



Overview on In-situ Floating Drug Delivery System

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Abstract:

The development of successful controlled release products is crucial for enhancing gastric residence time and improving patient compliance, both of which are effectively achieved by floating in situ gels. These gels offer numerous advantages over traditional dosage forms, including continuous and prolonged drug release, as well as excellent stability and biocompatibility, making them a dependable choice for drug delivery. In situ gels can be formulated using a variety of natural and synthetic polymers, allowing for their application across multiple administration routes such as oral, ocular, transdermal, buccal, intraperitoneal, parenteral, injectable, rectal, and vaginal. There is considerable potential for research and innovation in in situ gel systems, which can lead to advanced techniques in drug delivery systems.

Introduction:

Over the past 30 years, there has been increased focus on developing controlled and sustained drug delivery systems. The aim of these systems is to reduce the frequency of dosing and enhance the effectiveness of drugs by targeting the site of action, decreasing the required dose, and providing uniform drug delivery. The 'in situ gel' system has emerged as a leading novel drug delivery system. It facilitates sustained and controlled drug release, improving patient compliance and comfort through its unique 'sol to gel' transition feature. In situ gelling systems are liquids at room temperature but undergo gelation upon contact with body fluids or changes in pH. Unlike rigid gels, they can be easily applied in liquid form to the site of drug absorption, where they swell into a robust gel, prolonging the residence time of the active substance. In situ gel formation is triggered by various stimuli, such as pH change, temperature modulation, or solvent exchange. These gels can be administered via oral, ocular, rectal, vaginal, injectable, and intraperitoneal routes. In situ gel drug delivery systems have been employed to deliver drugs for systemic and local effects in the stomach. Various natural and synthetic polymers, including gellan gum, sodium alginate, xyloglucan, pectin, chitosan, poly (DL-lactic acid), poly (DL-lactide-co-glycolide), and polycaprolactone, are utilized in formulating in situ gels. Using biodegradable and water-soluble polymers enhances the acceptability and efficacy of these drug delivery systems. The gel formed from in situ gelling systems is lighter than gastric fluids, allowing it to float over stomach contents or adhere to gastric mucosa due to the bioadhesive nature of the polymer. This results in gastric retention of the dosage form, increased gastric residence time, and prolonged drug delivery in the gastrointestinal tract.

Keywords: Floating drug, Retention time, In-Situ system etc

Advantages:[2][3]

1. Ease of the drug administration
2. It can be administered to unconscious patient

Disadvantage:[2]

1. It required high levels of fluids
2. The solution form of the drug is more susceptible for degradation

Applicability of In-situ gelling system**Oral delivery:**

Pectin, xyloglucan, and gellan gum are natural polymers utilized in in situ forming oral drug delivery systems. The efficacy of an orally administered in situ gelling pectin formulation for the extended release of paracetamol has been established. The key advantage of using pectin in these formulations lies in its water solubility, which eliminates the need for organic solvents. An in situ gelling gellan formulation has also been investigated as a vehicle for the oral delivery of theophylline. This formulation includes a gellan solution with a calcium chloride and sodium citrate complex. Upon oral administration, calcium ions are released in the stomach's acidic environment, triggering the gelation of gellan and forming an in situ gel. Studies in rats and rabbits have shown that gellan formulations provide enhanced bioavailability and a sustained release profile of theophylline compared to commercial sustained-release liquid dosage forms.[5][6]

Ocular Delivery:

In situ gels for ocular drug delivery represent a significant advancement in improving the bioavailability of drugs intended for eye treatments. Natural polymers such as gellan gum, alginic acid, and xyloglucan are frequently utilized in these formulations due to their biocompatibility and ability to form gels upon contact with the eye's surface. Ophthalmic drug delivery faces challenges with conventional systems, particularly due to the rapid turnover of tear fluids, which leads to quick elimination of the drug and thus poor therapeutic efficacy. This issue is particularly problematic for drugs like antimicrobial agents, anti-inflammatory medications, and autonomic drugs used to manage intraocular pressure in glaucoma. To address these challenges, in situ gels were developed, which transition from a liquid to a gel state when administered into the eye. This gelation prolongs the drug's residence time on the ocular surface, thereby enhancing drug absorption and therapeutic outcomes. Gellan gum has been extensively studied for this purpose, as its gel-forming properties are well-suited for ophthalmic applications. For instance, Miyazaki et al. developed an in situ gel formulation using 1.5% w/w xyloglucan as the polymer. This formulation demonstrated a significant mitotic response in the rabbit eye for up to four hours when applied to the lower cul-de-sac, indicating its potential for sustained ocular drug delivery. Similarly, an ophthalmic delivery system for indomethacin, a nonsteroidal anti-inflammatory drug used to treat uveitis, was formulated using a water-soluble Carbopol system. The in vitro studies of this system showed a sustained release of indomethacin for up to eight hours, highlighting its potential as a viable alternative to conventional eye drops.[6]

Nasal Delivery :

A novel in-situ gel system was developed for the nasal delivery of mometasone furoate, aiming to enhance the treatment of allergic rhinitis. This system utilized gellan gum and xanthan gum as the primary polymers responsible for gel formation upon contact with the nasal mucosa. The efficacy of this formulation was tested in an established animal model of allergic rhinitis. Sensitized rats were exposed to antigens, and the effect of the in-situ gel on nasal symptoms was meticulously monitored. The results demonstrated that the in-situ gel significantly inhibited the onset and severity of nasal symptoms compared to the widely used marketed product, Nasonex (mometasone

furoate suspension 0.05%). Histopathological examinations of the nasal cavities from treated rats revealed that the in-situ gel formulation preserved the integrity of the ciliated respiratory epithelium and maintained the normal appearance of goblet cells. These findings confirmed that the formulation was not only effective but also safe for repeated nasal administration, with no observed tissue damage or adverse effects. In another innovative approach, Wu et al. developed a thermosensitive hydrogel aimed at improving the nasal delivery of insulin. This hydrogel was formulated by mixing N-[(2-hydroxy methyl trimethylammonium) propyl] chitosan chloride with poly(ethylene glycol) and a small amount of α, β -glycerophosphate. The formulation was designed to remain in a liquid state at room temperature but to rapidly transition into a gel when exposed to body temperature (37°C). In vivo studies in animals showed that this hydrogel could effectively reduce blood glucose levels by 40-50% within 4-5 hours after administration, demonstrating a prolonged hypoglycemic effect. Importantly, there was no evidence of cytotoxicity, underscoring the safety of the hydrogel for nasal administration.[4]

Vaginal and Rectal Delivery :

In situ gels are gaining attention for their potential in drug delivery via rectal and vaginal routes, offering advantages such as prolonged drug residence time and improved patient compliance. Miyazaki et al. explored the use of xyloglucan-based thermoreversible gels for rectal delivery of indomethacin. Their study demonstrated that administering indomethacin-loaded xyloglucan gels to rabbits resulted in a broader drug absorption peak and extended drug residence time compared to a commercially available suppository. This extended residence time enhances the drug's therapeutic efficacy and reduces the frequency of dosing, which can significantly improve patient comfort and compliance. For vaginal drug delivery, a mucoadhesive, thermosensitive, prolonged-release gel incorporating a clotrimazole- β -cyclodextrin complex was developed for the treatment of vaginitis. The formulation aimed to enhance therapeutic outcomes by ensuring that the drug remains in contact with the vaginal mucosa for an extended period. This approach not only improves the treatment's effectiveness but also reduces the risk of side effects and the need for frequent reapplication. Moreover, a significant reduction in the maximum concentration (C_{max}) of indomethacin was observed following the administration of the in situ polymeric system. This reduction in C_{max} is particularly noteworthy as it suggests a lower risk of systemic side effects, such as those affecting the nervous system, which can be a concern with indomethacin therapy.[6][7][8]

Injectable drug Delivery:

The development of injectable in situ gel-forming drug delivery systems has garnered significant attention in recent years, particularly for their potential in targeted cancer therapy. One such innovative system is a novel, injectable, thermosensitive in situ gelling hydrogel designed for tumor treatment. This hydrogel is composed of a chitosan solution, which is neutralized with β -glycerophosphate to enable the formation of a gel upon injection into the body. In a preclinical study, this hydrogel was used to deliver paclitaxel, a well-known chemotherapeutic agent, directly to tumors. The formulation was injected intratumorally into EMT-6 tumors that had been implanted subcutaneously in albino mice. The thermosensitive nature of the hydrogel allowed it to remain in a liquid state at room temperature, facilitating easy injection, but it rapidly formed a gel upon contact with the warmer body tissues, ensuring localized and sustained release of paclitaxel directly within the tumor site. The localized delivery system was designed to maximize the concentration of paclitaxel at the tumor site while minimizing systemic exposure, which is crucial for reducing the side effects typically associated with chemotherapy. The study demonstrated the potential of this injectable in situ gelling hydrogel to provide effective, localized tumor treatment, potentially offering a more targeted and less toxic alternative to conventional chemotherapy methods.[4]

Floating drug delivery systems

- ❖ The Floating Drug Delivery System (FDDS), introduced by Davis in 1968, is designed to extend the gastric residence time of drugs, thereby enhancing their bioavailability.

- ❖ This system is particularly useful for drugs with a narrow absorption window, short half-life, or those unstable in the intestinal environment. FDDS ensures that the drug remains buoyant in the stomach, providing a controlled and sustained release.
- ❖ While traditional solid forms like tablets and capsules are stable, they require swallowing whole and come in fixed strengths, making dosage adjustments challenging.
- ❖ An innovative solution involves using low-viscosity gel-forming solutions that, upon contact with gastric fluids, transform into a floating gel.
- ❖ This stomach-specific system enhances gastric retention and improves drug delivery in the stomach.[9][10][11][12]

Mechanisms of Floating Oral In-Situ Gel

- ❖ Various methods have been developed to increase the retention time of dosage forms in the stomach, enhancing drug absorption.
- ❖ Among these, Floating Drug Delivery Systems (FDDS) are the most common. FDDS have a lower density than gastric fluids, allowing them to float in the stomach and release the drug at a controlled rate, thereby increasing gastric residence time and stabilizing plasma drug levels.
- ❖ For effective buoyancy, FDDS require both sufficient gastric content and a minimal floating force (F). A specialized apparatus measures this force to optimize the system's stability and ensure consistent performance in maintaining buoyancy.[9][13]

Formula:

$$F = F \text{ buoyancy} - F \text{ gravity}$$

$$= (D_f - D_s) gv$$

Where,

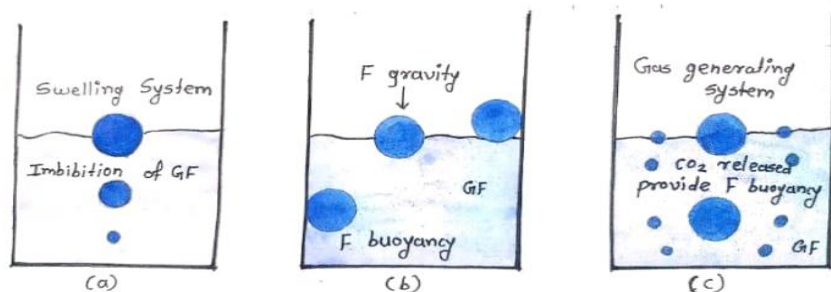
F = total vertical force,

D_f = fluid density,

D_s = object density,

v = volume and

g = acceleration due to gravity.



Factors Affecting the Floating System[13][14][15][16]

A. Physicochemical factors: Several factors influence gastric retention time (GRT) of dosage forms

Size: Dosage forms with a diameter over 7.5 mm tend to have better gastric retention than those with larger diameters like 9.9 mm.

Shape: Spherical or circular-shaped dosage forms generally exhibit better gastric retention compared to other shapes.

Density: The gastric retention time is influenced by the density of the dosage form; lower density forms typically float longer.

Feed Frequency: More frequent feeding can extend gastric retention time.

Nature of Meal: Meals containing indigestible polymers or fatty acids can shift stomach motility to a fed state, slowing gastric emptying and prolonging drug release.

Concomitant Drug Administration: Drugs that affect gastrointestinal motility, such as anticholinergics, can influence the efficiency of gastric retention.

B. Biological Factors:

Age: Children generally have shorter gastric retention times compared to adults.

Gender: Females typically have slightly longer gastric retention times (4-5 hours) compared to males (around 4 hours).

Fed vs. Unfed State: Gastric motility varies between fed and unfed states, affecting retention times accordingly.

Advantages:[13][17][18]

1. Floating dosage forms such as tablet and capsule will persist in the
2. solution for continue time even at the alkaline pH of the intestine Floating drug delivery systems are useful for presenting local stomach action drugs.
e.g. Antacid.

Disadvantage:

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
2. Some drugs present in the floating system causes irritation to gastric mucosa.

Approaches of floating In- situ Gelling System

A. Physiological stimuli

a. Temperature triggered in situ gel:

Temperature is a common catalyst in environmentally responsive polymers used in in situ gelling formulations. These hydrogels are liquid at room temperature (20-25°C) but gel upon contact with body fluids (35-37°C) due to the increase in temperature. This process requires no external heat, as the gelation is triggered by body temperature. There are three types of temperature-sensitive systems: negatively thermo-sensitive (e.g., poly(N-

isopropylacrylamide)), positively thermo-sensitive, and thermally reversible systems (e.g., poloxamers, pluronics).[3][19]

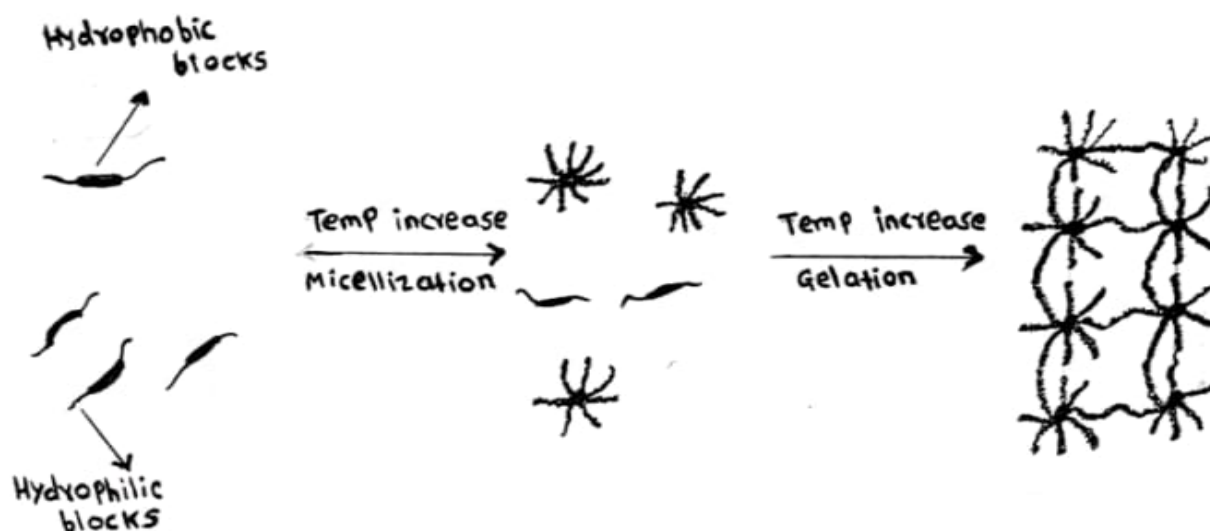


Fig. a) Mechanism of temperature triggered in situ gel system

b) pH-Triggered In Situ Gels: These gels form in response to pH changes, utilizing pH-sensitive polymers that contain acidic or basic groups. These polymers, known as polyelectrolytes, either accept or release protons in response to environmental pH shifts. An increase in external pH causes these polymers to swell, leading to in situ gel formation.[3][20]

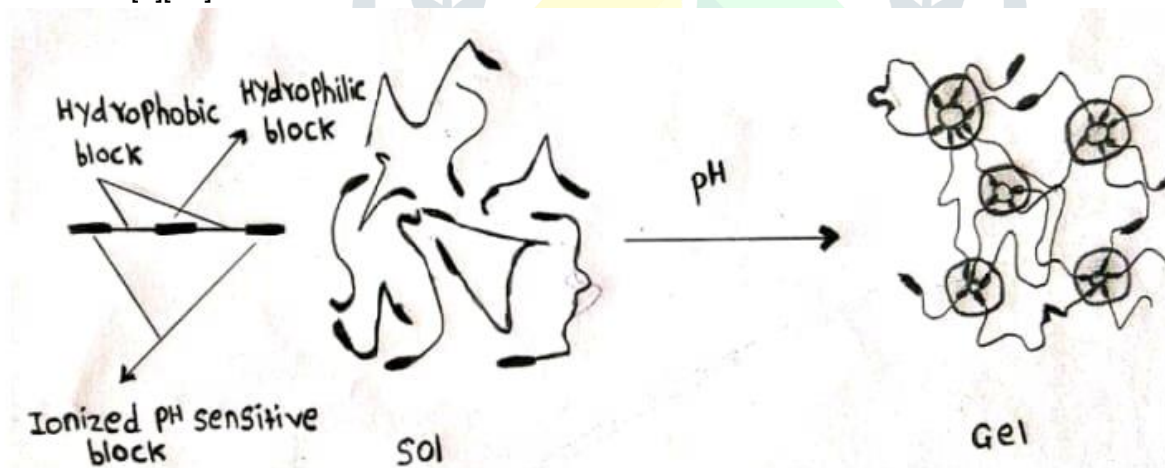


Fig. b) Mechanism of pH triggered in situ gel system

B. Physical

change in biomaterials

- a) **Swelling:** In this approach, the polymer absorbs fluid from the surrounding environment, causing it to swell and gradually release the drug. A commonly used substance is Myverol 18-99 (glycerol mono-oleate), a polar lipid that swells in water to form a crystalline lyotropic liquid phase structure. This material exhibits bio adhesive properties and can be broken down in vivo by enzymes.[1][21][22][23][24]

- b) **Diffusion:** This process involves the diffusion of a solvent from the polymer solution into surrounding tissue, leading to the precipitation of the polymer matrix. N-methyl pyrrolidone (NMP) is commonly used to form in situ gelling systems through this method.[2][21]

C. Chemical Reactions:

- a) **Enzymatic Cross-Linking:** Gel formation occurs through cross-linking with enzymes naturally present in body fluids. This method is advantageous because it operates under physiological conditions without harmful chemicals. It's particularly useful in stimuli-responsive systems, such as those tested for insulin delivery. The rate of gel formation can be controlled by adjusting enzyme levels, allowing the mixture to be injected before gelling.[2][9][25][26]
- b) **Ionic Cross-Linking:** In this process, ion-sensitive polymers undergo phase conversion in the presence of ions like Na⁺, K⁺, Ca²⁺, and Mg²⁺. Polysaccharides like kappa-carrageenan form rigid gels with K⁺, while iota-carrageenan forms elastic gels with Ca²⁺. Gellan gum also forms in situ gels in the presence of mono- and divalent cations.[1][23][25][27][28]
- c) **Photo-Polymerization:** Electromagnetic radiation is used to induce gel formation in situ. A solution of light-sensitive macromers or monomers is applied to the tissue site, where exposure to electromagnetic radiation initiates polymerization. Long-wavelength ultraviolet or visible light is typically used, as they are safer and more effective for photo-polymerization than short-wavelength UV, which has limited tissue penetration and is biologically harmful.[3][9][29]

Polymers used for floating oral in situ gelling system:

Sodium Alginate: A polysaccharide derived from brown seaweed, consisting of polyuronic acids (β -D-mannuronic and α -L-guluronic acids). It forms gels when exposed to gastric fluids through ion exchange (sodium to calcium), creating a three-dimensional network known as the "egg-box model." Sodium alginate is used in sustained-release formulations due to its bio adhesive properties.[30][31]

Gellan Gum: An anionic polysaccharide produced by *Pseudomonas* species. It forms a gel in the presence of cations like K⁺, Mg²⁺, Ca²⁺, and Na⁺. Gellan gum is used in oral floating dosage forms due to its gelling and stabilizing properties.

Pectin: An anionic polysaccharide extracted from plant cell walls, primarily composed of α -(1-4)-D-galacturonic acid. It forms gels in the presence of divalent ions like calcium, making it useful for in situ gelation in drug delivery systems.

Xanthan Gum: A high molecular weight extracellular polysaccharide produced by *Xanthomonas campestris*. It has a cellulosic backbone with a trisaccharide side chain and is used for its thickening and stabilizing properties.[6]

Alginate Acid: A polysaccharide composed of β -D-mannuronic and α -L-guluronic acid. It forms gels in the presence of divalent cations and is used in ophthalmic formulations due to its biodegradable and non-toxic nature.[2][32]

Chitosan: A biodegradable, thermosensitive polymer derived from chitin. It forms gels at pH levels above 6.2, making it suitable for pH-sensitive drug delivery systems.[1][27][33]

Hydroxypropyl Methyl Cellulose (HPMC): A partially methylated and hydroxy propylated cellulose used in various pharmaceutical formulations as a coating, thickening, and controlled-release agent. It exhibits thermoreversible gelation properties.[7]

N-isopropyl Acrylamide Copolymers: Non-biodegradable polymers with a lower critical solution temperature of 32°C, collapsing at this temperature, making them useful for thermo-responsive systems.

PEG/PLGA Block Copolymers: These combine thermogelation, biodegradability, and non-toxicity, offering safer and longer-lasting injectable gels.[34]

Poloxamer: A triblock copolymer consisting of polyethylene oxide and polypropylene oxide. It is used as a gelling, emulsifying, and solubilizing agent, providing transparent gels with good thermal setting properties.[3][35]

Methyl Cellulose: A thermoreversible gelling polymer that gels at 60–80°C and dissolves upon cooling. It is used in various pharmaceutical formulations for its gelling and thickening properties.

Ethyl (Hydroxyethyl) Cellulose (EHEC): A non-ionic, amphiphilic polymer with thermo-gelling properties, particularly in the presence of ionic surfactants. It forms stiff gels around 35°C, making it suitable for drug delivery systems[36].

Evaluation of floating in situ gel:

Clarity: Visual inspection under black and white backgrounds to assess the clarity of the formulated solution.[23]

Texture Analysis: A texture analyzer measures the firmness, consistency, and cohesiveness of the formulation, important for ease of in vivo administration. Higher adhesiveness is needed for intimate contact with tissues.[5]

In-Vitro Floating Study: Measures the time taken for the dosage form to become buoyant (floating lag time) and the total duration it remains buoyant (Total Floating Time) in simulated gastric fluid.[17]

pH Measurement: The pH of the formulation is checked using a pH meter after adding NaOH dropwise with continuous stirring. **Viscosity Measurement:** The viscosity and rheological properties of in situ gels are evaluated using viscometers such as the Brookfield viscometer.[23]

Gel Strength: Gel strength is measured using a rheometer, where the load changes on a probe are tracked as it is pushed through the gel.[5][6]

Fourier Transform Infrared (FTIR) Spectroscopy & Thermal Analysis: FTIR is used to study drug-polymer interactions, while thermal analysis (TGA and DSC) assesses the water content and thermal properties of the gel.[6][37]

In -Vitro Drug Release: Drug release from in situ preparations is tested using a plastic dialysis cell with cellulose membrane separation, and samples are analyzed periodically.[1]

Stability Studies: Formulations are stored at 40±2°C and 75±5% RH as per ICH guidelines. Samples are analyzed monthly for clarity, pH, gelling ability, drug content, and rheological properties.[5]

In Vivo Study: Conducted on male Wistar rats using the pylorus ligation method to induce ulcers. Groups are treated with control, placebo gel, plain drug solution, and optimized in situ gel to assess pharmacodynamics.[1]

Histopathological Studies: Mucosal tissue is treated with optimized organ gel and compared to control. Tissue sections are stained and examined microscopically to assess any structural changes, with no significant effects observed.[6][40]

Example of marketed Formulation [9][41][42][43][44]

Sr. No.	Type of Drug Delivery	Name of Drug	Marketed Formulation	Indication
1	Oral	Betamethasone	Celestone®	Use to treat conditions such as allergic reactions, dermatologic disease, endocrine disorder, gastrointestinal disease, haematologic disorder.
		Ferrous sulphate	Convicon®	Used in the treatment of megaloblastic anemia's, infancy, pregnancy, anemias of nutritional origin etc.
2	Nasal	Fluconazole	Diflucan®	Used to prevent the fungal infections.
		Zinc gluconate	Zicam®	Used to prevent cold and the relief of cold symptoms such as sore throat, runny



				nose, cough and congestion.
3	Ocular	Ganciclovir	Zirgan®	Used to treat cytomegalovirus disease in solid organ transplant recipients and in individuals
		Lidocaine	Akten®	Suitable for treating eye surface anesthetics during ophthalmological procedures
		Pilocarpine	Carpine®	Used to minimize the pressure in the eye and treat dry mouth
		Timolol	Timoptic®	Indicated in the prevention of raised intraocular pressure in patients with open ocular hypertension or angle glaucoma
4	Rectal and Vaginal	Diazepam	Diastat®	Used to prevent a range of conditions, including alcohol withdrawal syndrome, anxiety, benzodiazepine withdrawal syndrome, seizures, muscle spasms, restless legs syndrome and trouble sleeping

Conclusion:

In conclusion, in situ gels offer a promising approach to controlled drug release by increasing gastric residence time and enhancing patient compliance. These gels provide continuous, prolonged drug release, with good stability and biocompatibility. Both natural and synthetic polymers used in in situ gels are adaptable for various

administration routes, including oral, ocular, transdermal, buccal, and injectable. This delivery system holds significant potential for further research and development in advanced drug delivery techniques.

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