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# AN OVERVIEW ON *IN-SITU* GELLING SYSTEM

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**Abstract:**

*In recent times in-situ gel systems have emerged as an alternative approach to conventional drug delivery systems. These systems release the drug in a controlled manner by its special feature of 'Sol to Gel' transition. Further, this in-situ gelling system will stay as a solution before administering into the body and convert into a gel post administering into the body due to various physiological conditions. The drawbacks associated with conventional systems of both solutions and gels, such as accurate dosing, ease of administration overcome by using in situ gelling systems. The current review is mainly focused on giving a special emphasis on types, advantages, disadvantages, polymers used in the formulation, preparation of an in-situ gel, approaches, evaluations, and biomedical applications.*

***Keywords:*** *In-situ gel; Polymers; Controlled Release; Drug delivery; Gelling Mechanism*

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## INTRODUCTION:

A gel is considered as a stable, soft, and solid-like material with two major constituents in which one of which will be essentially liquid in considerable quantity [1]. Gels are present in a transitional state of matter with combined properties of both solids and liquids that are loaded in the gel [2]. The formulated gels consist of a three-dimensional network that is stable [3]. Further, this polymer network is formed by either formation of covalent bonds or non-covalent bonds between the polymer chains. Based on the nature of bonds gels are divided into two types (physical and chemical) where physical gels consist of weak bonds (hydrogen, electrostatic and Vanderwal bonds) and chemical gels have a strong covalent bond [4, 5].

Hydrogels are considered ass the three-dimensional structures of polymer chains which can be converted into various shapes and sizes [6]. The desired hydrogels possess various advantages like excellent absorbing ability and transitions between liquid to gel [7]. The polymer cross-links that are present in the hydrogel allow them to entrap a considerable amount of air and a huge payload of water to swell [8].

In recent times *in-situ* gels are emerged as an alternative drug delivery approach to deliver the drug in a sustained or controlled manner by improving patient compliance [9]. A typical *in-situ* gel is a formulation that will be a solution before administration into the body and changes into a gel after administration due to various physiological changes (temperature, change in pH, solvent exchange). This sol to gel transition can be used widely for either sustained or controlled delivery of the desired drug molecule. Further, these *in-situ* gels possess various advantages like improved ease of application, reduced dosage frequency, and protecting the drug from various physiological conditions [10].

Incorporation of various natural and synthetic polymers to formulate in situ gels can be used potentially for various routes of drug administration (oral, ocular, transdermal, buccal, intraperitoneal, parenteral, injectable, rectal, and vaginal). Natural polymers like Pectin, gellan gum, chitosan, alginic acid, guar gum, carbopol, xyloglucan, xantham gum, HPMC, poloxamer, etc are employed in the preparation of *in-situ* gels to improve drug absorption and patient compliance [11-13]. The current review mainly focuses on the *in-situ* gels, their mechanisms, method of preparation, various polymers used, characterizations, and their biomedical applications.

**Merits [14]**

1. They can be used for emergency medication.
2. Dosage frequency and drug toxicity can be minimized.
3. *In situ* gels offer an important "stealth" characteristic in vivo, owing to their hydrophilicity which increases the in vivo circulation time of the delivery device by evading the host immune response and decreasing phagocytic activities.
4. Usage of natural polymers makes this system biocompatible and biodegradable.
5. Targeted drug delivery can be achieved primarily through mucus membrane by non-invasive administration.

**Demerits [15, 16]**

1. A high level of fluids is required for the formulation.
2. The solution form is more prone to degradation.
3. Instability arises due to chemical degradation.
4. The quantity and homogeneity of drug loading into hydrogels may be limited, particularly for hydrophobic drugs.
5. Lower mechanical strength, may result in premature dissolution or flow away of the hydrogel from a targeted local site.

**Ideal characteristics of polymers for preparation of *in situ* gels [17, 18]**

1. The selected polymer should have a better mucoadhesive property.
2. It should be compatible and non-toxic.
3. It should have pseudo plastic behaviour.
4. The selected polymer should be capable of increasing the shear rate by decreasing the viscosity of the prepared gel.
5. The selected polymer should have good optical clarity and tolerance.

**Polymers used in *In-situ* gelling system**

**Pectin**

This polymer comes under the class of polysaccharides, which contains mainly α- (1-4-D galacturonic acid residues. Due to the presence of free calcium ions and low methoxy pectins they form gels fastly in aqueous medium. Further, as it is water soluble employing organic solvents in the preparation of gel is not required [19]. Furthermore, calcium ions can be added which induces gelation and sodium citrate to the above solution to form the complex with the added calcium ions. The formulation will stay in solution form until the breakdown of complex in the

stomach, where gelation occurs by the release of calcium ions from the complex [20].

**Xyloglucan**

This polymer exibits thermally reversible gelation when it gets partially degraded by β-galactosidase by lateral stacking of rod like polymer chains by change in the boy temperature. Xyloglucan is also called tamarind gum which is a polysaccharide obtained from the endosperm of the seed [21]. Xyloglucan consists of three different oligomers like heptasaccharide octasacharide, non-saccharide, which differ in the number of the galactose side chain. It is mainly used in oral, rectal, ocular drug delivery due to its non-toxic, biodegradable, and biocompatible properties like poloxamer it exhibits gelation [22].

**Gellan gum**

Gellan gum produces gels which are temperature dependent or cation induced. It is an anionic deacetylated exocellular polysaccharide secreted by pseudomonas elodea. Divalent cations like calcium or magnesium ions present in the polymer crosslinks to form a gel. Formation of gel from gellan gum happens when solution comes into contact with mucosal layer of stomach. An aqueous solution of gellan dropped into the eye undergoes a transition into a gel state due to the temperature and ionic condition ($Ca^{2+}$) in the tear fluid. Drug release from these in situ gels prolonged due to longer pre-corneal contact times of the viscous gels compared with conventional eye drops [23].

**Alginic acid**

It is a linear block co-polysaccharide consists of β D-mannuronic acid residues joined by 1,4-glycosidic linkages. In each block and the arrangement of blocks along the molecule varies depending on the algal source. Dilute aqueous solutions of alginates form firm gels on the addition of di and trivalent metal ions by a cooperative process that involves consecutive glucuronic residues in the α-L-glucuronic acid blocks of the alginate chain [24].

**Carbopol**

It is a well-known pH-dependent, which stays in solution form at acidic PH but forms a low viscosity gel at alkaline pH. In combination with HPMC, impart the viscosity of carbopol solution while reducing the acidity of the solution [25].

**Chitosan**

It is a biocompatible pH-dependent cationic polymer, which can remain dissolved in aqueous solutions up to a pH of 6.2. Neutralization of chitosan aqueous solution to pH exceeding 6.2 leads to formation of a hydrated gel. Further, formation of gel by using chitosan happens by changing the critical solution temperature [26].

**HPMC**

Cellulose is consists of a glucan chain that has a repeating β-(1,4)-D-glucopyranose unit. Cellulose material will increase its viscosity when the temperature is decreased while its derivates like HPMC, MC, will increase [27].

**Poloxamer**

It is commercially available as Pluronic and has good thermal setting property and increased drug residence time. It is mainly used as a gelling agent, emulsifying agent, and solubilizing agent, poloxamer gives colorless, transparent gel. It depends upon the ratio and distribution of hydrophilic and hydrophobic chains several molecular weights available, having different gelling properties [28].

**Approaches of *In-situ* gel system**

In general, three well-defined mechanisms trigger the formation of *in-situ* gel post-administration into the body.

1. Physiological stimuli
   a. Temperature
   b. pH
2. Physical stimuli
   a. Solvent exchange or diffusion
   b. Swelling
3. Chemical Stimuli
   a. Ionic cross-linking
   b. Enzymatic cross-linking
   c. Photopolymerization

**Physiological Stimuli**

**Temperature-induced or thermally triggered *in-situ* gel systems**

As depicted in Figure 1 it was evident that application of external heats other than body temperature is not required to initiate gelation. Further, three major strategies were applied in formulating thermoresponsive gels using various polymers (negative, positive, and thermally reversible). Some of the polymers incorporated to formulate these gels are poly-N-isopropyl acrylamide (PNIPAAm), polyacrylic acid (PAA), poly (acrylamide-co-butyl methacrylate), or polyacrylamide, poloxamer, pluronic (poloxamer), tetronics (poloxamines), poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide) [29, 30].

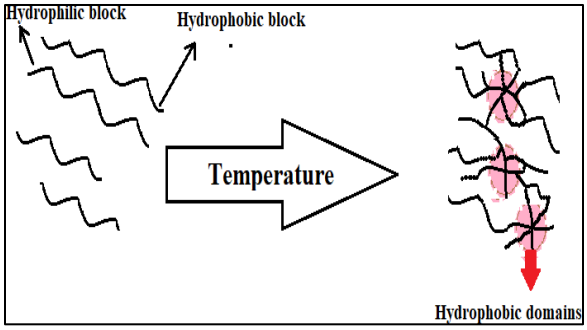


**Figure 1: Mechanism involved in temperature triggered system**

**pH triggered Systems**

In this approach formation of gel happens by the incorporation of pH-responsive or pH-sensitive polymers. Further, polymers that contain either acidic or alkaline ionizable functional groups and functional groups which either lose or accept the protons were selected. As depicted in Figure 2 these large numbers of ionizable groups are termed as poly-electrolytes increases the external pH leading to swelling of hydrogels which in turn leads to the formation of *in-situ* gels. Some of the polymers used as pH triggered systems are Cellulose acetate phthalate (CAP), polyethylene glycol (PEG), pseudo latexes, ploy methacrylic acid (PMC), carbomer, and its derivatives, etc [31, 32].

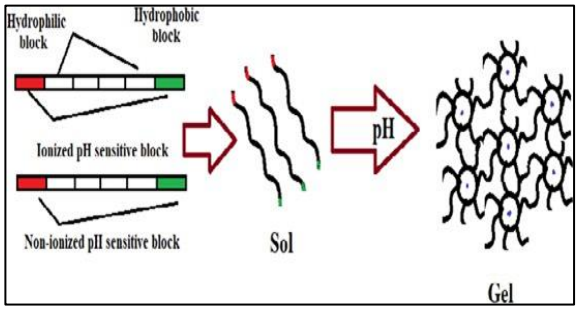


**Figure 2: Mechanism involved in the pH-sensitive system**

**Physical Stimuli**

**Solvent exchange or diffusion**

This process involves the diffusion of solvent from the polymer solution into surrounding tissue resulting in the formation of an *in-situ* gel by precipitation or solidification of the polymer matrix. The most commonly used polymer is N-methyl pyrrolidone [33].

**Swelling**

In this process, the gel is formed by swelling the polymer inside to outside. Further, the swelled system attaches to the mucus layer due to its bioadhesive nature and releases the desired drug in a sustained manner and the gel gets degraded via enzymatic action. The most commonly used polymer is Myverol 18-99 [34].

**Chemical Reactions**

**Ionic Cross-linking**

In this process induction of gelation happens by incorporating ion-sensitive polymers in the presence of ions like $Na^{+}$, $K^{+}$, $Ca^{+2,}$ and $Mg^{+2}$. As depicted in Figure 3 these ionic polymers undergo a phase transition to form a gel [35].

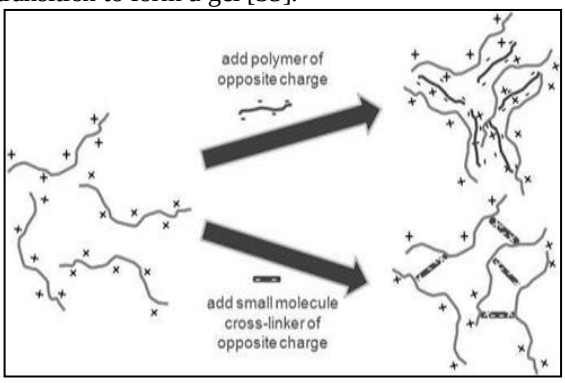


**Figure 3: Ionic cross-linking system**

**Enzymatic cross-linking**

In this approach formation of gel happens by the cross-linking of polymers with the enzymes that are present in the physiological fluids and it is advantageous compared to chemical and photochemical methods [36].

**Photo-initiated polymerization**

This is the most commonly used approach to formulate *in-situ* gels. Further, a typical procedure involves using monomers or reactive micromere solutions and the initiators are injected into the tissue and the gel is formed by application of electromagnetic radiation over the tissue. Usually, long-wavelength ultraviolet polymers like ketones and visible wavelength polymers like acrylates are used [37].

**Preparation of *in-situ* gel**

A typical procedure involves the preparation of polymer solution by dispersing the required quantities of polymers and co-polymers in the distilled water by using a magnetic stirrer until a clear solution is formed. Further, prepare the desired drug solution and add it into the polymer solution with continuous stirring until to get a homogenous solution, and then remaining excipients were added based on the requirement and the final volume is made up with distilled water [38].

**Evaluation of *In-situ* gels**

**Physical Evaluation**

**Compatibility studies**

Compatibility studies are carried out using Fourier Transform Infra-Red Spectroscopy (FTIR) or Differential Scanning Calorimetry (DSC) for both pure drug and physical mixture so that interaction between drug and excipients can be established [39].

**Appearance**

The appearance of the gel is observed by the naked eye for color, odour, and the presence of foreign matter. Preferably, the gels should be transparent [39].

**Clarity test**

The clarity of the product is checked using a black and white background. Preferably, the solutions should be clear without any particulate matter [40].

**pH**

The pH of the solution is analyzed by using a calibrated pH meter. The pH should be within the acceptable limits for example in the case of ocular preparations the pH should be near to pH so that it doesn't cause any irritation to the eye [40].

**Sol-gel transition temperature and Gelling time**

The temperature of phase transition of sol meniscus is noted first and heated at a specific temperature. Further, the formation of gel is indicated by lack of movement of the meniscus on tilting the test tube and the temperature was noted [19]. Furthermore, the time required for the first detection of gelation which is termed gelling time is noted down [41].

**Spreading coefficient**

The device consists of a ground glass slide fixed on the wooden block. Each formulation weighing about 2 grams was placed and studied on this ground slide. Gel preparation was then sandwich between this side and second slide having the same dimensions as that of the fixed glass slide The second slide was provided with a hook weight of 1 gram placed on top of the two slides for 5min to expel air and provide a uniform film of gel between two slides. Measured weight is placed on a pan attached to the pulley with the help of a hook. The time required by the top slide to separate from a ground slide was noted. A shorter interval indicates a batter spreading coefficient (S) [41].

**Gelling strength**

A rheometer is used to determine the gelling strength and it is dependent on the gel-forming capability of that particular polymer. A typical procedure involves the preparation of a specified amount of gel in a beaker. The gel containing beaker to be raised at a specific rate and the probe was pushed slowly through the gel. The load on the probe is measured by the depth of immersion of the gel surface [42].

**Gelling capacity**

The gelling capacity of the gel is measured by placing a drop of freshly prepared gel in a vial containing 2 ml of stimulating tear fluid (STF) and the time taken for the formation of gel is noted down and this test was performed to fix the suitable concentration of polymers to form *in-situ* gelling systems [43].

**Viscosity and Rheology**

The viscosity of the prepared *in-situ* gel is evaluated by Brookfield viscometer at both room temperature and body temperature. After the formation of gel, the formulated system should show pseudo-plastic and Newtonian flow. The viscosity value range during the solution stage should be within 5-1000 m Pas and after gelation, it should be 5-1000 m Pas respectively [44].

**Drug release studies**

***In vitro* drug release**

*In vitro*, drug release studies for the formulated *in situ* gel can be carried out by using Franz diffusion cell [45].

**Microbial evaluation**

**Sterility testing**

Sterility testing is considered an important parameter for ophthalmic preparations and it should be performed to detect the presence of aerobic, anaerobic bacteria and fungi by using suitable media under aseptic conditions. The test is performed by inoculating the sample into liquid media like (thioglycollate medium and soybean digest medium). Further, incubate the cultures for 7-14 days at different temperatures for thioglycollate medium (30-35 °C) and soybean digest medium (20-25 °C) and identified for microbial growth [46].

**Irritation studies**

Albino rabbits are used to perform these irritation studies. Where a single drop of the formulation is instilled into rabbit eyes and the eyes were observed periodically for 1, 24, 48, 72 hours and after one week of exposure. Further, changes in the eye were graded by using the scoring system that includes alteration in eyelids, conjunctiva, cornea, redness, swelling, watering, and iris [47].

**Antifungal Studies**
The test sample is placed in media containing Candida albicans, Aspergillus fumigatus, etc., with the help of a micropipette and set aside for 30 min. After the completion of 24h incubation at 25 °C zones of inhibition are measured and compared with positive and negative controls [48].

**Antibacterial studies**
This test was conducted to find out the effectiveness of antibacterial of active antibiotic substances, the concentrations that are referred to as antibacterial. Finally, the results of the growth of bacteria samples could compare with standard antibiotics [49].

**Biomedical applications**
**Oral drug delivery**
Hydrogels formulated using various polymers like cross-linked PEG & PAA derivatives for delivering the desired prednisolone showed the gastroprotective property in the gastric medium. Polymers like Pectin, xyloglucan, gellan gum, etc., are used for oral *in situ gel* formulations. Some of the in-situ gel formulations reported are clotrimazole with carbopol 934P, gellan gum, and HPMC and the formulated gel had shown a sustained zero-order drug release for 8 hours [50]. Similarly, in another study paracetamol is formulated as an in-situ gel using xyloglucan which is a natural polymer showing a release that is diffusion-controlled [11].

**Ocular drug delivery**
Conventional drug delivery systems used for ocular drug delivery result in reduced bioavailability and therapeutic effect due to tears which result in rapid elimination of the drug. Commonly, used polymers for ocular drug delivery are Alginic acid, gellan gum, and xyloglucan. pH-induced in-situ gels were prepared with various water-soluble polymers by incorporating viscosity enhancers like hydroxypropyl methylcellulose, carboxymethylcellulose, carbomers, PVA which improves bioavailability by prolonging the precorneal residence time [51].

**Nasal drug delivery system**
The nasal drug delivery system facilitates the delivery of the drug to the brain by bypassing the blood-brain barrier because its olfactory receptor cells are in direct contact with the central nervous system. An *in-situ* gel is formulated by using gellan gum and xanthan gum to effectively deliver momethasone furoate for allergic rhinitis. Results from animal studies suggested that formulated *in-situ* gel has inhibited the symptoms more effectively than the marketed formulation [52].

**Rectal & Vaginal drug delivery**
In-situ gels can also be used as a drug delivery system to the rectal and vagina. For example, Acetaminophen an anti-inflammatory drug formulated as a rectal in-situ gel by using polycarbophil and poloxamer F188 and poloxamer 407 as synthetic polymers, and it was observed that the formulated *in-situ* gel had shown enhanced bioavailability [53]. Similarly, in another study itraconazole which is an anti-inflammatory drug is formulated as a vaginal *in-situ* gel by using poloxamer 407,188 & HPMC as polymers for the treatment of vaginal candidiasis [54].

**Transdermal drug delivery**
Skin is considered an essential route of administration of drugs for both local and systemic effects. Even though it is considered an effective route for drug delivery it has some limitations like poor adherence reduced permeability, & compromised patient compliance. Further, in one of the research studies, it was suggested that a combination of iontophoresis and chemical enhancers results in a synergistic enhancement of insulin permeation [55].

**Injectable drug delivery**
It is one of the most used delivery systems to deliver the drug in a sustained manner or implant the system into the tissue and it is widely used to treat cancer. Commonly, used polymers are synthetic polymers and block copolymers (poly (D, L-Lactide), poly( D, L-lactide co-glycolide) & PLGA) [56]. Further, one of the research studies reported those injectable in-situ gel systems are formulated by loading Paclitaxel to treat the tumors [57]. A brief description of the marketed *in-situ* gel formulation is given in Table 1.

**Table 1: Summary of some of the marketed products of *in situ* systems**

| Manufacturing company | Name of the marketed product | Drugs used in the formulation |
|---|---|---|
| Akten | Akten TM | Lidocaine hydrochloride |
| Alcon Laboratories Inc. | Pilopine HS | Pilocarpine hydrochloride |
| Insite vision | Azasite | Azithromycin |
| Macromed | Cytoryn | Interleukin-2(IL-2) |
| Macromed | Regel Depot Technology | Human Growth Hormone |
| Merck and Co. Inc | Timoptic-XE | Timolol maleate |
| Spectrum Thea Pharmaceuticals | Virgan | Ganciclovi |

## CONCLUSION:

The exploitation of polymeric *in-situ* gel for the controlled release of various drugs provides some advantages over conventional dosage forms. Further, it possesses various advantages like releasing the drug in a sustained manner, enhancing the drug stability, improved biocompatibility, and improved patient compliance makes this a very reliable drug delivery system. By incorporating various natural and synthetic polymers in the formulation of these *in-situ* drug delivery systems makes them a potential alternative to deliver the drugs through oral, ocular, transdermal, buccal, intraperitoneal, parenteral, injectable, rectal, and vaginal routes. Therefore, from the above findings, it can be concluded that in-situ gel systems can be considered as an alternative approach for delivering the desired drug through various routes by improving patient compliance.

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## Conflict of Interest

The authors confirm that this article's content has no conflict of interest.

## REFERENCES:

[1] Rogovina LZ, Vasilev VG, Braudo EE. Definition of the concept of the polymer gel. Polym Sci Series C. 2008; 50:85-92.
[2] Whitlock DR, Weiss L, Ambrogio LN, Inventors, AOBIOME LLC, Assignee. Ammonia oxidizing microorganisms for use and delivery to the gastrointestinal system. United States patent application US 16/318,583; 2019.
[3] Carlfors J, Edsman K, Petersson R, Jornving K. Rheological evaluation of gelrite in situ gels for ophthalmic use. Eur J Pharm Sci. 1998; 6:113-9.
[4] Ullah F, Othman MB, Javed F, Ahmad Z, Akil HM. Classification, processing and application of hydrogels: a review. Mater Sci Eng C. 2015; 57:414-33.
[5] Crini G. Recent developments in polysaccharide-based materials used as adsorbents in wastewater treatment. Prog Polym Sci. 2005; 30:38-70.
[6] Kuo CK, Ma PX. Ionically cross-linked alginate hydrogels as scaffolds for tissue engineering: part 1. Structure, gelation rate and mechanical properties. Biomaterials. 2001; 22:511-21.
[7] Peak CW, Wilker JJ, Schmidt G. A review on tough and sticky hydrogels. Colloid Polym Sci. 2013; 291:2031-47.
[8] Fuchs S, Shariati K, Ma M. Specialty tough hydrogels and their biomedical applications. Adv Healthcare Mater. 2020; 9:1901-396.
[9] Nisha Patel, Gajanan Shinde and Rajesh KS. Ophthalmic In situ gel. Genesis. 2014; 2(4): 29-33.
[10] Suisha F., Kawasaki N., Miyazaki S., Shirakawa M., Yamatoya K., Sasaki M., Attwood D. Xyloglucan gels as sustained release vehicles for the intraperitoneal administration of mitomycin C. Int. J. Pharm. 1998; 172: 27– 32.
[11] Miyazaki S, Endo K, Kawasaki N, Kubo W, Watanabe H, Attwood D. Oral sustained delivery of paracetamol from in situ gelling xyloglucan formulations. Drug Dev Ind. Pharm. 2003; 29(2): 113-9.
[12] Nerkar Tushar, Gujarathi Nayan A, Rane Bhushan R, Bakliwal Sunil R, Pawar S.P. In situ gel: Novel Approch in sustained and controlled drug delivery system. Int. **J**. Pharm. Sci. 2013; 4(4): 1-18.
[13] Saraswat R, Bhan CS, Gaur A. A review on polymers used in in-situ gel drug delivery systems. Int J Pharm Innov. 2011; 1(2):110-8.
[14] Langmaier F, Mokrejs P, Kolomaznik K, Mládek M. Biodegradable packing materials from hydrolysates of collagen waste proteins. Waste Management. 2008; 28(3):549-56.
[15] 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; 350(1-2):247-56.
[16] Vodithala S, Khatry S, Shastri N, Sadanandam M. Formulation and evaluation of ion activated ocular gels of ketorolac tromethamine. Int J Curr Pharm Res. 2010; 2(3):33-8.
[17] Jothi M, Harikumar SL and Geeta Aggarwal. In-situ ophthalmic gels for the treatment of eye diseases. Int. J. Pharm. Sci. Res. 2012; 3: 1891-904.
[18] Rajas NJ, Kavitha K, Gounder T, Mani T. In-Situ ophthalmic gels a developing trend. Int J Pharm Sci Rev and Res. 2011; 7: 8-14.
[19] 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.
[20] Parekh HB, Jivani R, Jivani NP, Patel LD, Makwana A, Sameja K. Novel in situ polymeric drug delivery system: a review. J Drug Delivery Ther 2012; 2:136-45.
[21] Mishra A, Malhotra AV. Tamarind xyloglucan: a polysaccharide with versatile application potential. J Mater Chem 2009; 19:8528-36.
[22] Shastri DH, Patel LD. Novel alternative to ocular drug delivery system: Hydrogel. Ind J Pharma Res. 2010; 2: 1-13.
[23] Vashisth P, Singh H, Pruthi PA, Pruthi V. Gellan as novel pharmaceutical excipient. Handbook of Polymers for Pharmaceutical Technologies: Structure and Chemistry. 2015;1:1-21.
[24] Sechoy O, Tissie G, Sebastian C, Maurin F, Driot JY, Trinquand C. A new long acting ophthalmic formulation of carteolol containing Alginic acid. Int J Pharm. 2000; 207: 109-16.
[25] Davies N.M., Farr S.J., Hadgraft J., Kellaway L.W. Evaluation of mucoadhesive polymers in ocular drug delivery. I. Viscous solutions. Pharm. Res. 1991; 8(8): 1039–43.
[26] Gilbert JC, Washington C, Davies MC, Hadgraft J. The behaviour of Pluronic F127 in aqueous solution studied using fluorescent probes. Int J. Pharm. 1987; 40(1-2):93-9.
[27] Chenite A, Chaput C, Wang D, Combes C, Buschmann MD, Hoemann CD, Leroux JC, Atkinson BL, Binette F, Selmani A. Novel injectable neutral solutions of chitosan form biodegradable gels in situ. Biomaterials. 2000; 21(21):2155-61.
[28] Calonge M. The treatment of dry eye. Surv Ophthalmol. 2001; 45:S227-39.
[29] Mundada AS, Avari JG. In situ gelling polymers in ocular drug delivery systems: a review. Crit Rev Ther Drug Carrier Syst. 2009; 26:85-118.
[30] Gil ES, Hudson SM. Stimuli-responsive polymers and their bioconjugates. Prog Polym Sci. 2004; 29:1173-222.
[31] Jagur Grodzinski J. Polymeric gels and hydrogels for biomedical and pharmaceutical applications. Polym Adv Technol. 2010; 21:27-47.
[32] Cole MA, Voelcker NH, Thissen H, Griesser HJ. Stimuliresponsive interfaces and systems for the control of protein– surface and cell-surface interactions. Biomaterials. 2009; 30:1827-50.
[33] Agarwal P, Rupenthal ID. Injectable implants for the sustained release of protein and peptide drugs. Drug Discover Today. 2013; 18:337-49.
[34] Ju XJ, Xie R, Yang L, Chu LY. Biodegradable 'intelligent' materials in response to physical stimuli for biomedical applications. Expert Opin Ther Pat. 2009; 19:493-507.
[35] Qazvini NT, Bolisetty S, Adamcik J, Mezzenga R. Self-healing fish gelatin/sodium montmorillonite biohybrid coacervates: structural and rheological characterization. Biol Macromol. 2012; 13:2136-47.
[36] Oryan A, Kamali A, Moshiri A, Baharvand H, Daemi H. Chemical cross-linking of biopolymeric scaffolds: current knowledge and future directions of cross-linked engineered bone scaffolds. Int J Biol Macromol. 2018; 107:678-88.
[37] Vibha B. In-situ gel nasal drug delivery system-a review. Inter J Pharma Sci. 2014; 4:577-80.
[38] Radivojsa M, Grabnar I, Grabnar PA. Thermo-reversible in situ gelling poloxamer-based systems with chitosan nanocomplexes for prolonged subcutaneous delivery of heparin: design and in vitro evaluation. Eur J Pharm Sci. 2013; 50:93-101.
[39] Prasad RR, Kumar JR, Vasudha BA, Chettupalli AK. Formulation development and evaluation of allopurinol solid dispersions by solvent evaporation technique. Int J Appl Pharm. 2018; 10:168-71.
[40] Saini R, Saini S, Singh G, Banerjee A, Railmajra DS. In situ gelsnew trends in ophthalmic drug delivery systems. Int J Pharm Sci Res. 2015; 6:386-90.
[41] Asasutjarit R, Thanasanchokpibull S, Fuongfuchat A, Veeranondha S. Optimization and evaluation of thermoresponsive diclofenac sodium ophthalmic in situ gels. Inter J Pharm. 2011; 411:128-35.
[42] Kashyap N, Viswanad B, Sharma G, Bhardwaj V, Ramarao P, Kumar MR. Design and evaluation of biodegradable, biosensitive in situ gelling system for pulsatile delivery of insulin. Biomaterials. 2007; 28:2051-60.
[43] Mandal S, Thimmasetty MK, Prabhushankar GL, Geetha MS. Formulation and evaluation of an in situ gel-forming ophthalmic formulation of

moxifloxacin hydrochloride. Int J Pharm Invest. 2012; 2:78.
[44] Rao MA. Measurement of flow and viscoelastic properties. In: Rheology of Fluid, Semisolid, and Solid Foods, Springer, Boston, MA; 2014. p. 63-159.
[45] Sapavatu SN, Jadi RK. Formulation development and characterization of gastroretentive drug delivery systems of loratadine. Int J Appl Pharm. 2019; 11:91-9.
[46] Moondra S, Raval N, Kuche K, Maheshwari R, Tekade M, Tekade RK. Sterilization of pharmaceuticals: technology, equipment, and validation. In Dosage Form Design Parameters, Academic Press; 2018. p. 467-519.
[47] Kadam S, Kondawar M, Kamble K. Formulation and evaluation of in situ gelling system of ketrolac tromethamine for ophthalmic drug delivery. Int J Pharm Thera. 2010; 1:64-71.
[48] Leng KM, Vijayarathna S, Jothy SL, Sasidharan S, Kanwar JR. In vitro and in vivo anticandidal activities of alginate-enclosed chitosan–calcium phosphate-loaded Fe-bovine lactoferrin nanocapsules. Future Sci OA. 2017; 4: FSO257.
[49] Rodriguez Hernandez J. Antimicrobial/Antifouling surfaces obtained by surface modification. In: Polymers against Microorganisms, Springer, Cham; 2017. p. 95-123.
[50] Harish NM, Prabhu P, Charluyu RN, Subramanyam EVS. Formulation and evaluation of in-situ gel containing Clotrimazole for oral candidiasis. J Pharm Sci. 2012; 4: 1885-9.
[51] Paul S, Mondol R, Ranjit S, Maiti S. Antiglaucomatic niosomal system: recent trend in ocular drug delivery research. Int J Pharm Pharm Sci. 2010; 2:8-15.
[52] Swamy NG, Abbas Z. Mucoadhesive in situ gels as nasal drug delivery systems: an overview. Asian J Pharm Sci. 2012; 7:168-80.
[53] Choi HG, Oh YK, Kim CK. In-situ gelling and mucoadhesive liquid suppository containing Acetaminophen: Enhanced bioavailability. Int J Pharm. 1998; 165: 23-32.
[54] Sinem YK, Seda R, Zeynep AS, Esra B. A new in-situ gel formulation of Itraconazole for vaginal administration. J Pharm Pharmacol. 2012; 3: 417-26.
[55] Kathe K, Kathpalia H. Film-forming systems for topical and transdermal drug delivery. Asian J Pharm Sci. 2017; 12:487-97.
[56] Kranz H, Yilmaz E, Brazeau GA, Bodmeier R. In vitro and in vivo drug release from a novel in situ forming drug delivery system. Pharm Res. 2008; 25(6):1347-54.