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AN OVERVIEW ON THE OPHTHALMIC FORMULATION FOR *IN-SITU* GEL FORMATION

***Pavithra B., Deepshika P., Divya M., Nirmala S., Thilagavathi R. and Sankar C.**

Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore-641048.

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***Corresponding Author**
Pavithra B.
Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore-641048.

ABSTRACT

In situ gelling systems in ophthalmic preparations represent a significant advancement In the context of ocular drug delivery, this method yields superior therapeutic outcomes as well as patient compliance. These innovative formulations undergo sol-to-gel transitions upon instillation into the eye, triggered by physiological stimulation such as pH, thermal profile, or Ionic concentration. This change allows the medication to remain in the eye for a longer period, release slowly over time, and reduce the amount absorbed into the rest of the body, thereby overcoming the drawbacks of traditional eye drops This review provides a detailed analysis of the polymers used in these systems, focusing on their ability to respond to stimuli and their role in improving drug delivery. It covers various types of *in-situ* formulations, such as pH-sensitive, temperature-responsive, and ion-activated systems. The article also highlights the importance of assessing these gels through rheological, cell-based studies, and preclinical animal studies to ensure toxicity profile, efficacy, patient acceptance. By examining these factors, the review emphasizes the potential of *In situ gelling* systems to transform the treatment of eye diseases and enhance.

KEYWORDS: *in-situ* gels, Polymers, Types of *in-situ* gels, Rheology.

INTRODUCTION

The special features of the human eye, an isolated organ, make ocular medication administration a major struggle. Drug administration is made challenging by this. The short pre-corneal residence period and low absorption of conventional ophthalmic preparations are significant limitations, as the drug is rapidly eliminated through solution drainage, tear

production, and minimal absorption by the conjunctiva. To address these challenges, researchers have focused on developing Reliable, prolonged-release *In-situ* polymeric gel. These advanced drug delivery systems are designed to extend the contact time of the vehicle on the ocular surface while simultaneously slowing down the removal of the drug. *In-situ* gel systems are initially liquid formulations that, when instilled into the eye, transform into a gel upon exposure to the physiological environment. This transformation increases the precorneal residence time of the delivery system and significantly improves the ocular bioavailability of the drug.[1] The development of gels is impacted by variables like variations in particular physicochemical properties, such as pH, temp, and ions selectivity, which enable the drug's regulated and prolonged release. These gel systems are evaluated through various tests, including assessments of Evaluation of texture, sterilization, isotonicity, accelerated studies, amount of drug, clarity, pH, gelling capability, the viscosity in vitro drug release, and irritancy testing.The FT-IR method is employed to identify any incompatibilities between the drug and polymer. Additionally, several innovative drug delivery systems have been developed, such as *in-situ* gels, collagen shields, minidiscs, ocular films, ocuserts, nanosuspensions, nanoparticulate systems, lipid-based nanocarrier, vesicular nanocarrier, starburst polymers, and Transcorneal drug delivery.[1][2] One interesting method for medication delivery is the use of smart polymeric systems.These polymers undergo sol-gel transition after administration, existing as a solution prior to administration and forming a gel once exposed to physiological conditions. By extending the drug's retention time in the Conjunctival fornix and enhancing Corneal diffusion, these systems can significantly improve ocular bioavailability.[1][2] In situ gel formation can be triggered by various physical and chemical stimuli, such as Thermal conditions, hydrogen ion concentration, electrostatic forces, magnetic flux density, and Photon energy. Stimuli-responsive polymers mimic biological systems to some extent, where external factors like pH and temperature induce changes in the formulation's properties. In situ gels can be made from polymers that are synthetic as well as natural. There are several ways to give these gels, including intraperitoneal, injectable, rectal, vaginal, oral, and ophthalmic methods.[1][3]

IN-SITU GEL FORMULATION INVOLVES THE FOLLOWING POLYMERS

Carbomer

It is a high molecular weight derivative of interconnected polyacrylic acid with the strongest mucoadhesive properties. It has anionic charges and is synthetic. It is synthetic and contains anionic charges.[5] It is a vinyl polymer that dissolves in water. It is a water-based

solution, it exhibits a transition from sol to gel when the pH increases beyond and pka of 5.5.[6] As the carbomer level increases, its acidic nature may cause eye irritation. Cellulose addition will enhance gelling properties and lower polymer concentration.[7] Various grades of carbomer, such as

- carbomer 934 (lowest cross-linking density),
- carbomer 940 (maximum cross-linking density),
- carbomer 981 (middle cross-linking density),

are on the market. As a gelling, emulsifying, and suspending agent, carbopol is employed.[8]

Mechanism: The muco-adhesive characteristic results from hydrophobic, electrostatic, or hydrogen bonding interactions.[9] The carbopol molecule is an acidic molecule that is tightly wound. The molecule's carboxylic group partly dissociates to create a flexible coil after being distributed in water. Due of its sensitivity to pH, the polymer swells when the pH of the solution rises. Hydrogen bonding causes it to collapse in an acidic solution; Gel swelling results from electrostatic repulsion between the anionic groups when the pH rises.[10] Both carbopol dispersion and hydration, followed by the addition of sodium hydroxide, tri-ethanolamine, or potassium hydroxide to neutralize the solution, are steps that initiate the gelling effect. Because carbopol has an acidic nature, it irritates the eye as its concentration rises. Viscosity enhancers such as HPMC and MC can be added to lower concentrations without compromising gelling properties.[11]

Poloxamer

Water-soluble tri-block copolymers called poloxamers are made up of two polyethylene oxide (PEO) and polypropylene oxide (PPO) cores arranged in an ABA pattern. It serves as a solubilizing, emulsifying, and gelling agent, clear gel.[12] Based on the distribution and ratio of hydrophilic and hydrophobic chains, poloxamer produces colorless molecules with a range of molecular weights and distinct gelling properties.[13] Classification of poloxamer.

- Poloxamer 124 and their molecular weight is 2200
- Poloxamer188 and their molecular weight is 8400
- Poloxamer237 and their molecular weight is 795
- Poloxamer338 and their molecular weight is 14600
- Poloxamer407 and their molecular weight is 12600.[14]

Mechanism: Polyethylene oxide, which is hydrophilic, and polypropylene oxide, which is hydrophobic, make up this product.[15] At room temperature (25°C), it behaves as a viscous liquid, and at 37°C, it transforms into a translucent gel.[16] At low temperatures, it forms a small micellar subunit in solution; at higher temperatures, the viscosity rises and induces swelling, resulting in a huge micellar cross-linked network.[17][18]

Polycarbophil

Lightly cross-linked polyacrylic acid with more successful mucoadhesive effects is termed polycarbophil.[19]

Mechanism: Despite being insoluble in water, it may swell in a neutral media, which allows the polymer chain to become entangled in the mucous layer. Mucin as well as the polycarbophil's carboxylic acid group contribute to hydrogen bonds.[20]

Xyloglucan

Vascular plants have xyloglucan, a water-soluble hemicellulose that responds to heat when more than 35% of the galactose residues are eliminated. (1-2)-β-D-galactoxylose (GAL) partly replaces the (1,4)-β-D-glucan backbone chain (GLC) with (1,6)-α-D-xylose branches (XYL).[21] Xyloglucan is made up of three distinct oligomers with varying numbers of galactose side chains: octasaccharide, nonsaccharide, and heptasaccharide. Oral, rectal, and ocular medication administration all make extensive use of it because of its non-toxicity, biodegradable, and biocompatible qualities. Similar to polyxamer, it gels when heated to refrigerator temperature or cooled from a higher degree. The point of difference is that xyloglucan gels at lower concentrations (1–2%wt).[22]

Mechanism: Although xyloglucan does not gel in its initial condition, some β-galactosidase breakdown causes its diluted solutions to go through a so-gel transition when heated. The transition temperature is inversely correlated with the polymer concentration and galactose removal ratio.[23]

Cellulose Derivative

The glucan chain with the repeating β(1,4)-D-glucopyranose unit results in to cellulose.[24] Temperature-sensitive sol-gel phase transition is seen in natural polymers such as HPMC, MC, and EC.[25] The viscosity of cellulose material rises with decreasing temperature, but its derivatives, such as HPMC and MC, increase with increasing temperature. The chain of MC is

made up of native cellulose with an alternative methyl substitution group. A liquid solution exists at low temperatures (30°C), and gelation happens as the temperature rises to 40°C to 50°C.[26]

Mechanism: The chain of MC is made up of cellulose with an alternative methyl substitution group.[27] The solution is liquid at low temperatures (30°C), while gelation happens at higher temperatures (40°C to 50°C).[28]

Chitosan

Chitosan is a naturally occurring cationic polymer made up of copolymers of glucosamine and N-acetyl glucosamine, which are produced by deacetylating chitin.[29] Chitosan has mucoadhesive qualities because of the electrostatic interactions between positively charged amino groups and negatively charged mucin.[30] It is a polysaccharide with antibacterial and bioadhesive qualities that is non-hazardous biocompatible, and biodegradable.[31]

Mechanism: The negatively charged sialic acid residues make ionic contact to provide the mucoadhesive property, which is reliant on the pH of the surrounding environment. It is a valuable viscosifying element in the production of artificial tears due to its great spreading characteristics and bioadhesive properties.[34]

Sodium Alginate

Brown algae is the raw material of sodium alginate, a gum. It is an alginic acid salt. β-D-mannuronic acid and α-L-glucuronic acid residues are the two types of monomers that make up this linear block polysaccharide, which is connected by 1,4 glycosidic bonds.[35][36] Its carboxylic group gives it good mucoadhesive properties. It is non-toxic and biodegradable.[37]

Mechanism: β-D-mannuronic acid (M) and α-L-glucuronic acid (G), the alginate monomers, are arranged in an alternating sequence (M-G) block or M-M block. A homogenous gel is created when the polymer's G block forms a bond with calcium moieties. The mechanical strength and porosity of the hydrogel are altered by the G:M ratio, the type of cross linker used, and the concentration of alginate solution.[38][39]

TYPES OF *IN-SITU* GELS

In situ forming ophthalmic gels are one of the ways that cutting-edge pharmaceutical science is addressing the problem of effective ocular medication delivery. Polymers with reversible phase transitions are used to make *in-situ* gels. These *in-situ* gel systems are designed as drug-

containing liquids that can be injected into the eye and change into gel phases when exposed to physiological circumstances.[4] By reducing rapid pre-corneal removal, especially via nasolacrimal drainage and eye blinking, the corneal surface's transition to gel state prolongs the ocular residence and improves ocular bioavailability. Through pre-corneal clearance, it might also lessen the likelihood of unfavorable side effects linked to systemic drug absorption and poor compliance brought on by frequent dosing.[40] The sol-to-gel phase change on the surface of the eye is contingent upon the many techniques used, including pH sensitive, thermosensitive, ion-sensitive and electric-sensitive, magnetic field-activated, ultrasonic-activated and chemical material-sensitive.[41] Among these pH triggered, ion activated and temperature sensitivity are most commonly used.

pH sensitive *in-situ* gels

Changes in pH can result in the formation of in situ gels. They appear as solutions with a pH of 4.4 that coagulate when the pH increases. A viscous gel is created when coming into touch with the tear fluid.[3]

Polymers: Sodium alginate, Carbopol.

Mechanism: Any pH-sensitive polymer that contains pendant acidic or basic groups can either absorb or release protons in response to changes in the ambient pH concentration. The swelling of hydrogel increases for weakly acidic groups and decreases for weakly basic groups when the external pH rises.[1]

Table 1: Drugs formulated as pH sensitive *in situ* gels.

S.NO	DRUGS	POLYMERS USED	REFERENCE
1	Ciprofloxacin hydrochloride	Sodium alginate	[41]
		HPMC-K 4M	
2	Norfloxacin	HPMC-K 4M	[12]
		HPMC-E 50LV	
		HPMC-E 4M	
		HPMC-K 4M	
3	Ciprofloxacin hydrochloride	Carbopol-940	[42]
		HPMC (methocel E 50LV)	
4	Olopatadine hydrochloride	CarbopoL	[43]
		HPMC E-50LV	
5	Levofloxacin hemihydrate	HPMC	[44]
		Sodium alginate	
6	Moxifloxacin	Carbopol	[45]
		HPMC	

7	Ofloxocin	Carbopol-940 HPMC(Methocel E-50LV)	[46]
8	Sinomenine hydrochloride	Carbopol-940 HPMC	[7]

Ion-sensitive *in-situ* gels

When exposed to the ionic concentration of the lacrimal fluids in the ionstriggered in situ gelling systems, the viscosity of the solution increases.[3] Tear fluid often contains monovalent or divalent cations that combine to produce a transparent gel of aqueous polymer solutions. The sol to gel transition is typically started by the Na, Ca, and Mg ions found in tear fluid.[47]

Polymers: Xanthan gum, Gelrite(Gellan gum).

Mechanism: Mechanism: As the ionic strength rises, the formulation undergoes a liquid-gel transition. Gel formation results from association with polyvalent compounds (such Ca+) in the fluid from the lacrimal gland.[47]

Table 2: Drugs formulated as ion-sensitive *in-situ* gels.

S.N O	DRUGS	POLYMERS USED	REFERENCES
1	Moxifloxacin hydrochloride	Sodium alginate HPMC-E 50LV HPMC-K 4M	[48]
2	Pilocarpine nitrate	Sodium alginate HPMC-E 50LV HPMC-K 4M	[38]
3	Ciprofloxacin hydrochloride	Gelrite(Gellan gum)	[42]
4	Nepafenac	Sodium alginate Protanal PH1033	[49]
5	Gatifloxacin	Alginate HPMC(Methace lE 50LV)	[50]
6	Estradiol (E2) 17β	Deacetylated Gellan gum	[51]
7	Moxifloxacin	Gellan gum Sodium alginate HPMC	[40]
8	Basifloxacin	Sodium alginate Ethyl cellulose Xanthan gum	[52]

Temperature sensitive *in-situ* gels

A temperature shift from storage to physiological temperature, or the temperature of the eye surface, initiates the sol-gel transition of this type of in situ forming gels.[4] When a liquid

formulation of this type is applied to the eye, the gel can form at a precorneal temperature of 35 C. This type of gel needs to have a gelation temperature greater than room temperature and go through a gel-sol transition at the precorneal temperature.[3]

Polymers: Pluronic F-127, Poloxamers (P407 and P188), Poly(N-isopropyl acrylamide), chitosan.

Mechanism: Three mechanisms contribute to the sol-gel phase shift that happens as the temperature rises: enhanced polymer desolvation, micellar aggregation, and polymeric network entanglement. A phase transition from liquid to hydrogel results from the breakdown of the polymeric chain at higher temperatures, which creates a hydrophobic region.[53]

Table 3: Drugs formulated as temperature-sensitive *in-situ* gels.

S.NO	DRUGS	POLYMERS USED	REFERENCES
1	Ciprofloxacin hydrochloride	Pluronic F-127 HPMC	[42]
2	Dexamethasone sodium phosphate and Tobramycin sulphate	Poloxamer-407 HPMC K 4M	[54]
3	Methazolamide	Poloxamer (P407 and P188)	[55]
4	Ciprofloxacin hydrochloride	Poloxamer-407 HPMC	[56]
5	Tea polyphenols	Poloxamers(P407 and P188) Carbopol(940 P)	[57]
6	Timolol maleate	Pluronic F-127 Chitosan	[16]
7	Timolol maleate	Poly(N-isopropyl acrylamide)chitosan	[58]
8	Moxifloxacin hydrochloride	Pluronic F-127 Carbopol Gellan gum	[59]
9	Ciprofloxacin hydrochloride	Poloxamer 407.188 HPMC HEC(Hydroxy ethyl cellulose)	[60]
10	Diclofenac sodium	Pluronic F-127 Pluronic F68	[61]
11	Penciclovir	Pluronic F127	[62]
		HPMC K4M Carbopol 934P	
12	Fluconazole	Poloxamer 407 Carbopol 934	[6]

Table 4: Patent article as per European office.

S.NO	PATENT TOPIC	PATENT NUMBER
1.	Timolol maleate ion exchange resin compound insitu gel preparation and preparation method thereof	CN104188897A
2.	In-situ gelling nanoemulsion of brinzolamide	WO2020240451A1
3.	Ophthalmic compositions and methods thereof	WO2023079427A
4.	Ophthalmic nanoemulsion compositions	US2023201117A1
5.	Novel ocular in-situ gelling system	IN2331MU2013A
6.	Gel-type copolymer bead and ion-exchange resins made therefrom	US6251996B1
7.	Device for measuring drying, curing, film formation, and rheological properties of liquids and films	US10451533B2
8.	In-situ molecular composites based on rigid-rod polyimides	US5247057A
9.	Method and apparatus for forming in situ boron-doped polycrystalline and amorphous silicon film	US2002162505A1
10.	Stabilized ophthalmic formulation.	EP0037043A1
11.	Emd formulation comprising PGA	US2013210735A1
12.	Preservative system for ophtalmic formulations	EP0306984A1
13.	Hydrogel-based biological delivery vehicle	US2023080761A1
14.	High impact polymer and process for its production	US4115478A
15.	Aqueous solution preparation containing aminoglycoside antibiotic and bromfenac	US2007082857A1
16.	Stable bromfenac ophthalmic solution	US2017000889A1
17.	Ophthalmic solution comprising glycogen	US6486139B1
18.	Ophthalmic solution of antioxidant	US2021177746A1
19.	Antiinflammatory ophthalmic solution and process for preparing the same	US4474811A
20.	Novel ophthalmic formulation	WO2024105703A1

EVALUATION PARAMETERS FOR OPHTHALMIC *IN-SITU* GEL FORMULATIONS

Evaluation criteria for in situ gel formulations include clarity, pH measurement, gelling capability, drug content, rheological analysis, in vitro diffusion evaluation, isotonicity, antibacterial capability, in vivo ocular testing in rabbits, and accelerated stability tests. The composition should possess the optimal viscosity to facilitate easy ocular administration as liquid droplets that rapidly go through a sol-to-gel transition (due to temperature, pH, or ion exchange).

Clarity Test

Visual examination against a black and white backdrop determines the clarity of the solutions that have been produced.

Texture analysis

Investigation of textural profiles, which shows gel strength and application ease, The in situ gel's cohesion, stiffness, and consistency are evaluated. The polymer must have a high adhesiveness value in vivo to preserve the gel's close contact with the mucous surface.

pH Measurement

As per standard protocol, the pH of the different gels was measured at 25 ± 0.5℃ using a calibrated pH meter.[56] The pH of the formulation was ascertained using a pH meter; it was calibrated beforehand using buffered solutions of pH 4 and 7.[58]

Rheology studies

The rheological properties of solutions and gels were measured using a Brookfield synchroelectric viscometer. The angular velocity rose gradually from 10 to 100 rpm when the produced formulation was put into the Brook Field Synchroelectric Viscosometer's tiny adaptor. The angular velocity hierarchy was inverted. By averaging the two measurements, the viscosity was ascertained. After that, the formulation was transferred into an ointment jar, and simulated lachrymal fluid was added to raise the pH to 7.4.[59] Cone, Plate, and Brookfield viscometers can be used to compute the viscosity readings. The composition of the *in-situ* gel is put into the sample tube. Prior to gelling and during gel formation, the formulation's viscosity should be between 5 and 1000 m Pas and 50 and 50,000 m Pas, respectively.[1]

Drug Content

Using acetate buffer pH 4.5 and 0.2 ml of the formula, the volume was increased to 100 ml in order to determine the drug content. The absorbance was then measured using a UV-Vis spectrophotometer to determine the medication concentration.[60]

In vitro drug release

Using a changed USP XXIII dissolving testing apparatus, the in-vitro release of the drug from the produced formulations was investigated across a cellophane membrane.[42][56] Freshly made artificial tear fluid with a pH 7.4 buffer served as the dissolving media. One end of a specially made glass cylinder, which was open at both ends and had a diameter of 5 cm, was connected to a cellophane membrane that had been soaked in the dissolution medium during the previous night. A precise pipette was used to transfer 2 milliliters of the formulation into this assembly. Attached to the iron drive shaft, the cylinder was hung in 100 milliliters of

dissolving medium that was kept at 37±1℃ so that the membrane barely brushed the surface of the receptor medium. At hourly intervals, aliquots of 1 ml each were taken from the shaft, which was rotated at 50 rpm, and refilled with equal amounts of the receptor media. After diluting the aliquots with receptor media, the absorbance was assessed.[61]

Gelling Capacity

A drop of the created formulation is placed in a vial with 2.0 ml of freshly made simulated tear fluid, and the gelling capability of the formulation is visually observed. By adding a drop of the sample to a test tube containing two milliliters of pH 7.4 simulated tear fluids (STF) that had been equilibrated at 37±2C, the gelling capability of the hypothetical formulations was ascertained. evaluating the gel formation visually and recording the gelation and dissolution times. Three separate measurements were taken, and the mean value was determined. The batch that showed gelation temperature close to body temperature, reduced gelling duration, and gelling capacity for few hours was chosen for additional research based on the results of first batches of *in-situ* gel.[62]

Isotonicity Evaluation

One crucial aspect of ophthalmic preparations is isotonicity. To avoid eye discomfort or tissue damage, isotonicity should be preserved. Blood cellskeep their shape in an isotonic fluid (normal saline), contract in a hypertonic solution, and rupture in a hypotonic solution. according to the theory, Formulation combined with a few drops of blood was examined under a 40x magnification microscope and contrasted with an isotonic solution of 0.9% sodium chloride.[47][62]

Stability Studies

The formulation must be cultured in fluid thioglycolate media at 300–350 degrees Celsius for at least 14 days in order to perform sterility testing. formulation incubation in soy bean casein digest medium at 200–250 degrees Celsius. Thioglycolate medium is used to detect bacterial growth, although In formulation, soy bean casein medium is used for fungus.

Ocular irritancy test

Male albino rabbits weighing one to two kilograms are examined for the possibility of ocular discomfort using the modified draize procedure. 20 The formulation is put in a lower cul-de-sac, and the rabbits are observed for ocular watering, redness, and swelling at 1-, 2-, 48-, and 72-hour intervals as well as for a week following administration.[1][47]

Accelerated stability studies

As specified in the ICH, place the formulation in an amber-colored vial and cover it with aluminum foil to conduct accelerated stability studies at 40± 20 °C and 75±5% relative humidity. Every month, the sample is examined for drug content, gelling ability, pH, and clarity, drugcontent, in vitro dissolution, and rheological assessment.

Antibacterial activity

The antibiotic concentration used to gauge bacterial microbiological development must be compared to the growth caused by a known concentration of a standard antibiotic formulation.[64]

CONCLUSION

Compared to traditional delivery methods, the polymeric in situ gelling system offers a longer duration of drug release. Numerous synthetic, natural, and semi-synthetic. Ophthalmic insitu hydrogels work primarily by lengthening the duration of ocular residency through improved mucoadhesive and viscosity characteristics. Therefore, the *in-situ* gel dosage form's biocompatibility and sustained and prolonged drug release make it dependable. Polymer mixtures are the main focus of current technology in the creation of secure ocular delivery systems.

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