A REVIEW: IN-SITU GEL FOR OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT:

Ophthalmic In-situ gels are viscous polymer-based liquids that exhibit sol-to-gel phase transition on the ocular surface due to change in a specific physicochemical parameter like ionic strength, pH ortemperature Gel dosage forms are successfully used as drug delivery systems considering their ability toprolong the drug release. Intensive research is being conducted to significantly improve the efficacy, reliability, and safety of medicines. This interest was evoked by the benefits exhibited by the in-situ formed polymer delivery system such as improved patient compliance, ease of administration, and reduced frequency of administration. This review mainly focuses on introduction to in situ-gel, its advantages, its mechanism, various Temperature advancements triggered the in- situ gel system, Improvement in the pH triggered the in-situ gel system, In-situ formation based on chemical reactions. polymers Research has been conducted in the area of in –situ gel for the administration of eye medication.

KEYWORDS: In-Situ Gel, Drug Delivery System, Polymer, Ph, Eye.

INTRODUCTION:

The "in-situ gel" system has emerged as one of the best new drug delivery systems. The in-situ gelling system helps to improve the sustained and controlled release of the drug, patient compliance, and comfort due to the special features of the "Sol to Gel" transition (1). An in-situ gelling system is a formulation that is in the form of a solution before it enters the body, but it transforms into a gel under one or combinations of a variety of physiological conditions. The sol-to-gel transition depends on a variety of factors, including temperature, pH changes, solvent exchange, UV radiation, and the presence of specific molecules or ions (2). Drug delivery systems with the above "sol-to-gel" properties can be widely used in the preparation of sustained delivery vehicles for bioactive molecules.

The "in-situ gelling system" has several advantages, including ease of dose administration, reduced dosing frequency, and protection of the drug from changing environmental conditions.(3)

The ocular drug delivery system is considered as crucial and challenging as human eye is an isolated organ where the delivery of drug is quite difficult. Moreover, the conventional ophthalmic formulations exhibit a short pre-corneal residence time and poor bioavailability due to rapid and extensive elimination of drugs from pre-corneal lachrymal fluid by solution drainage, lachrymation, and non-productive absorption by conjunctiva (4). In order to supress the drawbacks associated with the conventional ophthalmic formulations, various attempts have been made towards the development of stable sustained release in-situ gels. Newer research in ophthalmic drug delivery systems is directed towards incorporation of several drug delivery technologies, that includes to build up systems which not only extend the contact time of the vehicle at the ocular surface, but which at the same time reducing the elimination of the drug. In-situ gel system is formulated as liquid preparation suitable to be instilled into eyes which upon exposure to the

physiologic environment changes to gel, thus increasing the precorneal residence time of the delivery system, and enhances the ocular bioavailability of the drug.(5)

Topical application of drugs to the eye is the well established route of administration for the treatment of various ocular diseases like dryness, conjunctivitis, keratitis, eye flu etc. New approaches have been investigated for delivery of drugs to the eye by making use of polymers that pays a key role in delivery of drugs to the pre and intra ocular tissue.(6)Such persistent attempts have resulted into achieving the increase in bioavailability and extending the duration of therapeutic action of ocular drug. Smart polymeric systems have proved to be promising means of delivering the drugs. These polymers undergo sol-gel transition after administered. They are in solution phase before administration.

The ocular bioavailability of the drugs can be improved by prolonging their residence time in thecul-de-sac and by increasing their corneal permeability.(7)

- **Importance of in-situ gelling system**: (8,9)

1) In-situ gel helps for the controlled and sustained release of the drugs by its,Sol-Gel transition.

2) It helps in reducing frequency of drug administration in the body.

3) Low doses of the drugs are required and there will be no drug accumulation and side effects.

4) It increases bioavailability of drugs.

5) Residence time of drug will be increased due to gel formation.

- **IN SITU FORMING GELS**:(10)

The progress has been made in gel technology for the development of droppable gel. They are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form visco-elastic gel and this provides a response to environmental changes. Three methods have been employed to cause phase transition in the eye surface. These are change in pH, change in temperature and ion activation.

- pH:(11)

In this method, gelling of the solution is triggered by a change in pH. CAP latex cross linked polyacrylic acid and its derivatives such as carbomers are used. They are low viscosity polymeric dispersion in water which undergoes spontaneous coagulation and gelation after instillation in the conjunctival cul-de-sac.

- TEMPERATURE:(11)

In this method gelling of the solution is triggered by change in the temperature. Sustained drug delivery can be achieved by the use of a polymer that changes from solution to gel at the temperature of the eye. But disadvantage of this is characterized by very high polymer concentration 21. Methyl cellulose and smart hydrogels are the examples.

- IONIC STRENGTH:(11)

In this method, gelling of the solution instilled is triggered by change in the ionic strength. For example, low acetyl gellan gum, which forms a clear gel in the presence of mono or divalent cations. The concentration of sodium in human tears is 2.6 g/l is particularly suitable to cause

gelation of the material when topically installed into the conjunctival sac.

- **ADVANTAGES OF IN-SITU OCULAR DRUG DELIVERY SYSTEMS**:(10)

1. Increased accurate dosing. To overcome the side effects of pulsed dosing produced byconventional systems.

2. To provide sustained and controlled drug delivery.

3. To increase the ocular bioavailability of drug by increasing the corneal contact time. This canbe achieved by effective adherence to corneal surface.

4. To provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.

5. To circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.

6. To provide comfort, better compliance to the patient and to improve therapeutic performanceof drug.

7. To provide better housing of delivery system.

- **In-situ formation based on physiological stimuli:**

- **Thermally trigged system**:

Temperature-sensitive hydrogels are probably the most commonly studied class of environment-sensitive polymer systems in drug formulation development. The use of polymers, where the transition from sol-gel is caused by increased temperature, is an attractive way to approach in-situ formation. The ideal critical temperature range for such systems is ambient and physiological temperatures, facilitating clinical manipulation and requiring no external heat source other than the body to gel the trigger. The useful system must be adjustable to account for small differences in local temperature that may be encountered on the surface of the skin or the appendages in the oral cavity.(11)

There are three main strategies for the formation of temperature-responsive sol-gel polymer systems. For convenience, temperature-sensitive hydrogels are classified into negative heat-sensitive, positive heat-sensitive, and heat-reversible gels (1,3). Negative temperature sensitive hydrogels have a low critical solution temperature (LCST) and shrink when heated above the LCST. Polymers with a low critical temperature (LCST) transition between ambient and physiological temperatures are used for this purpose. One of the most widely studied polymers showing useful LCST transitions is poly N-isopropyl acrylamide (12). Positive temperature-sensitive hydrogels have an upper critical solution temperature (UCST) and such hydrogels shrink when cooled below UCST. The polymer network of polyacrylic acid (PAA) and polyacrylamide (PAAm) has a positive temperature dependence of swelling (13,14). These polymers exhibit miscibility gaps at high or low temperatures and have upper or lower critical solution temperatures.(15)

- **Temperature advancements triggered the in-situ gel system**:

Numerous studies have been carried out combining certain polymers with other polymers.Several illustration of the polymers used in tests of the in-situ gelling systems.

After being tested in vivo on rabbits 20% (w/w),ofloxacin was used as model medication with the polymers (Pluronic PF -127 and PF-68) in combination with Sodium Alginate F127 Plurionic Ketorolac ocular bioavailability improved when it is combination with the two polymers Pluronic F-127 and HPMC K4M.

Brinzolamide is resin based, in-situ thermosensitive gelling method created by Liet al employing Polymer Poloxamer F127.

For the administration of ocular drug, Poly (N isopropyl acrylamide) Chitosan serves as athermosensitive in situ gel forming system.

These studies are conducted in order to advance and improve the in-situ gelling technology usedin ocular drug administration. (16)

- **pH triggered systems**:

In these systems solution to gel transition is triggered by pH change. All pH-sensitive polymers contain additional acidic or basic groups that accept or release protons in response to changes in environmental pH. Polymers with many ionizable groups are known as polymer electrolytes. The polyelectrolytes are present in the formulation causes an increase in external pH that leads to swelling of hydrogel that forms in-situ gel. (17) Swelling is dependent upon the external pH and functional group present on the hydrogel. For weakly acidic (anionic) groups hydrogel swelling increases with increasing external pH on the other hand it decreases with weakly basic (cationic) groups. Most anionic pH-sensitive polymers are based on PAA (Carbopol, carbomer) or its derivatives (18). Similarly, a low viscosity poly-vinylacetal-diethylaminoacetate (AEA) solution at pH 4 forms a hydrogel at neutral pH conditions. (19)

Drugs prescribed in liquid solutions have some limitations, including limited bioavailability and a tendency to be easily removed by tears. Low pH of the PAA solution was found to damage the surface of the eye before it was neutralized by tears. This problem was partially resolved by combining PAA with the viscosity-enhancing polymer HPMC, resulting in a sol at pH 4 and a pH-responsive polymer mixture gelled at pH 7.4 (20). A mixture of poly-methacrylic acid (PMA) and polyethylene glycol (PEG) has also been used as a pH sensitive system to achieve gelation (21)

- **Improvement in the pH triggered the in-situ gel system:**

For the preparation of the in-situ gelling system for odds, various highly potent and stable polymerare used. The polymer used in these formulation gives sustained ocular drug delivery system.

Numerous studies were conducted to advance the in-situ gelling technology.

Baicalin pH-triggered gel was created and tested by (Wu et al) as a drug for the sustained releasein the ocular drug delivery system.

In this formulation polymer, (HPMC E4M) (0.6 w/v) was employed as a viscosity agenttogether with polymer Carbopol 974 P as gelling agent.

studies were carried out both in vivo and in vitro to draw a conclusion from the investigation. Thisstudy looked into a variety of topics -

Through this investigation, a number of factors were brought to light, including the fact that the in –situ gel formulation had a lower plasma AUC than eye drops. This causes the systemic

absorptionto decline. (22)

For examples various pH triggered in –situ gelling system were –

Baicalin model drug combined with polymer carbopol 974P and HPMC E4M as examples of pH-triggered in-situ gelling system. The result of this research showed that the drug had better stability and ocular bioavailability as well as a, sustained release of drug as compared to commercial Baicalin eye drops.(16)

Benefits from the trails on ciprofloxacin included a lead in the drug ‘s sustained release. (23) The advantages of norfloxacin (the study‘s model medicine) were that it exhibits mucoadhesive property and antibacterial activity.(22)

The study also make use of a few other medication studies combining Timolol, Gatifloxacin ,Moxifloxacin with different polymers produced regulated , prolonged drug release as well as improvement in precorneal residence duration and ocular bioavailability.(24,25)

- **In-situ formation based on chemical reactions**:

Chemical reactions that result in in-situ gelation may include enzymatic processes, precipitation of inorganic solids from supersaturated ionic solutions, and photo-initiation processes.

- **Ionic crosslinking**:

Polymers can undergo a phase transition in the presence of various ions like Na+, K +, Ca+, and Mg+. Some of the polysaccharides fall into the ion-sensitive class (21). Gellan gum is an anionic polysaccharide that gels in-situ in the presence of monovalent and divalent cations such as Ca2 +, Mg2 +, K +, and Na +. Gelation of low methoxy pectin can be caused by divalent cations, especially Ca2 +. Similarly, alginic acid gels in the presence of divalent/polyvalent cations eg. Ca 2+ by the interaction of the alginate chain with the glucuronic acid block (26).

- **Enzymatic cross-linking**:

In this method, a gel is made by cross-linking with the enzymes which are present in body fluids. In-situ formation catalyzed by natural enzymes has not been extensively studied but appears to possess several advantages over chemical and photochemical approaches. For instance, enzymatic processes operate efficiently under physiological conditions without the necessity for potentially harmful chemicals like monomers or initiators. Intelligent stimulus- responsive delivery systems using hydrogels capable of releasing insulin are studied. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood sugar levels and the pulsatile release of trapped insulin. The quantity of enzyme can also be adjusted to control the rate of gel formation, which allows the mixture to be injected before gel formation (27).

- **Photo-polymerization**:

Photo-polymerization method of in-situ gel formation involves the use of electromagnetic radiation. A solution of monomer or reactive macromer and initiator can be injected into the tissue site and electromagnetic radiation can be applied to form a gel. The most suitable polymers for photo-polymerization are polymers that undergo dissociation by functional groups that are polymerizable in the presence of photo-initiators such as acrylates or similar monomers and macromers. Long wavelengths of UV light and visible wavelengths are generally used.
Short-wavelength UV light, however, is rarely used because of its limited penetration into tissues as well as its biologically harmful effects. Ketones such as 2, 2 dimethoxy-2- phenylacetophenone are often used as initiators for UV photopolymerization, while camphorquinone and ethyl eosin initiators are often used in visible light systems. These systems can be easily designed to be degraded by chemical or enzymatic processes, or for long-term persistence in vivo (28). The

photoreaction provides a rapid polymerization rate at physiological temperatures. Also, the system can be easily placed in volumes of complex shapes, leading to the formation of implants (29)

- **POLYMERS USED IN THE FORMULATION OF IN SITU GELS**:

❖ **Definition**:

A polymer is a macromolecule composed of repeating structural units and these subunits are connected by covalent chemical bonds. (30)

- **Ideal characteristics of polymers**:(31)

The polymers used for in-situ gelling systems should have following characteristics:

- It should be biocompatible. It should be capable of adherence to mucus.
- It should have pseudo plastic behaviour.
- It should be tolerable.
- It should have good optical activity.
- It should influence the tear behaviour.

- **Polymers used in in-situ gels**:

1) Carbpol

It is a pH sensitive polymer. It is also called as carbomer, acrylic acid polymer, etc. (32)

❖ Properties of Carbopol (33)

1) Carbopol is a high molecular weight, cross linked polyacrylic acid derivative and hasstrongest mucoadhesive property.

2) It is a water soluble vinyl polymer.

3) It shows sol to gel transition, in aqueous solution, when the pH is raised above its pKa valueof about 5.5.

4) As the concentration of carbopol increases, its acidic nature may cause irritation to eye.Addition of cellulose will reduce polymer concentration and will also improve gelling property.

❖ Uses of carbpol

a) Gelling Agent.

b) Emulsifying Agent.

c) Solubilizing Agent.

2) Poloxamer

It is a temperature sensitive polymer. It is commercially called as Pluronic.

❖ Properties of Poloxamer

1) It is a water soluble.

2) It has good thermal setting property and increased drug residence time.

3) It gives colourless, transparent gel. (33)

4) Concentrated aqueous solutions of Poloxamer form thermosreversible gels. (34)

❖ Uses of Poloxamer

a) Gelling Agent.

b) Emulsifying Agent.

c) Solubilizing Agent.

3)Gellan Gum

It is an ion-sensitive polymer. It is also known as Gelrite®(trade name).

❖ Properties of Gellan Gum:

1) Gellan gum is a linear,anionic heteropolysaccharide secreted by the microbe Sphingomonaselodea.(33,34)

2) The backbone of the polymer consists of glucose, glucoronic acid and rhamnose in the molarratio 2:1:1. These are linked together to give a tetrasaccharide repeat unit.

3) Gelrite is deacetylated gellan gum, obtained by treating gellan gum with alkali to remove theacetyl group in the molecule.

4) Upon instillation, gelrite forms gel due to the presence of calcium ions.

❖ Uses of Gellan Gum:

a) Thickening Agent.

b) Gelling Agent

c) Stabilizing Agent.

4)Sodium Alginate

It is an ion-sensitive polymer. It is also known as algin, alginic acid, sodium salt, Kelcosol, Keltone, sodium polymannuronate.(32)

❖ Properties of Sodium Alginate:(33)

1) Sodium alginate is a gum extracted from brown algae

2) It is a salt of alginic acid.

3) It is a linear block polysaccharide consisting of two types of monomers-β-D-Mannuronic acidand α-L-glucouronic acid residues joined by 1,4-glycosidic linkages.

4) It exhibits good mucoadhesive property due to presence of carboxylic group.

5) It is biodegradable and non-toxic.

6) It has high molecular weight of 20 to 600 kDa.(30)

❖ Uses of Sodium Alginate:(32)

a) Thickening Agent.

b) Suspending Agents.

5)Hydroxy Propyl Methyl Cellulose (HPMC)

It is a temperature sensitive polymer. It is also known as Hypromellose, Methocel etc.(32)

❖ Properties of HPMC:

1) It is water soluble cellulose ether.(35)

2) Widespread acceptance of HPMC due to:(36)

a) Solubility characteristics of the polymer in organic and aqueous solvent system.

b) Non-interference with drug availability.

c) Flexibility and absence of taste and odour.

d) Stability in the presence of heat, light, air or reasonable levels of moisture.

3) It increases its viscosity when temperature increases. (33)

4) At low concentrations (1-10 wt.%) aqueous solutions of HPMC are liquid at low temperaturebut gel upon heating.(37)

5) By reducing the hydroxyl propyl molar substitution of HPMC, its transition temperature canbe lowered to 40ºC.

- Uses of HPMC: (32)

a) Thickening Agent.

b) Suspending Agent.

- **APPLICABILITY OF IN-SITU POLYMERIC IN OCULAR DRUGDELIVERY SYSTEM**:

The unique properties of the ocular cavity and its effective clearance mechanism make ocular administration of the drug a difficult target with low therapeutic response. New generation ophthalmic formulations are tasked with improving the availability of drugs administered by the ocular route and thus improving their therapeutic efficacy. This can be achieved by using in-situ gelling formulations that increase pre-corneal retention time and achieve optimal drug concentrations at the target site.(38)

Such in-situ gelation systems receive a phase transition-forming viscoelastic gel in response to one or more environmental stimuli such as temperature, ions present in tears, and pH.(39)

Following topical application, gel formation in the conjunctival cul-de-sac provides sustained release of the loaded drug to ensure long-term therapeutic effects, reduce dosing regimens, and thus improve patient compliance. Polymers commonly used in the manufacture of such systems are biocompatible, well-tolerated, and preferably mucosal adherent. Further, pseudoplastic behaviour is desirable. Painful blinking can be avoided by ensuring that the viscosity of the polymer solution administered decreases with an increasing shear rate.(40)

The in-situ gelation system can also be used as a vehicle for drug-filled nanoparticles and is involved in improving both drug solubility and corneal permeability, which is characterized by the low bioavailability of the eye. Incorporation of low-viscosity colloids into semi-solid formulations results in longer retention on the ocular surface.(41)

- **Research has been conducted in the area of in-situ gel for the administrationof eye medication**:

Various Polymer Poloxamer -407 has the potential to gel and can lengthen the period before a medicine takes effect. The development of the in-situ gelling system for odds has been the subject of numerous articles and studies, including the creation and assessment of a novel sparfloxacin in situ gel for sustained ocular drug delivery both in vivo and in vitro characterization is done. solid the formulation was done using the in-situ approach as a substitute formulation for the ocular drug delivery system. This was a brand new formulation in which dry form solid was used and after administration of drug solid in situ gelling system immediately gel is formed in the ocular cavity gellan gum was a polymer used in this preparation.

- **Marketed In-Situ gels**:

Product Name	**Drug used**	**Manufacturing Company**	**Diseases/Application**	**Reference No**

PilocarpineHS	Pilocarpine Hydrochloride	Alcon Laboratories Inc.	It is sterile topic ophthalmic aqueousgel used to control intraocular pressure, used in glaucoma.	51
Timoptic-XE	Timolol Maleate	Merck and Co.Inc	Treatment of elevated intraocular pressure in patient with occular hypertension or open - angle glaucoma.	51
Cytoryn	Interleukin-2	Macromed	Highly effective forthe eye infections.	51
Virgan	Ganciclovir	Spectrum Thea Pharmaceutical	Opthalmic gel for the treatment of certain superficial and viral eye injections (cornea).	51
Akten TM	Lidocaine Hydrochloride	Akten	Topical Anesthetic agent, for cataract	51

Table no:1

- **Current researches in the field of in situ gel ocular drug delivery systems**:

Sr.No	Drug	Polymer	Conclusion	Reference No
1	Ketotifen	Deacetylase gellan gum	Author developed an ion activated ocular formulation using ketotifen drug with the polymer deacteylase gellan gum it has a potential to prolong the residence time of the formulation.	41
2	Sparfloxacin	pH sensitive gelling agent is used	In this formulation author combined ions and pH activated gellin agent for the enhanced drug delivery system	49

3	Nepafenac	Carboxymethy chitosan and poloxamer	This formulation undergoes sol to gel phase transition when came with contact with physiological changes like temperature and pH change at very low concentration.	50
4	Ciprofloxacin	pH triggered gelling agaents are used	Author developed an dual thermo and pH responsive nanocarriers this formulation improved antimicrobial activity as it also determined by minimal inhibitory concentration.	42

Table no :2

- **List of some patents of in-situ gelling system:**

Patent Number	Title of the patent	Year of publication	Reference No
US 2002/0114778A1	Reversible gelling system for ocular drug delivery	2002	43
US 6511660 B1	Ophthalmic drug delivery formulations and method for preparing the same	2003	44
US 6703039 B2	Reversible gelling system for ocular drug delivery	2004	45
US 2011/0082128A1	In-situ gel ophthalmic drug delivery system ofestradiol or other estrogen for prevention of cataracts	2011	46

Table no: 3

- **Drugs that may be used in In-situ technology for ocular delivery**:(48)

- Naphazoline HCL TI-ALLERGIC
- Ofloxacin
- Chloramphenicol
- Econazole
- Lignocaine HCL
- Proparacaine HCl
- Gentamycin NTIBIOTICS
- Dexamethasone
- Prednisolone
- Tobramycin
- Brimonidine
- Pilocarpine
- Pilocarpine Nitrate ophthalmic solution 2% w/v 5ml
- Timolol GENTS FOR GLAUCOMA
- Ketorolac tromethamine ANTI-INFLAMMATORY- NSAID
- Clotrimazole

CONCLUSION:

The major portion of pharmaceutical research focuses on the controlled and targeted delivery of a drug. Over the last decade, In-situ gels have proved to be reliable, safe, and efficient dosageform for controlled and targeted delivery of drugs. The use of various polymeric systems has afforded various advantages over conventional drug delivery systems. In-situ formulations show the ease of administration as these are in solution form, while shows controlled release after administration because of gel formation. Ease of administration, reduced dosing frequency, and good stability and biocompatibility characteristics have resulted in increased patient compliance and comfort. The research studies performed so far, have demonstrated theefficacy of in-situ gels as a potential therapeutic platform for the administration of bioactive agents for the treatment of various diseases. However, the in-situ gel system has been facing some challenges with drug delivery, such as enzymatic degradation of the drug molecule, lowmembrane permeability, initial drug burst, and extensive clearance. As well as challenges associated with their development that are related to drug stability, drug release kinetics, and the conditions under which the system is delivered to the body.

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