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A Review: in-situ Gel Drug Delivery System

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ABSTRACT

Over the past decade gel-based systems have emerged as a new approach to drug delivery system, attracting the interest of the scientific community. In-situ gels are a type of hydrogel which are in a solution form and are undergoes gelation under varying physiological conditions. The formation of the gel depends on factors such as temperature fluctuations, pH changes, ion exposure and ultraviolet radiation, electrical sensitivity, a critical enzyme from which the drug is released continuously and in a controlled manner. They are designed to detoxify the drug with long-term drug availability and ongoing drug use. Controlled discharge pattern offers the benefit of reduced administration frequency, improving patient compliance. The dose of the drug can also be reduced and that is why the toxicity, compared to conventional treatment. In controlled drug delivery, the drug is administered for a long time with zero order kinetics, so the availability of plasma drugs can be obtained. Significant progress has been made in the formulation of novels containing natural and synthetic polymers. There are several uses and benefits of an in-situ gelling system in modern life. This review mainly focuses on introduction to in situ-gel, its advantages and disadvantages, its mechanism, various approaches of in-situ gel formation, mechanism of drug release from the system, Temperature advancements triggered the in- situ gel system, Improvement in the pH triggered the in –situ gel system, Research has been conducted in the area of in –situ gel for the administration of eye medication.

Keywords: applications, *in-situ* gel, novel drug delivery system, release.

INTRODUCTION

RECENT PROGRESS IN SITU GEL POLYMER IN DRUG DELIVERY SYSTEMS.

The Pharmaceutical industry is now developing a variety of treatments that are effective , but the formulation of these drug delivery systems is one of the most challenging stages .One of the trickiest is the medicine delivery system for the eyes .These systems are employed to improve treatment outcomes as well as the bioavailability of medication release from formulation .One of the most difficult ocular medication delivery system is this formulation ‘s In –Situ gel.

Recent development have resulted in the development of labile macromolecular therapeutic medicines; their effective administration needs complicated preparation .when combined with the hydrophilic solvent ,N-

stearoyl L –alanine (m) ethyl ester was produced , allowing for the cfeation of an injectable , in situ forming organogel .Leuprolide –loaded organogel slowly decomposed and released leuprolide for 14 to 25d58 after subcutaneous injection.

In situ gelling drug delivery systems can be created using variety of mechanisms and techniques that are already in place at the application site.
In situ gelling systems can be used to create gels based on the triggers involved in the phase transitions from Sol – to –Gel phase.

Figure 1 In vitro hydrogel formation with in situ gels (0.6% DGG, w/v) and artificial tears (25:7, v/v).
Abbreviation: DGG, deacetylase gellan gum.

Importance of in situ gelling system [6, 7]
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.
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Advantages: [8,9,10]
1) Provide controlled and sustained release of the drug
2) Ease of the drug administration
3) Can be administered to unconscious patients
4) Increased patient compliance and comfort
5) Decrease the dose frequency and drug toxicity
6) Increased bioavailability

Disadvantages of in situ gel system [11,12]
1) It requires high level of fluids.
2) The sol form of the drug is more susceptible for degradation.
3) Chances of stability problems due to chemical degradation.
4) After placing the drug eating and drinking may become restricted up to the few hours.
5) The quantity and homogeneity of drug loading into hydrogels may be limited, particularly for hydrophobic drugs.
6) Only drugs with small dose requirement can be given.
7) Lower mechanical strength, may result into premature dissolution or flow away of the hydrogel from a targeted local site.

Ideal characteristics of polymers for preparation of in situ gel [13,14]

1) The polymer should be capable of adhering to the mucous membrane.
2) It should be well compatible and should not provide any toxic effects.
3) It should have pseudo plastic behavior.
4) The polymer should be capable of decreasing the viscosity with increase in shear rate.
5) Preferred pseudo plastic behavior of polymer.
6) Good tolerance and optical clarity are more preferred.

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 isopropylacrylamide)Chitosan serves as a thermosensitive in situ gel forming system .

These studies are conducted in order to advance and improve the in-situ gelling technology used in ocular drug administration . [23]

Table 1- **Examples of some thermo-sensitive in situ gelling system .**

Model Drug	**Polymers**	**Applications**
Brinzolamide	Poloxamer F127 and Carbopol 934P	A sol-gel at 33.2 +- 1.1 celsius . controlled release of drug over aperiod of 8 hours.
Ofloxacin	Pluronic (PF -127 and PF-68) and sodium alginate .	In vivo evalution in rabbits 20% (w/w)Pluronic F127when it is compared with Pluronic F68.
Ketorolac tromethamine	Pluronic F-127 HPMC K4M	It Prolonged the residence time and it enhances the ocular bioavailability.
Sparfloxacin	Pluronic (PF 127 and PF 68)	It shows an Promising antimicrobial property in vitro and in vivo.
Fluconazole	Poloxamer /tween /carbopol	It has an highly impact in vivo ophthalemic absorption with comparison to conventional eyedrop.

Lomefloxacin	Pluronic F127,Pluronic F68 and Sodium Alginate.	It has an sustained release profile of 8 hours.
Methazolamide	Poloxamer 407 and Poloxamer P188.	It has an ability to retain drug in comparison to eye drops.
Diclofenac Sodium	Pluronic 127	Diclofenac sodium has an effective bioavailability in aqueous humor .

Improvement in the pH triggered the in –situ gel system

For the preparation of the in –situ gelling system , various highly potent and stable polymer are 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 release in the ocular drug delivery system .

In this formulation polymer, (HPMC E4M) (0.6 w/v) was employed as a viscosity agent together 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 . This study 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 absorption to decline . [28]

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 . [23]

- Benefits from the trails on ciprofloxacin included a lead in the drug ‘s sustained release .[17]

The advantages of norfloxacin(the study ‘s model medicine) were that it exhibits mucoadhesive property and antibacterial activity . [28]

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.[29][30]

Table 2- **Examples of pH – triggered in –situ gel.**

Model Drug	Polymer	Major Finding
Baicalin	Carbopol 974Pwith HPMC E4M.	It enhances the stability ,bioavailability , sustaining of the drug released when it is compared to baicalin eye drops.

ciprofloxacin	Calcium Alginate with HPMCK4M and E50LV.	It gives sustained drug release.
Norfloxacin	Carbopol 934P	It has Mucoadhesive , antibacterial properties and it cure the ocular irritancy.
Timolol Maleate	Carbopol and Chitosan	It has controlled and prolonged release of drug for long period of time.
Brimonidine	Carbopol 974P and HPMC E4M	Increased efficacy and reduced systemic absorption .
Gatifloxacin	Carbopol 940 combined with HPMC and HPMC K15M	It shows sustained drug release for 8 hours .
Moxifloxacin	Carbopol /HPMC	It enhances the precorneal residence time and ocular bioavailability .

Ion triggered in situ gel system advancements

Different ion activated in situ gelling system have been developed .

Through this research , it was determined that the formulation improves precorneal retention time and ocular irritancy .

Rupenthal et al . created an ion activated gelling system using the polymer Gellan gum , xanthan gum and carrageenan.[25]

With an increase in AUC and the 2.5- fold rise in pilocarpine ‘s miotic response when compared to an aqueous solution , the in situ system was non irritating .

Natural polysaccharides deacetylase gellan gum were used in this formulation of ketotifen that Zhu et al. developed it demonstrated prolonged residence time , this study also provided an overview of in situ gel demonstrates a sustained and longer pharmacological effects when compared to conventional eye drops at the same dose , according to study .[24]

Another formulation created by Kesarla et al. was Nanoparticles – loaded ophthalamic in –situ gel using ion-sensitive polymer gellan gum as a gelling agent in the formulation. After gel was administration l in the ocular tissues , it formed a gel and stayed there for a long time . This formulation reduced the frequency of administration, improved corneal contact time, and was a stable preparation .[6]

In this investigation, it was determined that the formulation was demonstrating that an optimal in- situ ophthalemic nanoemulsion gels with terbinafine hydrochloride was created by Tayel et al. ,

In situ gels, the Cmax significantly larger , t max delayed ,

The mean residence duration prolonged and the ocular bioavailability is improved.[5

Table 3- **Examples of Ion activated in –situ gel -**

Model Drug	**Polymer**	**Major Finding**
Gatifloxacin	Alginate with HPMC	It has higher ocular bioavailability and has extended residence time in aqueous humor in comparison to convention ophthalemic solutions.
Fluconazole	HPBCD complexed gellan Gum and K-Carrageenan	It has good mucoadhesive properties and it shows effective control of fluconazole release.
Acetazolamide	Gellan gum with xanthan gum ,HPMC or Carbopol	It enhances intraocular pressure by lowering effect when compared to that of conventional eye drops and oral tablets.
Terbinafine Hydrochloride	Gellan Gum	It has high Cmax , delayed tmax and has prolonged mean residence time , it also enhances the bioavailability.
Antisense Oligodeoxynucleotide	Gellan gum and carrageenan	It has greatest reduction in wound size , least stromal edema and hypercellularity.

Research has been conducted in the area of in –situ gel for the administration of eye medication.

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 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 .

Electrospun another discovery in this area is the use of the Nanofibers in a novel formulation for an in situ gelling system for the ocular drug delivery system . solid the formulation was done using the in situ approach as a substitute formulation for the ocular drug delivery system [13]. 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 .

M ore researches was done , including the formulation and assessment of a Mucoadhesive and ion – activated in situ gelling system based on Gellan gum and

another polymer utilised for the delivery of phenylephrine and tropicamide, hydroxyethyl cellulose . This study had a significant impact on the development of a new rheological technique for measuring gel resistance during induced eye blinking.

Table 4-**Various Marketed In -Situ gels:**

Product Name	**Drug used**	**Manufacturing company**	**Diseases /Application**
PilocarpineHS	Pilocarpine Hydrochloride	Alcon Laboratories Inc.	It is sterile topic ophthalmic aqueous gel used to control intraocular pressure , used in glaucoma.
Timoptic-XE	Timolol Maleate	Merck and Co.Inc.	Treatment of elevated intraocular pressure in patient with occular hypertension or open -angle glaucoma.
Cytoryn	Interleukin -2(IL -2)	Macromed	Highly effective for the eye infections.
Virgan	Ganciclovir	Spectrum Thea Pharmaceutical.	Opthalmic gel for the treatment of certain superficial and viral eye injections (cornea).
Akten TM	Lidocaine Hydrochloride	Akten	Topical Anesthetic agent, for cataract surgery, refractive surgery.
Azasite	Azithromycin	In site vision	Increased precorneal contact time and prolonged drug delivery . Bacterial Conjuctivities.

Table 5 Current **researches in the field of in situ gel ocular drug delivery systems**

S.NO	Research investigator	Drug	Polymer	Conclusion
1	Zhu et al.	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 .
2	Khan et al.	Sparfloxacin	pH sensitive gelling agent is used .	In this formulation author combined ions and pH activated gellin agent for the enhanced drug delivery system .
3	Yu et al	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.
4	Davaran et al	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 .
5	Pandurangan et –al	Voriconazole	Gellan gum	Author has formulated solid lipid nanoparticle loaded in situ gels with voriconazole , this formulation was an excellent zone of inhibition in the microbial assay of voriconazole.

CONCLUSION

All pertinent information about the ocular medication delivery system, including different methods , is covered in this review article .In –Situ gelling system is one of the subjects covered in – depth in this review article .

To improve the bioavailability of the drug release into ocular cavity , as in situ gelling system in the drug delivery system for the eyes has been developed .

One of the best new medicine delivery systems has evolved .Patient compliance was improved by in –situ gelling device , which also assisted in the drug's regulated and prolonged release.

In-situ gel is prepared using variety of polymers ; these formulations may also be employed for oral, transdermal,buccal , and intraperitoneal , applications in addition to ocular ones.

Due to the features of in –situ gel and the developments in drug delivery twchnologies , it has a large market potential today .

All the development connected to various in situ gel systems are highlighted in this article .

Numerous studies were carried out to improve the in –situ gelling mechanism in the ocular medication delivery system .

These produced formulation were very successful in improving the sustained and regulated release of the drug in the ocular drug delivery system .

The in situ gelling technology has undergone recent improvements , which are discussed in this article .These formulation improve the bioavailability in the ocular tissues and also prolonged the retention contact time. It was an appealing technique for the improvement in the ocular drug delivery system (i.e nanoparticle loaded in-situ gelling)

It is important to perform more studies and research on in-situ gel in ocular drug delivery system , new drug designing and nano gel systems .Although it is a promising method of medication administration , there are presently just a few in-situ gels drugs available for clinical usage .

More development should be made in future for the effective and sustained release of drug for eye disorders. New innovation and development that are more dependable in situ polymer formation and those which are highly responsive to the biochemical markers linked to various eye diseases should be formulated.

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