Polymeric *in situ* drug delivery system: An insight mini review

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Abstract:

In contemporary pharmaceutical design, controlled and sustained drug delivery has become the standard, leading to extensive research to improve drug product effectiveness, reliability, and safety. In situ gelling systems are polymeric formulations that initially exist as sol forms before being administered in the body but transition to gel forms under physiological conditions. The benefits of in situ-forming polymeric delivery systems, such as ease of administration, reduced frequency of administration, and enhanced patient compliance and comfort, have generated this interest. Elements like temperature variation, pH alteration, ion presence, and ultraviolet irradiation influence the production of gels, this drug delivery system includes these features that enable its extensive application in the production of sustained delivery vehicles for bioactive compounds. Several biodegradable polymers, such as poloxamer, gellan gum, hydroxypropyl methylcellulose (HPMC), carboxymethylcellulose (CMC), pectin, chitosan, xanthan gum, and carbapol, are utilized in the development of *in situ* gels. From a manufacturing perspective, the production of such devices is less complicated, thereby reducing both investment and manufacturing costs. This review provides an overview of in situ gelling drug delivery systems, explores various approaches for these systems, discusses different types of polymers utilized, examines their evaluation and applications, and outlines some marketed products.

Keywords: Gels, In-situ gelling system, Sol-gel Transition, temperature, ion, pH, Cross-linking

نظام توصيل الأدوية البوليمري المتشكل في الموقع: مراجعة تحليلية مصغرة

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الخلاصة:

في تصميم الأدوية المعاصر، أصبح التوصيل المتحكم به والمستمر للعقاقير هو المعيار، مما أدى إلى إجراء أبحاث مكثفة لتحسين فعالية المنتجات الدوائية وموثوقيتها وسلامتها. أنظمة التجلط في الموقع هي تركيبات بوليمرية تكون في البداية في صورة محلول قبل أن تُعطى داخل الجسم، لكنها تتحول إلى شكل هلامي تحت الظروف الفسيولوجية. وقد أثار هذا الاهتمام بسبب الفوائد التي توفرها أنظمة التوصيل البوليمرية المتشكلة في الموقع، مثل سهولة الإعطاء، وتقليل تكرار الجرعات، وتحسين امتثال المريض وراحته. تؤثر عوامل مثل تغير درجة الحرارة، وتغير درجة الحموضة، ووجود الأيونات، والتعرض للأشعة فوق البنفسجية على تكوين الهلام. يشمل نظام توصيل الدواء هذا هذه الخصائص التي تمكنه من التطبيق الواسع في إنتاج وسائل التوصيل المستدامة للمركبات النشطة بيولوجيًا. يتم استخدام العديد من البوليمرات القابلة للتحلل الحيوي، مثل البولوكسامر، وصمغ الجيلان،

والهيدروكسي بروبيل ميثيل سلولوز (HPMC) ، وكاربوكسي ميثيل سلولوز (CMC) ، والبكتين، والكيتوسان، وصمغ الزانثان، والكاربوبول في تطوير الهلام المتشكل في الموقع. من منظور التصنيع، فإن إنتاج مثل هذه الأنظمة أقل تعقيدًا، مما يقلل من كل من الاستثمار وتكاليف التصنيع. يقدم هذا الاستعراض نظرة عامة على أنظمة توصيل الأدوية المتجلطة في الموقع، ويستكشف مختلف النهج المستخدمة في هذه الأنظمة، ويناقش الأنواع المختلفة من البوليمرات المستخدمة، ويفحص طرق تقييمها وتطبيقاتها، ويستعرض بعض المنتجات المتوفرة في السوق.

الكلمات المفتاحية : الهلام، نظام التجلط في الموقع، انتقال السائل-جل، درجة الحرارة، الأيون، درجة الحموضة، الربط المتبادل.

Introduction

The primary objective of every drug delivery system is to optimize the drug's pharmacokinetics and/or tissue distribution effectively. There is a continuous rise in the demand for dosage forms that enhance patient compliance. Owing to the high development costs associated with new chemical entities, pharmaceutical companies are concentrating on advancing novel drug delivery methods for existing medications, aiming to enhance efficacy and bioavailability while decreasing dosage frequency and minimizing side effects (1).

In the last 30 years, there has been increased emphasis on the development of regulated and prolonged drug delivery systems. Researchers have conducted extensive studies on the design of polymer-dependent drug delivery devices. The advancement of *in-situ* gelling techniques has attracted significant interest in recent years (2). The literature first introduced the terms stimuli-responsive hydrogel and smart hydrogel' in 1990 and 1991, respectively. In 2021, the synthesis and application of smart hydrogels received direct attention in about 2,800 papers, with 70% published in the last five years (3). The beneficial properties of in situ-forming polymeric delivery systems, for instance, their ability to demonstrate expected viscosity and drug content, their potential to modulate drug release by modifying their structure in response to external stimuli, and their ease of administration with reduced dosing frequency, have generated this considerable interest (4, 5).

There are several significant benefits to the in situ polymeric gel-based formulations, including improved patient compliance, a longer duration of drug residency at the desired site, a reduction in the frequency of drug administration, a low dose needed for treatment, and a decrease in systemic and local negative effects. Additionally, long-term local administration of drugs can be achieved with these polymeric gel-based systems (6, 7).

In situ-forming polymeric systems for drug delivery exist in a sol state before administration, but upon administration, they undergo gelation to form a gel. The gel formulation is triggered by various elements such as temperature, ionic strength, pH, magnetic or electric field ,or chemicals (8).

The main explanation for this delivery system's tremendous effectiveness is its capacity to be supplied via various routes for both local and systemic effects. Additionally, the implementation of innovative drug delivery methods, such as liposomes, nanoparticles, microspheres, pegylation, nanoemulsion, and microemulsion, enhances the promise of this delivery system (9).

Approaches of in situ gel drug delivery

Three primary processes for producing *in-situ* gelation are illustrated in **Figure 1**, encompassing physical alterations in biomaterials (e.g., solvent exchange and

swelling), physiological stimuli (ex: temperature, pH), and chemical reactions (e.g., enzymatic, chemical, and photo-initiated polymerization) (10).

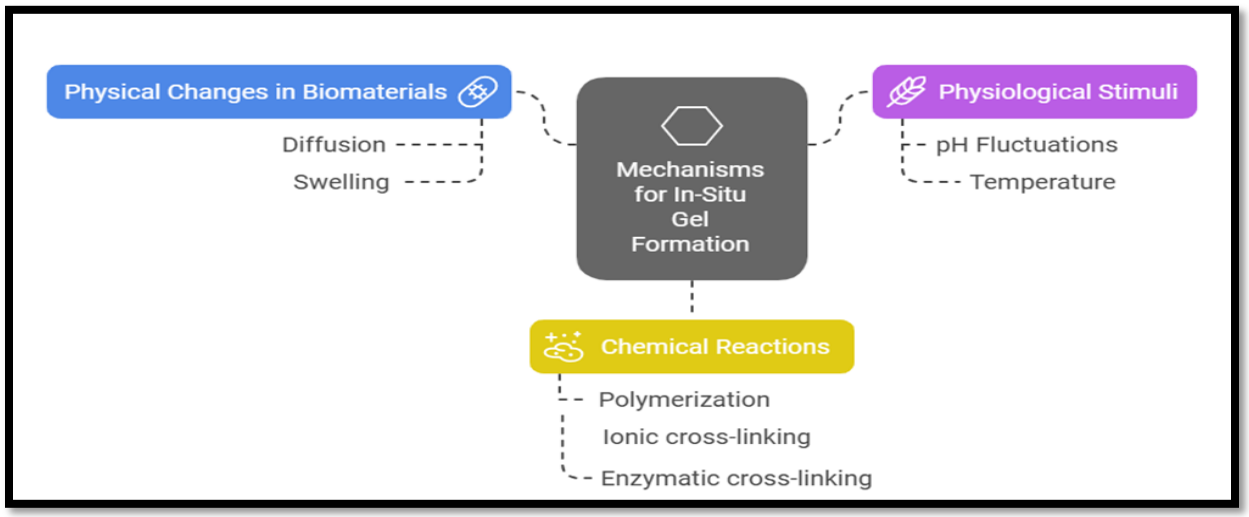

Figure 1: Mechanisms for inducing *in-situ* gel formation (10)

Physical *in situ* gelation

a) Solvent exchange or diffusion

In this technique, a pharmaceutically approved organic solvent dissolves the water-insoluble polymer, for instance, Ethocel (EC), making it either miscible or partially miscible in an aqueous environment. The drug is included in this polymeric solution. the solvent from the polymer solution diffuses into the surrounding tissue, causing the polymer matrix to precipitate or solidify and form a depot that releases the drug in a controlled manner. An example of this system, N-methyl pyrrolidone (NMP), which has been demonstrated to be a useful solvent (11).

b) Swelling

In situ gel formation occurs when a polymeric substance swells to occupy a certain area after absorbing water from the surrounding environment. One such substance is myverol 18-99 (glycerol mono-oleate), which is a polar lipid that forms lyotropic liquid crystalline phase structures by swelling in water. This amphiphilic molecule organizes into an ordered array based on the water content and the system's temperature. At water contents below 15% w/w, a bilayer conformation is observed, resulting in the formation of a lamellar phase gel. When water content exceeds 15% w/w, a cubic phase is established, comprising two interpenetrating networks of curved lipid bilayers. This cubic structure creates a rigid gel that incorporates a hydrophobic entity, thereby meeting the requirements for sustained adhesion (12, 13).

Physiological *in situ* gelation

a) pH-triggered *in situ* gelation

Gelling agents employed in *in-situ* gel formation are polymers with pH-sensitive acidic or alkaline groups. These polymers are classified as polyelectrolytes, synthesised with weakly ionizable basic or acidic groups. These polyelectrolytes can dissociate or associate hydrogen ions in reaction to

fluctuations in environmental pH (14). The majority of pH-sensitive polymers with anionic (acidic) groups are derived from PAA (Carbopol®, Carbomer) and its derivatives. This technique is primarily employed in ocular drug delivery systems to enhance the precorneal residence period of drugs, hence improving bioavailability. Since this formula is prepared at pH 4.4 as solution, However, at pH 7.4, which corresponds to the pH of tear fluid, gelation happens (1).

Mechanisms of action

"Polyanions" or "polyacids" are terms attributed to pH-sensitive polymers with several acid groups, such as carboxylic acid (15). As shown in **Figure 2** at high pH levels, protons are lost, and cations from the outer solution enter the hydrogel for charge neutralization, creating a negatively charged polymer chain. The diffusion of these counterions with water elevates the osmotic pressure, leading to the expansion of the hydrogel (16). However, it accepts protons at an acidic pH (17). The "polybases" or "polycations," characterized by a high number of essential groups, have contrasting behavior. The basic groups in these polymers are protonated in an acidic environment, resulting in these being positively charged; however, deprotonation occurs at basic pH (17).

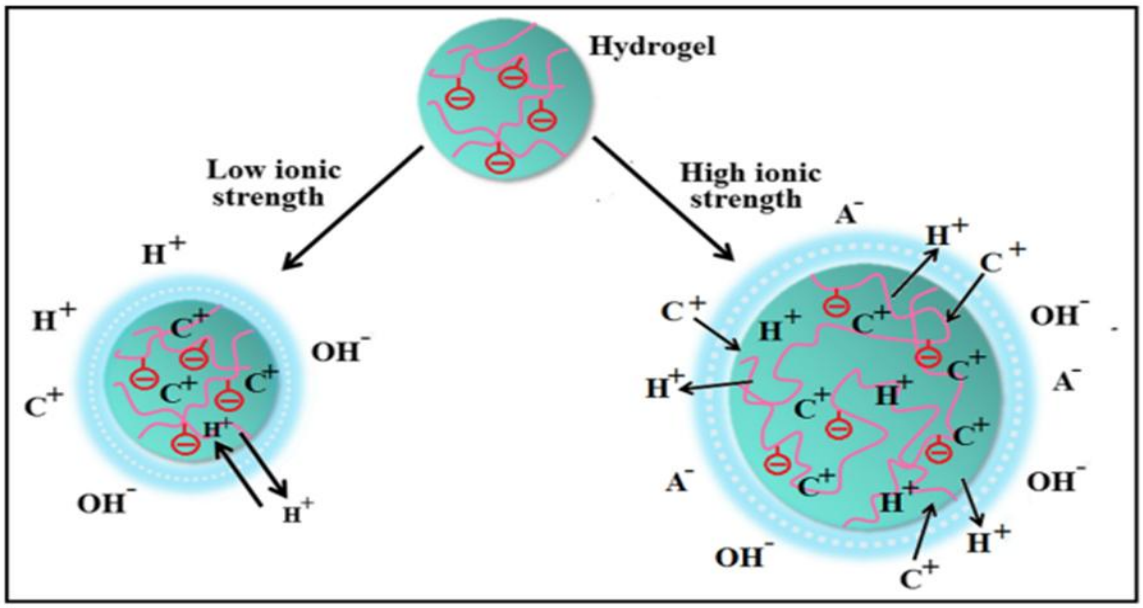

Figure 2: Schematic depiction of the volumetric and polymeric structural transition in hydrogels in response to changes in the ionic strength of the electrolyte solution (18).

b) Temperature-triggered *in situ* gelation

In drug delivery research, temperature-sensitive hydrogels are probably the most commonly studied class of environment-sensitive polymer systems (19).

There are three categories for thermally sensitive in situ gel systems (20):

1. Negative-type polymers, for instance, PNIPAAm (poly-N-isopropyl acrylamide), shrink as the temperature rises. This is called a negative temperature response.

2. Positive-type polymers, for instance, PAA (polyacrytic acid), swell as the temperature rises. This is called a positive temperature response.
3. Reversible-type polymers, like poloxamers (pluronics) and tetronics, undergo shrinkage and swelling in response to temperature changes.

Mechanisms of gelation

The process that underlies the abrupt shift in solubility of polymers in response to surrounding temperature fluctuations is that these polymers can self-assemble into micelles in an aqueous solution because of their hydrophilic and hydrophobic moieties. As the temperature rises, the individual micelles condense into densely packed formations owing to the hydrophobic interactions of the core resulting in gelation (21).

On the other hand, the balance between the hydrophobic and hydrophilic segments governs the gelation processes (**Figure 3**). Temperature variations have an impact on the hydrophobic interactions between hydrophobic segments and the hydrophilic interactions between hydrophilic segments and water molecules. Thus, the sol-gel transition can be induced and the initial equilibrium is disrupted by a minor temperature change (22).

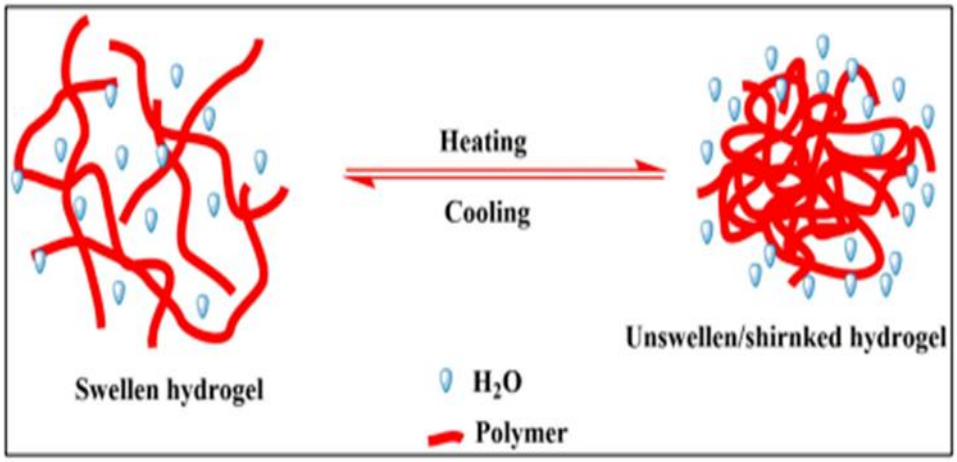

Figure 3: Thermo-sensitive hydrogels undergo a volume-phase transition in response to temperature variations (23).

Thermosensitive hydrogels exhibit a volume-phase transition at the lower or upper critical solution temperatures (LCST and UCST) (**Figure 4**). A lower critical solution temperature (LCST) is observed in the mixture if the increase in temperature results in the production of two immiscible liquid phases and leads to gel formation, resulting from a shift from hydrophilic to hydrophobic. When the binary mixture exhibits an upper critical solution temperature (UCST), the two liquid phases appear as the temperature falls. Since hydrophilic components constitute the majority of (UCST) hydrogels, their capacity to swell in an aqueous solution rises with increasing temperature. Below the critical temperature (UCST), the polymer matrix contracts and expels its water content. They thus display a gel state at a temperature lower than UCST (24). On the other hand,

LCST-type hydrogels have hydrophilic and hydrophobic constituents that undergo sol-gel transitions due to variations in temperature. Whenever the temperature falls beneath the Lower Critical Solution Temperature (LCST), the gel transitions into a solution or viscous liquid (25).

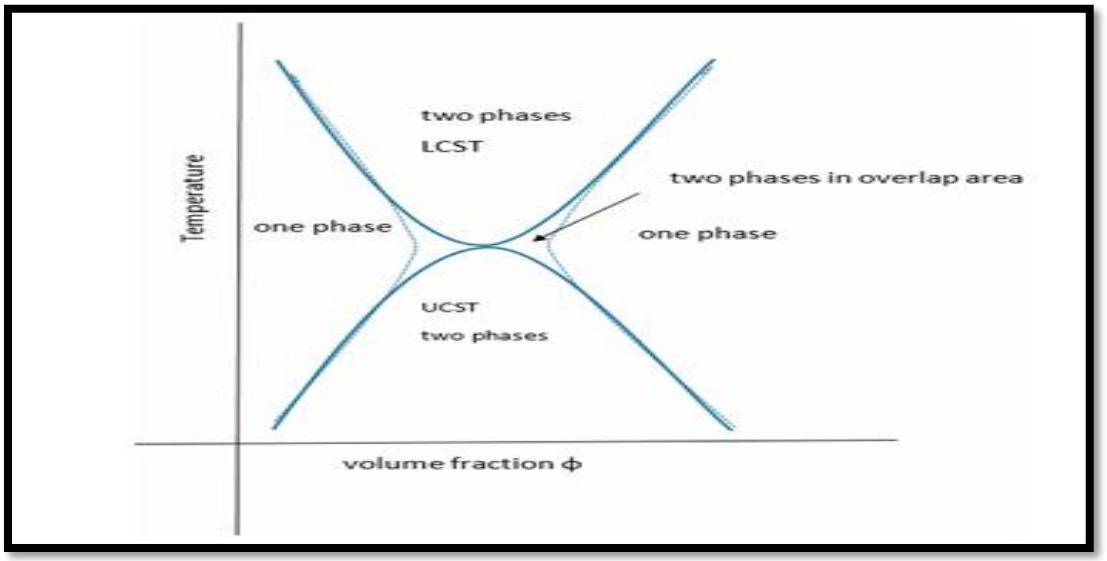

Figure 4: Volume phase transition at critical temperatures (26).

Chemical in situ gelation

Three types of chemical responses can cause in situ gelation: enzymatic cross-linking, ionic cross-linking, and photopolymerization.

a) Enzymatic cross-linking

Recently, the enzymatic cross-linking technique has been utilized for developing innovative injectable hydrogels that have gained interest due to their low cytotoxicity, excellent site specificity, rapid gelation, and capacity to function in typical physiological settings (27, 28). Hydrogels with the ability to release insulin have been used in intelligent stimuli-responsive delivery devices that have been studied. When blood glucose levels rise, cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can expand and release the trapped insulin in a pulsatile manner (29).

b) Ionic cross-linking

Polymers might undergo a phase transition when there are various ions present. These ionizable group polymers show sensitivity to ionic strength. The electrostatic attraction between oppositely charged objects accounts for their delicate character. For this reason, the polymer becomes soluble at an appropriate concentration of electrolyte solution but becomes insoluble in deionized water (30). For instance, some members of the polysaccharide family are ion-sensitive polymers (31). Commercially marketed as Gelrite®, gellan gum is an anionic polysaccharide that undergoes in situ gelling when it comes into contact with mono- and divalent cations such as Ca^{2+}, Mg^{2+}, K^{+}, and Na^{+}. Divalent cations, particularly Ca^{2+}, have the potential to trigger the gelation of the low-methoxy pectins. Similar to this, the interaction between guluronic acid segments in alginate chains and divalent or polyvalent

cations, such as Ca^{2+}, causes alginic acid to gel (31).

c) Photo-polymerization

Photopolymerization is a frequently utilized technique in the production of *in situ* hydrogels (32). Electromagnetic radiation with a suitable wavelength can be used to produce gel after injecting a solution of monomers or reactive macromers and an initiator into a target tissue. Acrylate or equivalent polymerizable functional groups are employed as the polymerizable groups on individual monomers or macromers due to their rapid photopolymerization when an appropriate photoinitiator is available (33). Typically, visible and long-wavelength UV light is employed. Because short-wavelength ultraviolet light can only penetrate tiny parts of tissue and is biologically dangerous, it is not widely used (34). The in situ polymerization systems are highly applicable for suture-less closure of wounds. In this regard, Smeds et al. fabricated methacrylated alginate hydrogel through UV or visible photolysis as the corneal wound sealant (35). However, a photoinitiator must be present at the gelation site for photopolymerization to occur. which may be toxic. In addition, the number of application sites is limited by the radiation source's penetration capacity, and the reaction has the potential to generate enough heat to cause tissue damage nearby (36).

Polymers used in the instruction of *in situ* gel

Poloxamer 407 (PoloX 407)

Poloxamer 407, which is primarily marketed under the registered trademarks of Pluronic F127\ (BASF labs, Wyandoote, USA) and Synperonic F127\ (ICI laboratories, Wilton, UK), has a molecular weight of about 12,600 (9,840-14,600)(37). The FDA guide includes poloxamer 407 as an inactive component for a variety of preparations, such as IV, inhalation, oral solution, rectal, and ophthalmic or topical formulations (38). These polymers are synthetic triblock copolymers of poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide) (PEO-PPO-PEO) as shown in **Figure 5** (39). About 70% of its composition is polyoxyethylene, which contributes to its hydrophilicity (40).

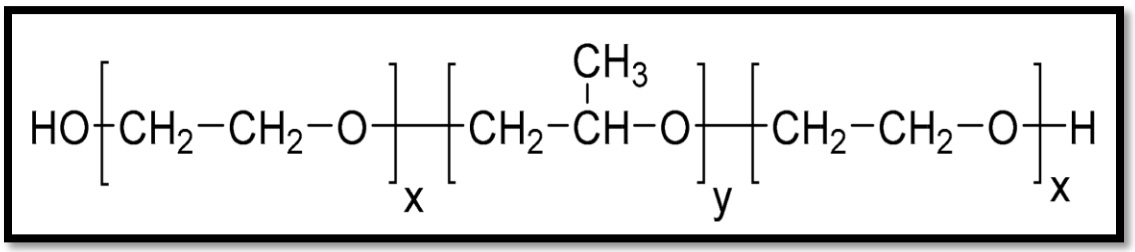

Figure 5: The chemical formula for poloxamers is defined by the lengths of PEO (polyethylene oxide) and PPO (polypropylene oxide) chains, denoted as x and y, respectively(39).

Combination with other excipients, such as Poloxamer 188 or mucoadhesive polymers, improves the sol-gel transition temperature or enhances the bioadhesive characteristics of Poloxamer 407, which promotes its action (41).

Poloxamer 188 (PoloX 188)

Poloxamer 188(Pluronic F-68, Flocork, and Kolliphor®) is an amphiphilic copolymer made up of three blocks: one central poly (propylene oxide) (PPO) chain that is hydrophobic flanked at either end by two

poly (ethylene oxide) (PEO) hydrophilic chains (42). **Figure 6** shows the chemical structure of poloX 188.

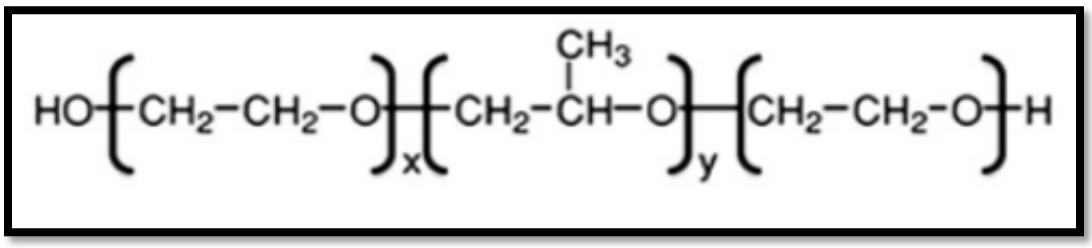

Figure 6: **Chemical structure of poloxamer 188 (42).**

Because of its surfactant characteristics, it is highly beneficial in the industrial, medicinal, and cosmetic domains (43). P188 is well known for its low toxicity, superior water solubility, high solubilizing capacity, good drug release characteristics, compatibility with other materials, and reduced occurrence of skin irritation (44). P188 is a popular ingredient in many over-the-counter medications like mouthwash, toothpaste, and laxatives, and it has a well-tolerated profile after repeated exposure (45).

Carbopol

Carbopol polymers stood for a brand name and were the first carbomers to enter the market. Conversely, "carbomer" serves as a generic name. Carbopol polymers are high-molecular-weight, cross-linked polymers based on acrylic acids (46). It is a polyacrylic acid polymer (PPA). The carboxylic groups of PAA receive protons at low pH and release protons at high pH.

The polymer has a highly coiled configuration in its powdered form, but the cross-linked structure begins to uncoil upon dispersion in water. In the presence of a base (At elevated pH), PAA expands and elevates the viscosity of the solution produced by the deprotonation of carboxylic acids into carboxylate ions. The resultant negative charge ions induce electrostatic repulsion, resulting in the extension of polymer chains into an expanded configuration (47, 48).

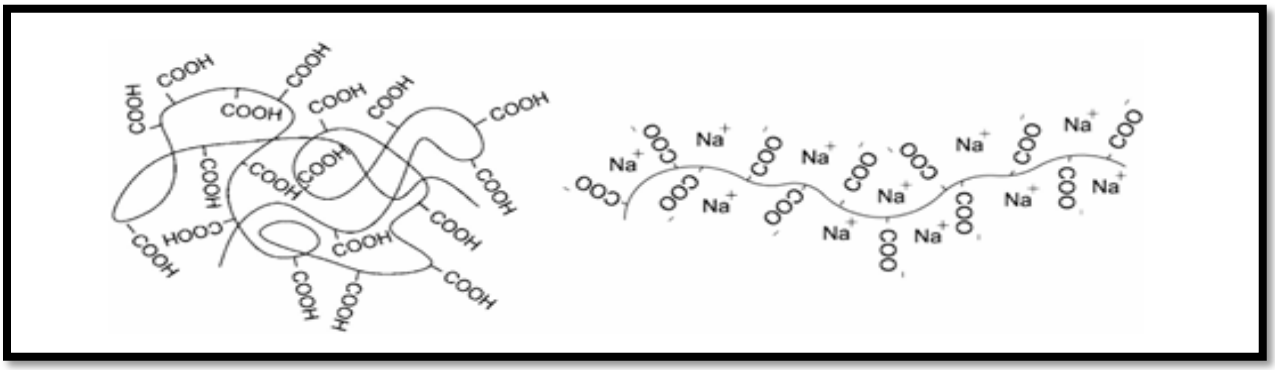

Figure 7: **The thickening steps of Carbopol gel, entangled polymer (left) and deionized microgel (right) (48).**

Ionization (protonation or deprotonation) significantly influences the swelling behavior of pH-sensitive gels; therefore, understanding the mechanisms that impact the swelling equilibrium in ionic gels is crucial. The components include the free energy of mixing between the network chains and the solvent, the ionic osmotic pressure, and the response of the expanding gel network to tensile and compressive forces (49). In Maryam Kouchak et al study, a pH-triggered *in situ* gel was developed for ophthalmic delivery of DRZ HCl by using Carbopol® (50).

Hydroxypropyl methylcellulose (HPMC)

Hydroxypropyl methylcellulose (HPMC) or Hypromellose is an odorless and flavorless powder dissolved in water; these properties are crucial for the manufacture of medications, foods, and cosmetics (51). An ionic strength or pH (within the pH range of 1 to 10) of the environment has no apparent impact on HPMC solubility (52).

Hydroxypropyl methylcellulose (HPMC) exhibits inverse thermoreversible gelation in aqueous solutions (53). It is a nonionic polymer with a linear glucose molecule structure, and hydrogen bonds stabilize its matrix (54). Because its structure contains neither permanent charges nor ionizable groups. This is significant because proteins and/or enzymes found in body fluids, together with electrolytes, should be unaffected by the polymer (51).

Pectin

Pectin, a polysaccharide that can be naturally found in plant cell walls, mostly consists of repeating units of α-(1-4)-linked D-galacturonic acid. The pectin structure might include homogalacturonan (HG), rhamnogalacturonan I (RG-I), and rhamnogalacturonan II (RG-II) domains (55). Both hydrophilic functional groups, including hydroxyl and carboxyl, and hydrophobic functional groups, such as carboxylic esters and amides, are affixed to pectin molecules. This renders pectin highly effective as an amphiphilic agent (56). The gelation mechanism entails divalent cations, including calcium ions, engaging with the carboxyl groups in the galacturonic acid residues. This results in the development of "egg-box" structures, wherein calcium ions link adjacent HG chains, forming a three-dimensional gel network characterized by increased strength and stability(57). In Kubo *et al.*'s study, they applied a similar mechanism for the *in situ* gelation of pectin (58).

Gellan gum

Gellan gum is an anionic heteropolysaccharide produced by the bacterium Sphingomonas elodea. It comprises glucose, rhamnose, and glucuronic acid and is interconnected to form a tetrasaccharide unit. Gelrite is a deacetylated gellan gum obtained by treating gellan gum with alkali to remove the acetyl group in the molecule. Gelrite creates a gel upon installation in the presence of calcium ions. The gelation process involves the creation of double helical junction zones, which subsequently aggregate to create three-dimensional networks through complexation with cations and hydrogen bonding with water (59).

Chitosan

The gelling of chitosan happens due to two factors: pH-responsive alterations and temperature variations. Chitosan is a natural part of crab and shrimp shells. It is a thermosensitive, biodegradable, polycationic polymer that is made by alkaline deacetylation of chitin. Chitosan is a biocompatible, pH-dependent cationic polymer that remains soluble in aqueous solutions up to a pH of 6.2. Neutralizing the chitosan aqueous solution to a pH above 6.2

results in the formation of a hydrated gel that precipitates (60).

Xanthan gum

An anionic extracellular polymer with a high molecular weight that is obtained from Xanthomonas campestris. Xanthan gum is used as a thickening, stabilizing, or suspending agent in a wide range of products, including food, cosmetics, and pharmaceuticals. As a result of several stimuli, including pH, ionic strength, temperature, and shear, xanthan gum changes conformation in water, going from a helix to a random coil (61).

Carboxymethyl cellulose (CMC)

CMC is a water-soluble, anionic biopolymer that is derived from cellulose. The feathers of CMC, which are frequently employed in drug administration and other biomedical studies, include characteristics such as hydrophilicity, bioadhesiveness, non-toxicity, and ability to gel-form (62). Carboxymethyl cellulose (CMC), present as the sodium salt NaCMC, is a polyelectrolyte and a smart cellulose derivative. At low concentrations, it shows sensitivity to pH, but at higher concentrations, the molecules overlap, coil up, and then entangle to form a physically thermoreversible gel (63).

Methods of in-situ gel formulation

Two primary techniques exist for the preparation of in situ gel:

Hot method

This preparation technique is applicable when utilizing gellan gum or pectin as gelling polymers. At elevated temperatures, chains of gellan gum dissolve in water, resulting in the formation of a random coil network conformation that remains soluble. Gellan gum solution undergoes gelation upon cooling in the presence of ions such as Ca^{2+} or K^{+} as shown in **Figure 8**. Pectin undergoes demethoxylation at elevated temperatures, resulting in a polymer solution. Moxifloxacin *in situ* gel was formulated utilizing gellan gum through a hot method (64, 65).

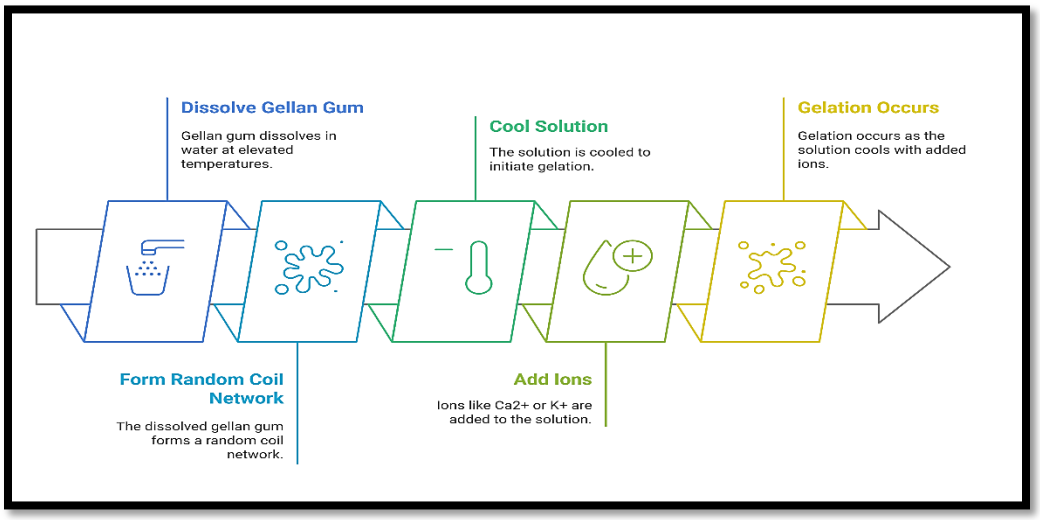

Figure 8: Gelation process of gellan gum using the hot method of preparation (64)

Cold method

The cold method involves dissolving a precisely weighed amount of gelling polymer (such as poloxamer) in the proper volume of distilled water (DW) using an ice bath (4°C) and stirring continuously for 30 minutes to achieve uniform dispersion. To obtain a transparent preparation, the resulting dispersion was then refrigerated for the entire night. The precise weight of the mucoadhesive polymer was dissolved in an appropriate volume of distilled water and continuously stirred using a magnetic stirrer. Then the gelling polymer and mucoadhesive polymer dispersions were continuously blended in an ice bath at 4°C on a magnetic stirrer. To this mixture, a solution of an accurately weighed amount of drug in DW was added with continuous stirring, and the volume was measured and completed to the required volume utilizing cold DW. The mixture was then left at 4°C in the refrigerator overnight to obtain clear solutions (66). **Show Figure 9**.

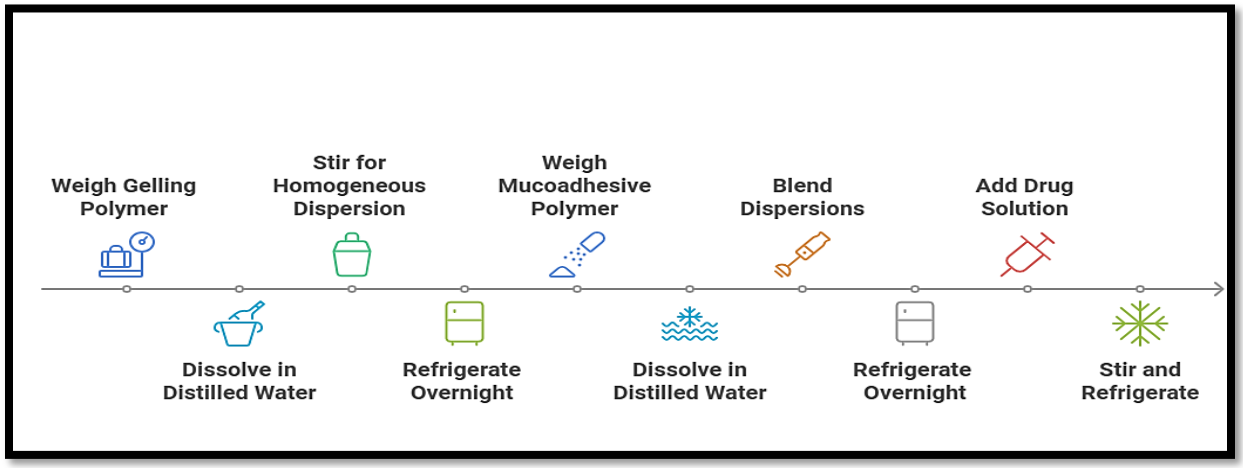

Figure 9: The cold formulation method of in situ gel (66).

Evaluation and characterization

In situ gels may be evaluated and characterized for the following parameters:

Appearance and Clarity

The clarity of the prepared solution is assessed through visual inspection against a black-and-white background. A visual analysis of selected formulas is conducted to identify potential incompatibilities arising from interactions between excipients or between excipients and the active ingredient (67).

Texture analysis

The texture analyzer is utilized to evaluate the cohesion, hardness, and consistency of the hydrogels, hence enhancing their injectability *in vivo*. This instrument offers a substantial indicator of the solution's syringeability. Gels with elevated adhesiveness levels are essential to provide adequate surface contact (68).

pH measurement

The pH of the prepared *in situ* gel is measured using a calibrated pH meter. The pH meter probe was immersed in each formulation, and the mean of three measurements for each formulation was determined (69, 70). Variations in pH can lead to discomfort or damage to the mucosal tissues, as well as impact the stability of formulations (71).

Sol-Gel transition temperature determination

Ten-milliliter clear vials containing a magnetic stir bar and a specified amount of thermosensitive liquid suppository are positioned in a thermostatic water bath and heated at a rate of 1 °C every 2 minutes while maintaining continuous stirring at 50 rpm. The temperature displayed on the thermostat is utilized to determine the gelation temperature when the magnetic bar stops movement owing to gelation. Solution-gelation temperature (sol-gel T) is the temperature at which the liquid phase makes a transition to gel (72, 73).

Measurement of gelation time (GT)

The specified method is utilized to ascertain the gelation time. A 30 mL universal tube containing 10 mL of the formulation is stirred magnetically at 100 rpm while the temperature increases gradually at a rate of 1°C/min. The gelation time is identified as the point at which the magnetic bead ceased rotation (74). Gelation time is critical, similar to sol-gel temperature, as the mixture must convert into a gel post-installation and maintain this gel state for a sufficient period to facilitate drug release. As a result, the formulas exhibit optimal gel strength, and a relatively short GT will remain in the correct location, preventing leakage from the intended site (75).

Gel Strength determination

The determination of gel strength involved weighing 5 g of prepared formula, and then placed in a 10 mL measuring cylinder within a temperature-controlled water bath. Once the formula reaches the gelation point and is congealed, the gel is subjected to pressure using a 3.5 g weight applied through a circular cup. The duration required for a weight of 3.5 g to pass 0.5 cm through the gel is measured in seconds (76). The gel strength is essential in the formulation of liquid suppositories, as it influences the optimal conditions for ease of insertion and prevention of leakage from the anus (77).

Osmolarity measurement

Osmotic pressure is determined using an osmometer, calibrated with purified deionized water, and subsequently with a 300 mOsmol NaCl (1% NaCl) reference solution. Subsequently, 50 µL of the formulations are utilized in a sterile, dry microtube. Following the inspection for air bubbles, the measurement was conducted (78).

Spreadability Test

The spreadability of the formulations is assessed by applying 0.5 g of the gel onto a 2 cm diameter circle premarked on a glass plate, followed by the use of a second glass plate. A weight of 0.5 kilograms is allowed to lie on the upper glass plate for 5 minutes. The overall diameter of the circle following the spreading of the gel is measured in centimeters (79).

Rheological study

This test is essential for evaluating in situ gels. The Brookfield rheometer and various other viscometers are utilized to evaluate the viscosity and rheological characteristics of *in situ* gelling drug delivery systems. *In situ* gelling solutions, primarily designed for parenteral and ocular administration, should possess a viscosity that facilitates drug delivery (80, 81).

Fourier Transform Infra-Red Spectroscopy and Thermal Analysis

Fourier transform infrared spectroscopy is conducted to examine the compatibility of components. Differential scanning calorimetry is employed to detect alterations in thermograms relative to the pure components, hence showing interactions (82).

***In vitro* Release Study**

It assists in evaluating the drug's release profile from its formulation. A modified

technique was utilized to mimic *in vivo* drug release from formulated *in situ* gels. The analysis was conducted using a USP Class II dissolution apparatus. A carefully quantified volume of formula was positioned within a dialysis bag constructed from a dialysis membrane that had been immersed in dissolving media for one day to ensure proper hydration and equilibration of the dialysis membrane. Before applying the gel, we firmly fastened the dialysis membrane on one side using rubber bands. The reverse side of the bag was effectively secured following the gel settling process using a similar technique, subsequently attached to the paddle using adjustable plastic clamps, and immersed in an appropriate volume of dissolution media, which was kept under controlled conditions (maintained at 37 ± 0.5°C and rotated at 50 rpm). At a predetermined time interval, a 5 ml sample from the dissolution media is taken out and substituted with fresh medium to maintain sink conditions to analyze the drug release spectrophotometrically at its λ max after being filtered using a 0.45 µm Millipore filter syringe (82, 83).

The acquired data were analyzed using mathematical equations (zero order, first order, Higuchi model) to elucidate the kinetics and mechanism of drug release from the implant formulations. The best drug release model depends on the type of drug formulation and therapeutic goals.

Uses of in situ polymeric drug delivery systems

In situ gelling systems can be categorized based on the route of administration as follows:

Oral drug delivery system

Researchers have thoroughly investigated the use of pH-sensitive hydrogels for targeted drug delivery to particular regions of the gastrointestinal tract. Polymers employed in oral *in situ* gel delivery systems are pectin, xyloglucan, and gellan gum. The efficacy of an orally administered *in situ* gelling pectin formulation for the sustained release of paracetamol has been documented (2). A formulation of in situ gelling gellan is shown as a way to deliver theophylline orally. The formulation comprised a gellan water dispersion in conjunction with a calcium chloride and sodium citrate complex. The acidic environment of the stomach releases calcium ions upon oral administration, leading to the gelation of gellan and the *in-situ* formation of a gel. Gellan formulations demonstrated enhanced bioavailability and a prolonged drug release profile of theophylline in rats and rabbits in comparison to the commercial sustained-release liquid dosage form (84). A floating *in situ* gelling system for amoxicillin, designed to enhance gastric residence time, was previously developed utilizing sodium alginate as the gelling polymer and HPMC K100 as the thickening agent. The formulated preparation enables site-specific delivery of amoxicillin for a duration of 10 to 12 hours, exhibiting zero-order release kinetics (85). An *in-situ* gel of roxatidine was previously formulated for the treatment of peptic ulcer, utilizing gellan gum and sodium alginate at varying concentrations of (0.1-0.4% W/V) and (0.2-1.0% W/V) as the gel matrix. It was concluded that the formulated preparation enhances patient compliance and bioavailability, making it ideal for peptic ulcer treatment (86).

Ocular drug delivery system

In situ gels for ocular delivery primarily utilize natural polymers, including gellan gum, alginic acid, and xyloglucan. Local ophthalmic drug delivery has been utilized for various compounds, including antimicrobial agents, anti-inflammatory agents, and autonomic drugs aimed at alleviating intraocular pressure in glaucoma. Previous delivery strategies frequently yield inadequate bioavailability and therapeutic

efficacy due to the rapid turnover and dynamics of high tear fluid, which lead to fast medication removal from the ocular surface. To address bioavailability issues, ocular *in situ* gels were formulated (2). The development and assessment of an ocular delivery system for the antibacterial drug gatifloxacin, utilizing the principle of ion-activated *in situ* gelation, has been previously described. Alginate (Kelton®) served as the gelling agent, while HPMC functioned as a viscosity-enhancer. The prepared gel, *in vitro*, enhanced prolonged drug release over an 8-hour duration. Furthermore, *in vitro* release experiments and *in vivo* pre-corneal retention investigations demonstrated that the alginate/HPMC solution resulted in superior drug retention compared to the individual alginate or HPMC solutions (87). R. Asasutjarita, R. *et al.*, optimized and evaluated thermoresponsive diclofenac sodium ophthalmic *in situ* gels. This study used poloxamer and carbopol. Poloxamer increases viscosity, while carbopol, through the salt effect, increases the solubility of diclofenac sodium and improves the systems' adhesion to the mucosa (88). In 2010, Gupta H. *et al.* developed an innovative *in situ* gel technology, activated by ions and pH, for the sustained ocular administration of Timolol maleate. Chitosan combined with gellan gum served as a gelling agent, resulting in a formulation that was non-irritant, improved transcorneal drug penetration, and extended retention at the corneal site (89).

Nasal drug delivery system

The nasal cavity is commonly employed to treat localized conditions, including rhinitis and nasal congestion. In recent decades, nasal medication delivery has attracted more attention as a possible approach for systemic therapy. A gel solution for nasal administration designed for the *in situ* application of mometasone furoate was created and assessed for its effectiveness in treating allergic rhinitis. The *in-situ* gel demonstrated a reduction in the severity of nasal symptoms in comparison with the available marketed product (0.05% memethasone furoate solution)(60). Mucoadhesive *in situ* gel formulations have shown an increase in residence time in the nasal cavity and an improvement in the drug's permeation properties (90). *In situ* gel formation was accomplished using polymers, for instance, gellan gum and xanthan gum. The mucoadhesive *in situ* gel is used to improve the bioavailability of the sumatriptan succinate that was previously evaluated and proved to be suitable for the nasal *in situ* route of administration. Hence, this can be viewed as a viable alternative to conventional nasal drops, which are valued for their ability to enhance the nasal residence time that influences intranasal bioavailability (91). Shah *et al.* developed and improved a pH-triggered mucoadhesive *in situ* nasal gel of sodium cromoglycate utilizing the pH-sensitive polymer carbopol 940 alongside several grades of mucoadhesive polymer HPMC (HPMC K100, HPMC K4M, and HPMC K15M). The optimal formulation, which contained carbopol 940 (0.75%) and HPMC K4M (0.5%), continuously released the drug *in vitro* for eight hours (92). Mahajan *et al.* formulated xyloglucan *in situ* gels including ondansetron hydrochloride as a model pharmaceutical agent. The intranasal delivery of the *in situ* gel in rabbits exhibited significantly higher bioavailability compared to the orally delivered drug solution, indicating the formulation's potential (93).

Injectable drug delivery system

The advancement of injectable drug delivery systems has garnered significant attention in recent years. An injectable *in situ* gel matrix including metoprolol succinate was previously prepared and evaluated utilizing the thermosensitive polymer Pluronic F 127

(20%) in conjunction with carbopol 934P, HPMC, and SCMC. The findings indicate that the temperature-sensitive injectable *in situ* gel is effective for achieving controlled drug release (94). The local administration of paclitaxel via intratumoral injection was examined using EMT-6 tumors implanted subcutaneously in albino mice. The research showed that one injection of the thermosensitive hydrogel containing paclitaxel into the tumor worked just as well as four intravenous doses of Taxol® (marketed injection) (95). Chiu *et al*. developed a pH-responsive injectable hydrogel utilizing N-palmitoyl chitosan (NPCS). Chitosan (a cationic polymer) exhibits a sol-gel transition at around pH 6.5 when the pH shifts from acidic to neutral. *In vitro* studies showed that the synthesized NPCS hydrogel was safe for a rat model and could break down naturally, with a strong response from macrophages that decreased over time as the breakdown process continued. Therefore, researchers concluded that biomedical applications could potentially utilize the synthesized hydrogel (96). Wang *et al*. made an injectable hydrogel with horseradish peroxidase (HRP) mediated gelatin–hydroxyphenylpropionic acid (Gtn-HPA) acid to help cartilage grow back. They then looked at how the stiffness of the hydrogel affected the activities of chondrocytes. The hydrogel is synthesized through the oxidative coupling of HPA moieties with HRP and H_2O_2. The findings indicate that the formulated Gtn-HPA injectable hydrogel influences cartilage tissue regeneration (97).

Rectal drug delivery system

The rectal route provides a noninvasive and effective method for drug administration when systemic or local effects are necessary. Suppositories are a popular method of rectal administration. However, the utilization of traditional solid suppositories frequently results in discomfort. Moreover, conventional solid suppositories may reach the distal colon, subjecting the administered drugs to first-pass metabolism (95). Choi *et al*. created and tested new *in situ* gelling liquid suppositories that can gel between 30 and 36°C. These suppositories use Poloxamer 188 and/or Poloxamer 407 to give them temperature-sensitive gelling properties for rectal use (98). The development and evaluation of a liquid suppository loaded with regorafenib for rectal delivery was previously mentioned. The study indicated that a regorafenib-loaded liquid suppository possesses significant potential for targeting colorectal cancer (CRC) due to better drug localization, enhanced bioavailability, and the absence of adverse effects at the application site (99). Metoclopramide HCL (MET HCL)-loaded liquid suppositories (LSs) were previously developed and evaluated using Poloxamer 407 (P407) as a thermosensitive polymer with one of the following mucoadhesive polymers: HPMC, HEC, or PVP at different concentrations (0.5%, 1.5%, or 2.5%). The results showed that the prepared MET HCL-loaded LS was successful in efficiently delivering MET HCL. All thermosensitive liquid suppositories exhibited continuous MET release for 8 hours (100). In their study, Jaafar *et al.* prepared and evaluated a thermosensitive mucoadhesive liquid suppository containing promethazine (PMZ) to enhance its absorption and bioavailability while reducing its adverse effects. The thermogelling agents used were poloxamer 407 (12–20%) and poloxamer 188 (4–12%), while the mucoadhesive polymer used was HPMC (0.5–2%). The formulas poloxamer 407/Poloxamer 188/HPMC K4M (16/4/0.5%) and poloxamer 407/poloxamer 188/HPMC K4M (16/4/0.75%) were selected for promethazine-loaded thermoresponsive liquid suppositories owing to their enhanced physical properties, such as gelation

temperature, gel strength, increased mucoadhesive force, and a moderate *in vitro* release of PMZ (101).

Vaginal drug delivery system

The vagina is a possible route for medication administration. Formulations utilizing a thermoplastic graft copolymer that undergoes *in situ* gelation have been developed for the sustained release of active ingredients such as estrogens, peptides, progestins, and proteins (102). A mucoadhesive in *situ gel* formulation containing clotrimazole (CLO) for the management of vaginal candidiasis was previously developed. It was concluded that the mucoadhesive *in situ* gels of clotrimazole represent a viable alternative for the treatment of vaginal candidiasis due to their favorable gel characteristics and effective vaginal retention (103). The formulation and enhancement of vaginal poloxamer *in situ* gels with a combination of metronidazole (MET) and curcumin (CUR) for the treatment of parasitic protozoan infections has been previously discussed. The study's findings indicated that the incorporation of MET and CUR into the PLX407/PLX188/PHR gel base efficiently maintained and marginally enhanced the efficacy of MET. The viability test results were analogous to those of the MET solution alone (104). Aboud *et al.* constructed cubosomal in situ gelling sponges (CIS) for the targeted delivery of sildenafil citrate (SIL) to the uterus for the treatment of female infertility. SIL-loaded cubosomes exhibited a sustained drug release for a duration of 8 hours. Following intravaginal CIS injection, they observed a significant enlargement in endometrial thickness, along with congestion and dilation of endometrial blood vessels (105).

Marketed product

Product name	Active ingredient(s)	Application	Marketed use	Company	Delivery type
Zymar®	Gatifloxacin	Ophthalmology	Bacterial conjunctivitis treatment	Allergan	Ophthalmic gel drops
Timoptol XE	Timolol Maleate	Ophthalmology	Glaucoma and ocular hypertension treatment	Merck and Co Inc	Ophthalmic gel-forming drops
Vigamox®	Moxifloxacin Hydrochloride	Ophthalmology	Bacterial eye infections	Alcon Pharmaceuticals	Ophthalmic gel drops
ReGel®	Paclitaxel	Oncology	Sustained release for cancer therapy	Macromed	Injectable gel
Cymetra	Micronized AlloDerm	Soft Tissue Repair	Tissue augmentation	LifeCell Corporation	Injectable gel
Akten TM	lidocaine hydrochloride	Ophthalmology	ocular surface anesthesia	Thea Pharma USA	Ophthalmic gel drops
AzaSite	azithromycin	Ophthalmology	Bacterial eye infections	Insite vision	Ophthalmic gel drops
Virgan	Ganciclovir	Ophthalmology	Viral eye infections	Thea Pharma USA	Ophthalmic gel drops

Conclusion

Drug delivery systems utilizing *in situ* gelling demonstrate superiority over oral dosage forms due to enhanced bioavailability, avoidance of first-pass metabolism, immediate exposure to systemic circulation, and consistent dosage forms. One of the most critical features of *in situ* gelling systems is the sol-gel phase transition, which involves transitioning from a liquid state to a solid phase upon exposure to physical and chemical parameters such as pH, temperature, and the presence and concentration of ions. Additionally, patients can receive them through various methods in a controlled release manner, including oral, ocular, rectal, and nasal. These unique properties of in situ gelling systems have prompted extensive research and development, resulting in more efficient systems suitable for drug delivery.

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