;6:113–6

**[17].** Tinu TS, Litha T, Kumar Anil B. Polymers used in ophthalmic in situ gelling system. Int J Pharm Sci Rev Res 2013;20:176-83.

 

ISSN: 2519-9889
Impact Factor: 5.721

**[18].** Rajoria G, Gupta A. In-situ gelling system: a novel approach for ocular drug delivery. Am J PharmTech Res 2012;2:24-53

**[19].** Chang C, Zhang L. Cellulose-based hydrogels: present status and application prospects. Carbohydr Polym 2011;84:40-53.

**[20].** Maheswaran A, Padmavathy J, Nandhini V, Saravanan D, Angel P. Formulation and evaluation of floating oral in situ gel of diltiazem hydrochloride. Int J Appl Pharm 2017;9:50-3.

 