Content available at: https://www.ipinnovative.com/open-access-journals

IP International Journal of Comprehensive and Advanced Pharmacology

Journal homepage: https://www.ijcap.in/

Review Article

A review: In-situ gel drug delivery system

Rakhi Verma[1]*, Kamal Singh Rathore[2], Surendra Singh Saurabh[2]

[1]*Dept. of Pharmaceutics, BN. College of Pharmacy, B.N. University, Rajasthan, India*
[2]*Dept. of Formulation and Development, Precise Biopharma Pvt Ltd, Gujarat, India*

ARTICLE INFO

Article history:
Received 03-08-2024
Accepted 11-09-2024
Available online 05-10-2024

Keywords:
Nanoemulsified
Bloodbrain barrier (BBB)
Nmethyl pyrrolidone (NMP)

ABSTRACT

The eye is the body's most delicate organ. Pharmaceutical scientists find that designing ocular drug delivery systems is the most difficult because only 5% of administered drugs reach the eye due to the complex anatomical structure of the eye, the cornea's small absorptive surface and low transparency, the cornea's lipophilicity, pre-keratitis (from nasolacrimal drainage), the drug's bonding with proteins in tear fluid, blinking, and the conjunctival sac's low capacity, all of which limit the entry of drug molecules at the site of action and ultimately result in suboptimal ocular therapy. Considerable research is being done on developing more advanced drug delivery methods for ocular administration in an attempt to increase the bioavailability of ophthalmic medications. These innovative drug delivery methods have many benefits over traditional ones, including better release profiles that boost drug delivery efficiency and lower drug toxicity. Numerous studies in this field support the idea that in situ gelling devices can be helpful for the transport of drugs into the eyes. Drug delivery systems known as "in situ gel-forming systems" are in solution before being supplied to the body, but thereafter go through a process called "in situ gelation" to form a gel in response to an external stimulus like pH or temperature. A brief overview of in situ gels, several methods for in situ gelling systems, types of polymers utilized in in-situ gels, their mechanisms of gel formation, and an assessment of polymeric in situ gel are all included in this review.

1. Introduction

Any drug delivery system's main goal is to alter the drug's tissue distribution and pharmacokinetic characteristics effectively. A lot of focus has been placed on the creation of controlled and sustained-release drug delivery devices during the previous 60 years. One of the most cutting-edge medication delivery systems has emerged: the "in situ gel" technology. The in-situ gel drug delivery system's unique feature of switching from "sol to gel" facilitates a more comfortable and sustained release of the medication while also improving patient compliance. An in situ gelling system is a formulation that, before entering the body, is in solution form but, under certain physiological conditions, transforms into gel form.

Combinations of several stimuli, such as pH changes, temperature changes, and solvent exchanges, are what cause a solution to transform into a gel. Numerous investigations have been conducted using injectable, parenteral, intraperitoneal, nasal, rectal, oral, and vaginal methods. Numerous polymeric systems with the ability to distribute medications have been created. When these polymers come into contact with physiological stimuli, they go through a sol-gel transition. A variety of synthetic and natural polymers are employed in the creation of in situ gel drug delivery systems. [1–5]

* *Corresponding author*.
E-mail address: rakhi91verma@gmail.com (R. Verma).

https://doi.org/10.18231/j.ijcaap.2024.025

1.1. Advantages of in situ ocular gel

1. Improved Local Bioavailability.
2. Reduced dose frequency.
3. Patient-friendly.
4. Prolonged drug release.
5. Due to gelation precorneal residence time is increased and nasolacrimal drainage is decreased.[6]

1.2. Disadvantages of in situ gel system

1. It requires a high level of fluids.
2. The sol form of the drug is more susceptible to degradation.
3. Chances of stability problems due to chemical degradation.
4. After placing the drug eating and drinking may become restricted up to a 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 requirements can be given.
7. Lower mechanical strength, may result in premature dissolution or flow away of the hydrogel from a targeted local site.[7,8]

2. Mechanism of in Situ Gels

The mechanism of in situ gels is based on the following mechanisms:

2.1. Based on the physical mechanism

2.1.1. Swelling

The substance expands to the necessary area in this in situ gel formation procedure by absorbing water from the surrounding environment. For instance, polar lipid glycerol mono-oleate expands in water to create lyotropic liquid crystalline phase formations. Enzymes in vivo can break it down and have certain bioadhesive qualities.[9]

2.1.2. Diffusion

This process precipitates or solidifies the polymer matrix by allowing solvent from the polymer solution to diffuse into the surrounding tissue. It has been demonstrated that N-methyl pyrrolidone (NMP) is a helpful solvent for such a system.[10]

2.2. Based on the chemical reaction mechanism

Enzymatic, photo-initiated, and precipitation of inorganic particles from supersaturated ionic solutions are examples of chemical reactions that lead to in situ gelation.[11–18]

2.3. Novel approaches to in situ gels

Drug delivery is extended by in situ gelling systems using a range of special methods. These systems both increase a drug's corneal penetration and postpone the removal of active components from the eye.

2.4. Nanoparticles incorporated in situ gel

Recently, problems with topical formulations have been addressed with nanoparticles. These show promise as drug carriers for ocular tissues because they stay at the application site and offer sustained release through erosion, drug diffusion, or a combination of the two.

2.5. Liposome incorporated in situ gel

It can also be used to deliver drugs for a longer period of time under strict control. Active ingredients in lipid vesicles are enclosed and move the medicine through the cornea.

2.6. In situ gelling ocular films or inserts

Ocular inserts or films typically consist of a polymeric vehicle that contains the medicine and is shaped and sized specifically for use in the eye. They can have a semisolid or solid consistency.

2.7. Nanoemulsified in situ gels

Since nanoemulsions have inherent benefits such as easier sterilization, longer medication release into the cornea, and increased penetration into deeper layers, they are used extensively.

2.8. Polymers used in in-situ gels

2.8.1. Gellan gum

Gellan gum exhibits a temperature-dependent or cation-induced gelation propensity. The gellan solution containing calcium chloride and sodium citrate complexes was the basis of the in situ gelling systems. When taken orally, it releases calcium ions into the stomach's acidic environment, which causes gellan to gel and form an in situ gel.

2.8.2. Pectin

H+ions, a source of divalent cations, are necessary for the gelation of pectin; in general, calcium ions are needed to create gels that are appropriate for use as drug delivery vehicles.[19] The primary benefit lies in its water solubility, which eliminates the requirement for organic solvents in the mixture. When pectin is taken orally, divalent cations in the stomach facilitate the transition of the substance into a gel state. The formulation for inducing pectin gelation may contain calcium ions in compound form. To create a complex that contains the majority of the calcium ions, add sodium citrate to the solution mentioned above.

Up until the complex dissolves in the stomach's acidic environment and produces gelation due to the release of calcium ions, the fluid condition, or "sol," is maintained. To keep the fluidity, the amounts of calcium and citrate ions can be adjusted. The formulation causes gelation before being administered into the stomach.

2.8.3. Xyloglucan

β-galactosidase partially breaks down xyloglucan, and the resulting substance gels at a temperature that can be changed by warming to body temperature or by the rod-like chains stacking lateral to one another.

The temperature of the sol-gel transition also varies depending on the extent of galactose removal. Its possible use in the delivery of drugs orally takes advantage of the delayed gelation time that has been suggested, which would enable in situ gelations in the stomach after the oral administration of a cold xyloglucan solution. Xyloglucan has a gelation behavior akin to that of Pluronic F127, albeit at a far lower concentration.

3. Applications

3.1. Oral drug delivery systems

For oral in situ gels, ingredients including xyloglucan, pectin, and gellan gum are employed. The pH-sensitive gels may be used to deliver medications to particular gastrointestinal tract locations.

3.2. Ocular drug delivery systems

Because of their high tear fluids, conventional delivery techniques frequently result in lower bioavailability and therapeutic impact; dynamics cause medications to be eliminated quickly. For the most part, xyloglucan, gellan gum, and alginic acid are utilised in ocular medication administration. Locally acting medications used to reduce intraocular tension in glaucoma, such as antibacterial, anti-inflammatory, and autonomic medications. Numerous pH-induced in situ precipitating polymeric systems including water-soluble polymers, including carbopol, HPMC, and PMA-PEG.[20,21]

3.3. Nasal drug delivery systems

Drugs that are only permitted to be administered intravenously may be used through the nose as an alternative delivery method.

The olfactory receptor cells' proximity to the central nervous system makes nasal drug administration an additional means of entering the brain that gets beyond the blood-brain barrier (BBB).[19,22]

It is thought that the nasal mucosa is a desirable location for vaccine administration due to its vast absorptive surface and low proteolytic activity. Comparing nasal vaccines to parental products will enhance patient compliance and lower production costs. This method can deliver mostly proteins and peptides.

3.4. Dermal and transdermal drug delivery systems

Drugs are thought to be administered through the skin for both local and systemic effects. Typical topical and dermatological medication preparations have a few drawbacks, including low patient compliance, decreased permeability, and poor adherence. According to in vivo research, 20% w/w aqueous gel may be utilised as the basis for topical medication administration.[23]

Iontophoresis plus chemical enhancers work together to increase insulin penetration synergistically.

3.5. Rectal drug delivery systems

Despite being the most practical method of drug delivery, oral administration is not feasible from a pharmacological or therapeutic standpoint. Rectal administration is a viable option in certain situations and can be utilised to provide medication for both local and systemic effects. Compared to other parts of the GIT, the rectum's environment is thought to be steady and consistent, and its enzyme activity is lower. However, because of the low adherence to the rectal membrane and the possibility of dosage form evacuation, irregular drug absorption can provide a challenge to the rectal cavity. These can stop dosage form leaks, which happen frequently when rectal suspensions and enemas are used.[12,24,25]

3.6. Vaginal drug delivery systems

Aside from the management of vaginal infections, contraception, local menopausal symptoms, and labour induction, it is a largely underutilised region. It is a possible path for a therapeutic portfolio that might include chemotherapy and vaccination administration. The vaginal epithelium's blood supply and broad surface area can facilitate the efficient administration of systemic medications. Thermoreversible, mucoadhesive gels and pessaries have been investigated as formulation platforms for the delivery of hormones that induce labour, antiretroviral and antibacterial chemicals, and even intravaginal vaccinations.[26,27]

3.7. Parenteral drug delivery systems

Chitosan is a biocompatible pH-dependent cationic polymer that stays dissolved in aqueous solutions until its pH rises beyond 6.2, at which point it precipitates as a hydrated gel-like substance. The primary issue with chitosan is that it is not biodegradable; however, this could be resolved with the subsequent process. By adding polyol salts with a single anionic head, such as glycerol, sorbitol, fructose,

and glucose phosphate salts, to chitosan aqueous solution, the pH-gelling cationic polysaccharides solution is changed into a thermally sensitive pH-dependent solution without any chemical modification or cross-linking. The issue of chitosan's nonbiodegradability has been resolved by this change. For parenteral formulations, synthetic polymers are a popular option. Biodegradable polymers are becoming more and more popular in drug delivery techniques, as they don't need to be surgically removed again after the drug supply runs out.[2,28]

4. Evaluation of Ocular in Situ Gel

4.1. Visual appearance and clarity

Under fluorescent light against a white and black background, the created in situ formulation's visual appearance and clarity are examined for the presence of any particle matter.[29]

4.2. pH

pH has an impact on a drug's stability and solubility in ocular formulations. It must be such that the formulation will not irritate the patient after ingestion while also remaining stable at that pH.[30]

Digital pH meters are used to measure it.

4.3. Gelling capacity

A drop of the formulation is added to a vial holding 2.0 ml of freshly made simulated tear fluid to measure the formulation's gelling capability. The gelling time is then recorded[31] .

4.4. Isotonicity

One crucial aspect of ophthalmic formulations that must be preserved to avoid tissue damage or ocular discomfort is isotonicity. It speaks of the osmotic pressure that dissolves salts in water exert.

The osmotic pressure of an ophthalmic formulation needs to be between 290 and 310 mOsmol/kg. A tonicity osmometer is used to measure it.[32,33]

4.5. In vitro drug release study

Pharmacological release studies in vitro are conducted with Franz diffusion cells. Freshly manufactured artificial tear fluid (ATF) is inserted into the receptor compartment. The dialysis membrane sits between the donor and receptor compartments. To replicate in vivo circumstances, the entire assembly is kept on a thermostatically controlled magnetic stirrer, with the medium temperature regulated at 37 ± 0.5 °C. Continuous stirring of the medium occurs at 20 rpm. The donor compartment is filled with 1 ml of the formulation. At a prearranged period, a 0.5 ml sample is removed and replaced with ATF.[34,35]

Samples are examined using an HPLC or a UV spectrophotometer.

4.6. Rheological studies

The primary purpose of the Brookfield viscometer is to measure the viscosity of in situ ophthalmic gels.

Before and after gelation, viscosity is measured by progressively increasing the angular velocity from 0.5 to 100 rpm.[36]

4.7. Texture analysis

The cohesiveness, stiffness, and consistency of in situ gel are evaluated using a texture profile analyzer. This mostly shows the gel's strength and ease of use. Texture study yields data on hardness, compressibility, and adhesiveness that can be linked to several characteristics, including good spreadability on the surface of the cornea, ease of removal from the container, and adherence to the mucous layer to extend the duration of residence.[37]

4.8. Transcorneal permeability study

To test a drug's transcorneal permeability, goat eye corneas are used. Fresh goat eyeballs in their entirety are purchased from the neighborhood butcher store and brought into the lab in a standard saline solution at 4oC. After that, the cornea is gently removed, along with 2-4 mm of the sclera tissue that surrounds it, and it is cleaned with saline solution. The excised cornea is positioned with its epithelial surface towards the donor compartment, between the donor and receptor compartments of the Franz diffusion cell. Artificial tear fluid (ATF) that has been freshly manufactured is poured into the receptor compartment. The entire system is set up on a thermostatically controlled magnetic stirrer, which maintains both the temperature (37 ± 0.5 °C) and the stirring rate (20 rpm). One milliliter of the ready-made mixture is added to the donor chamber.[38,39]

Samples (0.5 ml) are taken out between one and five hours in advance, and the same volume is replaced with ATF. Samples are then diluted to a maximum of 10 milliliters and examined using an HPLC or UV spectrophotometer.

4.9. Ocular irritation study

Since Draize research is prohibited in many nations, one of the following methods can be used to undertake an in situ formulation evaluation of ocular irritation.[40]

4.10. Histological study

Corneas are taken out of the eyes of recently slaughtered goats and incubated in formulation for five hours at 37 degrees Celsius to assess the impact of in situ formulation on

the corneal structure and investigate the irritation potential. The positive control is a solution of sodium dodecyl sulfate (SDS) in phosphate buffer saline (PBS) at 0.1% (w/w). Following incubation, corneas are fixed in formalin (8%, w/w) right away after being cleaned with PBS. The tissues are deposited in melted paraffin, dried in an alcohol gradient, and then hardened into blocks. After cutting, cross sections are stained with hematoxylin and eosin (H&E). Cross-sections are examined under a microscope to look for any changes.

5. Hen's Egg Test-Chorioallantoic Membrane (HET-CAM)

The HET-CAM test involves incubating the eggs for ten days at 37 °C and roughly 70% relative humidity, with an automated rotating process once per hour. Following the incubation time, a part of each eggshell is removed, and to prevent capillary damage during its removal, a drop of water is applied to the air sack membrane. After being carefully exposed for 30 seconds to 0.1 ml or 0.1 gram of test chemicals, the CAM is cleaned off using a regular saline solution. 1% SDS solution (positive control) and saline solution (negative control) are applied to CAM simultaneously.[41,42]

After five minutes, each CAM is examined under a microscope to check for coagulation, lysis, and bleeding. For every CAM, an irritation score (IS) is determined using the algorithm below.

IS= 301− hemorrhage 300×5+(301−lysis)300×7+301−coagulation 300×9

Irritation score is given according to following scheme; 0 = no reaction; 1 = slight reaction; 2 = moderate reaction; 3= severe reaction.

6. In vivo Scintigraphy Studies

An established method for assessing ocular retention duration in vivo is gamma scintigraphy. Human volunteers are preferred for this study despite the rabbit being the generally suggested animal model for evaluating ophthalmic medications. This is because humans and rabbits have different physiological characteristics, particularly about blinking rate.[43]

6.1. Accelerated stability study

To ascertain the physical stability of the formulation under accelerated storage circumstances, an in situ formulation stability study is conducted following ICH principles. The formulation process is exposed to high temperatures and humidity levels of 25±1°C/60%RH, 30±1°C/65%RH, and 40±2°C/75±5%RH. After0,30,60, and 90 days, samples are removed and their active drug content is assessed.[44]

6.2. Sterility testing

One crucial evaluating factor for ophthalmic preparations is sterility testing. The Indian Pharmacopoeia is followed for performing the sterility test. Using the direct inoculation approach, 2 ml of liquid is extracted from the test container using a sterile pipette, sterile syringe, or sterile needle. Next, the test liquid is aseptically transferred to separate 20 ml containers of fluid thioglycollate medium and 20 ml containers of soybean-casein digest medium. The medium is combined with the liquid. The infected media is incubated for a minimum of 14 days at 20°C to 25°C for soyabean-casein digest media and 30°C to 35°C for fluid thioglycolate medium.[45]

7. Conclusion

The majority of researchers in the developing field of ocular medication delivery systems are taking on challenges to address the numerous issues related to this delivery. Continuous technological advancements along with a steady progress in our understanding of the principles and processes underlying ocular medication absorption and disposition have undoubtedly improved the effectiveness of ophthalmic administration systems. The in situ gels meet the main need of a successful controlled release solution, which is to increase patient compliance. Because in situ gelling systems can overcome the limitations of traditional ocular dosage forms, they are a viable option for ocular administration. As a result, in situ gelling drug delivery systems for ophthalmology have received a lot of attention from researchers in recent years. They have better patient compliance and are simple to administer.

In the nascent field of ocular medicine delivery systems, most researchers are taking on challenges to tackle the myriad problems associated with this delivery. Ophthalmic administration systems have certainly been more effective due to ongoing technological improvements as well as consistent progress in our understanding of the principles and processes underpinning ocular medicine absorption and disposition. The primary requirement of a successful controlled release solution, which is to improve patient compliance, is satisfied by the in situ gels. In situ, gelling devices are a good alternative for ocular administration since they can get beyond the drawbacks of conventional ocular dosage forms. As a result, researchers have focused a lot of emphasis in recent years on in situ gelling drug delivery devices for ophthalmology.

8. Source of Funding

None.

9. Conflict of Interest

None.

References

1. Devasani SR, Dev A, Rathod S, Deshmukh G. An overview of in situ gelling systems. *Pharmaceut Biolog Evaluat*. 2016;3(1):60–9.
2. Hb N, Bakliwal SR, Pawar SP. In-situ gel: new trends in controlled and sustained drug delivery system. *Int J Pharm Tech Res*. 2010;2(2):1398–408.
3. Mohanty D, Bakshi V, Simharaju N, Haque MA, Sahoo CK. A review on in-situ gel: a novel drug delivery system. *Int J Pharm Sci Rev and Res*. 2018;50(1):175–81.
4. Sarasija S, Shyamala B. Nasal Drug Delivery: An Overview. *Indian J Pharm Sci*. 2005;67:19–25.
5. Nirmal HB, Bakliwal SR, Pawar SP. In situ gel: New trends in controlled and sustained drug delivery system. *Int J PharmTech Res*. 2010;2(2):1398–408.
6. Kondepati HV, Kulyadi GP, Tippavajhala VK. A Review on In-situ Gel Forming Ophthalmic Drug Delivery Systems. *Res J Pharm Tech*. 2018;11(1):380–6.
7. Ma WD, Xu H, Wang C, Nie SF, Pan WS. Pluronic F127-g-poly(acrylic acid) copolymers as in situ gelling vehicle for ophthalmic drug delivery system. *Int J Pharm*. 2008;28(350):247–56.
8. Vodithala SS, Khatry N, Shastri M. Formulation and evaluation of ion activated ocular gels of ketorolac tromethamine. *Int J Curr Pharm Res*. 2010;2(3):33–8.
9. Parekh HB, Rishad J, Jivani NP, Patel LD, Makwana A, Sameja K. Novel In situ polymeric drug delivery system: A Review. *J Drug Deliv Therap*. 2012;2(5):136–45.
10. Nirmal HB, Bakliwal SR, Pawar SP. Situ Gel: New trends in controlled and sustained drug delivery system. *Int J PharmTech Res*. 2010;2(2):1398–408.
11. Nerkar TS, Gujarathi NA, Bhushan R, Bakliwal SR, Pawar SP. Situ Gel: Novel Approach in Sustained and Controlled DrugDelivery System. *Indian J Pharm Sci*. 2013;4:1–18.
12. Almeida H, Amaral MH, Lobao P, Lobo JM. In situ gelling systems: a strategy to improve the bioavailability of ophthalmic pharmaceutical formulations. *Drug Disc Today*. 2014;19:400–12.
13. Vibha B. In-situ gel nasal drug delivery system-a review. *Inter J Pharma Sci*. 2014;4:577–80.
14. Wu Y, Liu Y, Li X, Kebebe D, Zhang B, Ren J, et al. Research progress of in-situ gelling ophthalmic drug delivery system. *Asian J Pharm Sci*. 2019;14(1):1–5.
15. Kumar L, Verma R. Chemical stability studies of bioadhesive topical gel. *Int J Pharm Pharm Sci*. 2011;3(1):101–5.
16. Yadav KS, Rajpurohit R, Sharma S. Glaucoma: current treatment and impact of advanced drug delivery systems. *Life Sci*. 2019;221:362–76.
17. Karthikeyan D, Bhowmick M, Pandey VP, Nandhakumar J, Sengottuvelu S, Sonkar S, et al. The concept of ocular inserts as drug delivery systems: an overview. *Asian J Pharm*. 2014;2(4):192–200.
18. Morsi N, Ibrahim M, Refai H, Sorogy E. Nanoemulsion-based electrolyte triggered in situ gel for ocular delivery of acetazolamide. *Eur J Pharm Sci*. 2017;104:302–16.
19. Tiwari G, Tiwari R, Sriwastawa B, Bhati L, Pandey S, Pandey P. Drug delivery systems: an updated review. *Int J Pharm Invest*. 2012;2(1):2–11.
20. Paul S, Mondol R, Ranjit S, Maiti S. Antiglaucomatic niosomal system: recent trend in ocular drug delivery research. *Int J Pharm Pharm Sci*. 2010;2:15–23.
21. Nayak AK, Bera H. Polysaccharide-Based Nanogels to Overcome Mucus, Skin, Cornea, and Blood-Brain Barriers: A Review. *Pharmaceutics*. 2019;15(10):615–53.
22. Swamy NG, Abbas Z. Mucoadhesive in situ gels as nasal drug delivery systems: an overview. *Asian J Pharm Sci*. 2012;7:168–80.
23. Kathe K, Kathpalia H. Film forming systems for topical and transdermal drug delivery. *Asian J Pharm Sci*. 2017;12(6):487–97.
24. Hua S. Physiological and pharmaceutical considerations for rectal drug formulations. *Front Pharmacol*. 2019;10:1196.
25. Jannin V, Lemagnen G, Gueroult P, Larrouture D, Tuleu C. Rectal route in the 21st Century to treat children. *Adv Drug Delivery Rev*. 2014;73:34–49.
26. Dodou K. Exploring the unconventional routes-rectal and vaginal dosage formulations. *Pharma J*. 2012;289(2):32–8.
27. souza D. The hot topic: a life-changing look at the change of life. Simon and Schuster. and others, editor; 2016. Available from: https://www.amazon.in/Hot-Topic-Life-Changing-Look-Change/dp/B06Y17SL5H#audibleproductdetails_feature_div.
28. 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.
29. Darwhekar G, Jain P, Jain DK. Development and optimization of Dorzolamide HCl and Timolol Maleate in situ gel for glaucoma treatment. *Asian J Pharm An*. 2011;1(4):93–7.
30. Pawar SD, Pawar RG, Gadhve MV. Controlled release in situ forming gatifloxacine HCl for ophthalmic drug delivery. *Int Res J Phar*. 2012;3(1):86–9.
31. Rathore KS. In situ gelling ophthalmic drug delivery system: an overview. *Int J Pharm Sci Res*. 2010;2(4):30–4.
32. Patel HA, Patel JK, Patel KN. Ophthalmic drug delivery system- a review. *Sch Res Lib*. 2010;2(4):100–15.
33. Avis KE, Liberman HA, Lachman L. Pharmaceutical dosage forms parenteral medication. and others, editor. Marcel Dekker, Inc; 1993. p. 592.
34. Singh V, Bushetti SS, Raju SA. A treatment by hydrogel. *An Int J Pharm Sci*. 2011;2:174–83.
35. Geethalakshmi A, Karki R, Sagi P. Temperature triggered in situ gelling systems for Betoxolol in glaucoma. *J Appl Pharm Sci*. 2013;3(2):153–9.
36. Basaran B, Bozkir A. Thermosensitive and pH-induced in situ ophthalmic gelling system for ciprofloxacin hydrochloride: hydroxypropyl cyclodextrin complex. *Acta Poloniae Pharm Drug Res*. 2012;69(6):1137–47.
37. Patil AP, Tagalpallewar AA, Rasve GM. A novel ophthalmic drug delivery systems: in situ gel. *Int J Pharm Sci Res*. 2012;3(1):2938–46.
38. Mudgil M, Pawar PK. Preparation and in vitro/ex vivo evaluation of Moxifloxacin loaded PLGA nanosuspension for ophthalmic application. *Sci Pharmaceutica*. 2013;81(2):591–606.
39. Vodithala S. Formulation and evaluation of ion-activated ocular gels of Ketorolac Tromethamine. *Int J Curr Pharm Res*. 2010;2(1):33–8.
40. Jain GK, Pathan SA, Akhter S. Microscopic and spectroscopic evaluation of novel PLGA-chitosan nanoplexes as an ocular delivery systems. *Colloids Surface B*. 2011;82(2):397–403.
41. Deshmukh G. Evaluation of eye irritation potential of aqueous leaf extract of Achyranthes aspera by in vitro and in vivo method. *Int Schol Res Network*. 2012;12(2):1–5.
42. Heppenheimer A. Comparative evaluation of cosmetic formulation with different alternative methods for eye irritation. *Japanese Soc Altern Animal Exper*. 2007;74:505–7.
43. Urtti A, Pipkin J, Rork G, Repta A. Controlled drug delivery devices for experimental ocular studies with timolol in vitro release studies. *Int J Pharm*. 1990;61(2):235–40.
44. Annex to the ICH Harmonised Tripartite Guidelines on stability testing of new drug substances and products. Q1A (R2). 2003;Available from: https://www.ema.europa.eu/en/ich-q1a-r2-stability-testing-new-drug-substances-drug-products-scientific-guideline.
45. Kute PR, Gondkar SB, Saudagar RB. Ophthalmic in-situ gel: an overview. *World J Pharm Pharm Sci*. 2015;4(1):549–68.

Author biography

Rakhi Verma, Research Scholar

Surendra Singh Saurabh, Senior Scientist

Cite this article: Verma R, Rathore KS, Saurabh SS. A review: In-situ gel drug delivery system. *IP Int J Comprehensive Adv Pharmacol* 2024;9(3):177-182.