INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

In Situ Gel for Gastro-Retentive Drug Delivery -A Comprehensive Review

Salma Sulthana, Sana Farheen, Konda Shravan Kumar*

M. Pharmacy. Department of Pharmaceutics, Sarojini Naidu Vanita Pharmacy MahaVidyalaya, Tarnaka, Hyderabad, Telangana, India.

ARTICLE INFO

Published: 16 Sept 2026

Keywords:
Gastro-retentive drug delivery systems (GRDDS), In situ gelling systems, Sol–gel transition, Gastric retention, Controlled drug release, Sodium alginate, Gellan gum, Chitosan, Carbopol, Drug delivery systems

DOI:
10.5281/zenodo.22793279

ABSTRACT

Gastro-retentive drug delivery systems (GRDDS) have emerged as a promising strategy to address the limitations of conventional oral drug delivery, particularly for drugs with narrow absorption windows, poor stability in the intestinal environment, or low bioavailability. These systems are designed to prolong the residence time of dosage forms in the stomach, thereby enhancing drug absorption and therapeutic efficacy. Among the various approaches within GRDDS, in situ gelling systems have gained significant attention due to their ease of administration and effective performance.In situ gelling systems are liquid formulations that undergo a sol-to-gel transition when exposed to physiological conditions such as changes in pH, temperature, or ionic composition in the gastric environment. Upon oral administration, these low-viscosity solutions rapidly transform into viscous gels, which remain in the stomach for an extended period. This gel formation helps in sustaining drug release, improving bioavailability, and reducing dosing frequency. The mechanism of gelation typically depends on the type of polymer used and the specific physiological trigger involved.Various natural and synthetic polymers, such as sodium alginate, gellan gum, chitosan, and Carbopol, are commonly utilized in the formulation of these systems due to their biocompatibility and gel-forming ability. Additionally, evaluation parameters such as gelation time, viscosity, drug release kinetics, floating behavior, and stability play a crucial role in determining the effectiveness of the formulation.Overall, in situ gelling systems represent an innovative and efficient approach in GRDDS, offering improved gastric retention, controlled drug release, enhanced patient compliance, and better therapeutic outcomes.

***Corresponding Author:** Konda Shravan Kumar
Address: *M. Pharmacy. Department of Pharmaceutics, Sarojini Naidu Vanita Pharmacy MahaVidyalaya, Tarnaka, Hyderabad, Telangana, India.*
Email ✉: shravankonda@yahoo.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

INTRODUCTION

Oral drug delivery systems are widely accepted due to their convenience, cost-effectiveness, and high patient compliance. Despite these advantages, certain drugs exhibit poor bioavailability because of limited gastric residence time, instability in intestinal pH, or a narrow absorption window in the upper gastrointestinal tract. Rapid gastric emptying can significantly reduce drug absorption, leading to suboptimal therapeutic response.

To overcome these limitations, gastro-retentive drug delivery systems (GRDDS) were developed to prolong the residence of dosage forms in the stomach. Among the various gastro-retentive approaches, in situ gelling systems have gained considerable attention due to their unique ability to transform from a liquid to a gel after administration. This transformation enhances gastric retention while offering ease of swallowing compared to conventional solid dosage forms.

In situ gels are typically formulated as low-viscosity solutions that undergo gelation in response to physiological triggers such as acidic pH, gastric ions (e.g., calcium ions), or body temperature. Once gelled, the system forms a three-dimensional polymeric network capable of entrapping the drug and releasing it in a controlled manner over an extended period.

2. Gastro retentive drug delivery system

Gastro retentive system ensures that whole drug delivery system remains within the gastric region for longer duration of time. This improves gastric retention time for such drug in comparison to conventional dosage form and further minimum effective concentration of drug remains maintained in systemic circulation for longer duration [1].

This also improves the solubility of drugs which are less soluble at alkaline pH of intestine and wastage of drug during the absorption process is reduced remarkably.

Gastro retentive drug delivery systems prolong the dosing intervals and thus improve patient compliance.

Presence of drug in solution form is the most essential requisite for a drug to get absorbed. But, if the solubility of drug is poor then the time required for drug to get dissolve within stomach would be high and transit time becomes most stringent. Gastro retentive drug delivery systems provide a support to reduce the frequent dosing of such drug by producing a controlled delivery within stomach for longer duration. Though, other formulations or novel dosage forms like nanoparticle, microspheres, liposome etc. can also be used for controlled release effect, but gastro retentive system are considered much better alternative for improved absorption through stomach [2].

Drugs which can be given by gastro retentive drug delivery systems belong to various categories involving antibiotics (sulphonamides, cephalosporins), antivirals, antifungals, H2 receptor antagonists (cimetidine, ranitidine and famotidine) etc. In addition to these, gastro retentive drug delivery systems may also be utilized for the oral delivery of proteins and peptides (calcitonin, erythropoietin, insulin, protease inhibitor, low molecular weight heparin etc.) [3, 4]

3. Factors affecting gastric retention [5,6]

To increase the retention time, various attempts have been made to retain the dosage form in the stomach. These attempts include the use of floating dosage forms (gas generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric emptying delaying devices and co-administration of gastric-emptying delaying drugs. Most of these approaches are affected by

various factors that influence the bioavailability and overall effectiveness of the gastro-retentive system. These factors are as follows:

3.1 Formulation Related Factors

Density:

Gastric retention time (GRT) depends on the buoyancy of the dosage form, which is influenced by its density. The density of the dosage form must be lower than that of the gastric contents (1.004 g/ml) to ensure buoyancy.

Size:

Dosage forms with a diameter greater than 7.5 mm have been shown to exhibit increased gastric retention time compared to smaller units.

Shape of Dosage Form:

Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch are reported to have a better GRT at 24 hours compared with other shapes.

Single or Multiple Unit Formulation:

Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow coadministration of units with different release profiles compared with single unit dosage forms.

Fed or Unfed State:

Under fasting conditions, gastrointestinal motility is characterized by periods of strong motor activity that occurs every 1.5 to 2 hours. The GRT of the unit can be expected to be very short if the timing of administration of the formulation coincides with that of the MMC.

Nature of Meal:

Consumption of indigestible polymers or fatty acid salts can alter gastric motility patterns to resemble the fed state, thereby reducing the rate of gastric emptying.

Caloric Content:

Meal's rich in proteins and fats can prolong GRT by approximately 4 to 10 hours.

Frequency of Feed:

GRT may increase by more than 400 minutes when multiple meals are consumed compared to a single meal, due to reduced occurrence of MMC.

3.2 Patient Related Factors

Gender & Age:

Gastric emptying rate may differ in the male & female. Generally, the gastric emptying in women is slower than in men. Especially those over 70 years have a longer gastro-retentive time. Thus, gastric emptying time is slowed down.

Body Posture:

Gastric retention times are different in supine and upright patient states. In the upright position, the floating systems floated to the top of the gastric fluid and remained for a longer time, showing prolonged GRT. However, in the supine position, the floating units are emptied faster than the non-floating units of similar size

Disease State:

In the case of partial or total gastrostomy and duodenal ulcers there is a decrease in gastric residence time. Diseases like gastroenteritis, pyloric stenosis, and diabetes show an increase in gastric residence time.

The Volume of the GI Fluid:

The volume of liquids administered affects the gastric emptying time Higher volumes of fluid intake tend to accelerate gastric emptying. The cold fluids delay gastric emptying while warmer fluids fasten gastric emptying.

Effect of Gastrointestinal Fluid:

On comparison between the floating and non-floating dosage form, it was concluded that regardless of their sizes the floating units remained buoyant on the gastric contents protected from the peristaltic waves during the digestive phase, while the non-floating units stayed close to the pylorus and were sink; thus, they are subjected to propelling by the digestive phase for emptying.

4. Introduction to floating oral in situ gel [7]

4.1 Gels

Gels are an intermediate state of matter which contains both liquid and solid components. It consists of three-dimensional solid networks. As it has three dimensional solid networks, gels are classified into two types based on the nature of the bonds.

They are: Physical gels which arise, when weak bonds like hydrogen bonds, electrostatic bonds and Vander Waal bonds constitute together to maintain the gel network.

Chemical gels are formed through strong covalent bonding that stabilizes the gel structure. The gel network indicates the presence of cross-linking which helps to avoid the dissolution of the hydrophilic polymer in an aqueous medium.

4.2 Hydrogels

Hydrogels are three-dimensional polymeric networks capable of absorbing and retaining significant amounts of water or biological fluids, leading to swelling.

Classification of Hydrogels:

Hydrogels are of two types. They are:

Preformed hydrogels are simple viscous systems that remain unchanged after administration.

In-situ gels are the solutions or suspensions that undergo gelation after reaching the site due to physicochemical changes.

4.3 In-Situ Gelling System

In-situ gelling system has become one of the most prominent among novel drug delivery systems due to many advantages such as improved patient compliance, reduced frequency of drug administration The term 'in-situ' originates from Latin, meaning ‘in its original place.’ In-situ gel systems can be triggered by various factors such as pH variation, temperature changes, or solvent exchange. These systems, being less dense than gastric fluids, float over stomach contents due to the bio adhesive characteristics of the polymers, thereby enhancing gastric retention time. In-situ gels are the formulations that are in sol form before administration in the body, but once administration undergo gelation to form gel.

Various routes of administration of in-situ gelling systems is oral, nasal, ophthalmic, vaginal, injectable, intraperitoneal and rectal route.

5. Polymers frequently used for in situ gelling for Floating drug delivery system [8,9,10]

Polymers that undergo solution to gel transition in aqueous solution at body temperature were used in the preparation of floating in-situ gel. Some of them are:

5.1 Pectin

Pectin is originated from plant origin; it is an anionic polysaccharide isolated from the cell wall of most plants comprising mainly esterified D-galacturonic acid residues in a-(1-4) chain. In

natural pectin, the acid groups present along the polymer chain are predominantly esterified with methoxy groups, and some hydroxyl groups may also undergo acetylation. Pectin gelation characteristics can be divided into two types: high-methoxy and low-methoxy gelation. Gelation of high methoxy pectin usually occurs at pH < 3.5. Low methoxy pectin is gelled with calcium ions and is not dependent on the presence of acid or high solid content.

5.2 Gellan Gum

a) Gellan gum secreted by *Sphingomonas elodea (Pseudomonas elodea)* is an anionic deacetylated polysaccharide with repeating tetra saccharide units composed of -D-glucuronic acid (1 unit), -L-ramose (1 unit) and -D-glucuronic acid (2 units) residues. Gellan gum undergoes gel formation due to change in temperature or due to presence of cations (e.g. Na+, K+, Ca2+).
b) Gellan gum secreted by Pseudomonas elodea is an anionic deacetylated exocellular polysaccharide with a tetra saccharide repeating unit of one α-L rhamnose, one β-D-glucuronic acid and two β-D glucuronic acid residues. It is a water-soluble polysaccharide. It forms a gel via formation of double helices, followed by their ionic crosslinking.

5.3 Sodium Alginate (Alginic Acid)

Alginic acid is a polysaccharide consisting of β-D mannuronic acid (M) and L-guluronic acid (G) residues joined by 1,4-glycosidic linkage. Alginate is a well-known polysaccharide which is widely used due to its gelling properties in aqueous solutions related to the interactions between the carboxylic acid moieties and bivalent counter ions, such as calcium, lead, and copper. It is also possible to obtain an alginic acid gel by lowering the environmental pH value. Sodium alginate has been employed in the preparation of gels for the delivery of biomolecules such as drugs, peptides and proteins.

5.4 Pluronic Acid F127

The Poloxamers or pluronic consist of more than 30 different non-ionic surface-active agents. Poloxamers, commercially available as Pluronic R, are the most commonly used thermal setting polymers. They are formed by central hydrophobic part (polyoxypropylene) surrounded by hydrophilic part (ethylene oxide). Pluronic F-127 gives colourless transparent gels which is most commonly used polymer in pharmaceutical technology. Pluronic F 127 was used as an in situ gel forming polymer together with mucoadhesive polymers such as Carbopol 934 and hydroxyl propyl methyl cellulose to ensure long residence time at the application site.

5.5 Xanthan Gum

Xanthan gum is a high molecular weight extracellular polysaccharide produced through fermentation by the gram-negative bacterium *Xanthomonas campestris*. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (βD-glucose residues) and a trisaccharide side chain of β-D-mannose-β-D-glucuronic acid-α-D-mannose attached with alternate glucose residues of the main chain. The anionic character of this polymer is due to the presence of both glucuronic acid and pyruvic acid groups in the side chain.

5.6 Xyloglucan

Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1-4)-β-D-glucan backbone chain, which has (1-6)-α-D xylose branches that are partially substituted by (1-2)-β-D galactoxylose. Xyloglucan consists of hepta-, octa-, and nonasaccharide units that vary based on the number of galactose side chains

present. Although xyloglucan itself does not gel, dilute solutions of xyloglucan which has been partially degraded by galactosidase exhibit a thermally reversible sol-gel transition on heating.

5.7 Carbopol

Carbopol is a well-known pH dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH HPMC is often combined with carbopol to enhance viscosity while simultaneously reducing the acidic nature of the formulation. A 25-40% aqueous solution of this material will become gel at body temperature, and drug release from such a gel occurs over a period of up to one week.

6. Applicability of in situ polymeric drug delivery system

6.1 Oral Drug Delivery System

The pH-sensitive hydrogels have a potential use in site specific delivery of drugs to specific regions of the GI tract. Hydrogels made of varying proportions of PAA derivatives and crosslinked PEG allowed preparing silicone microspheres, which released prednisolone in the gastric medium or showed gastroprotective property. [11]

Cross-linked dextran hydrogels with a faster swelling under high pH conditions, likewise other polysaccharides such as amide pectins, guar gum and insulin were investigated in order to develop a potential colon-specific drug delivery system.

W. Kubo et al. formulated gellan gum and sodium alginate systems containing complexed calcium ions, which undergo gelation upon release of these ions in the acidic gastric environment, and evaluated them for oral delivery of paracetamol.

Natural polymers such as pectin, xyloglucan, and gellan gum are commonly utilized in oral in-situ gel drug delivery systems. Pectin formulation for sustained delivery of paracetamol has been reported. [12] Advantages of pectin is water soluble so, no need to add organic solvent.

6.2 Ocular Drug Delivery System

In ocular delivery system natural polymers like gallan gum, alginic acid & xyloglucan are most commonly used. For local ophthalmic delivery system various compounds like antimicrobial agent, anti-inflammatory agent & autonomic drugs are used to relieve intra ocular tension in glaucoma.

Conventional delivery system often results in poor availability & therapeutic response because high tear fluid turns over & dynamics which cause rapid elimination of the drug from the eye so, to overcome the bioavailability problem ophthalmic in-situ gel was developed. [13]

To improve the bioavailability viscosity enhancers such as Hydroxy Propyl Methyl Cellulose, Carboxy Methyl Cellulose, Carbomers, Poly Vinyl alcohol used to increase the viscosity of formulation in order to prolong the precorneal residence time & improve the bioavailability, ease to manufacture. Penetration enhancer such as preservatives, chelating agent, surfactants are used to enhance corneal drug penetration. [14]

6.3 Nasal Drug Delivery System

In nasal in-situ gel system gellan gum & xanthan gum are used as in-situ gel forming polymers. Momethasone furoate was evaluated for its efficacy for the treatment of allergic rhinitis. [15]

An animal study using an allergic rhinitis model was performed to evaluate the effect of the in-situ gel on antigen-induced nasal symptoms in sensitized rats. In-situ gel was found to inhibit the increase in nasal symptoms as compared to marketed preparation Nosonex (Momethasone furoate suspension 0.05%).

6.4 Rectal Drug Delivery System

The rectal route may be used to deliver many types of drugs that are formulated as liquid, semisolid (ointments, creams and foams) and solid dosage forms (suppositories). Conventional suppositories often cause discomfort during insertion. In addition, suppositories are unable to be sufficiently retained at a specific position in the rectum, sometimes they can migrate upwards to the colon that makes them possible for drug to undergo the first-pass effect.
Choi et al. developed innovative in-situ gelling liquid suppositories with a gelation temperature range of 30–36°C, utilizing Poloxamer 407 and/or Poloxamer 188 to impart temperature-sensitive gelation properties, showing potential for rectal and vaginal applications.
Miyazaki et al. explored the application of xyloglucan-based thermoreversible gels for rectal delivery of indomethacin.

6.5 Vaginal Drug Delivery System

Apart from its reproductive role, the vagina also serves as an effective route for drug delivery. Thermoplastic graft copolymer-based formulations capable of in-situ gelation have been designed to provide sustained release of active agents such as nonoxynol-9, progestins, estrogens, peptides, and proteins. [16]
Chang et al have recently reported a mucoadhesive thermo-sensitive gel (combination of poloxamers and polycarbophil), which exhibited, increased and prolonged antifungal activity of clotrimazole in comparison with conventional PEG-based formulation.

6.6 Injectable Drug Delivery System

One of the most obvious ways to provide sustained release medication is to place the drug in delivery system and inject or implant the system into the body tissue. Thermoreversible gels mainly prepared from poloxamers are predominantly used. [17]
The suitability of poloxamer gel alone or with the addition of hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose (CMC) or dextran was studied for epidural administration of drugs in vitro. [18] The compact gel depot acted as the rate limiting step and significantly prolonged the dural permeation of drugs in comparison with control solutions.
J. M. Barichello et al. evaluated Pluronic F127 gels, which contained either insulin or insulin-PLGA nanoparticles with conclusion, that these formulations could be useful for the preparation of a controlled delivery system. Likewise, poloxamer gels were tested for intramuscular and subcutaneous administration of human growth hormone [19] or with the aim to develop a long-acting single dose injection of lidocaine [18].

6.7 Dermal and Transdermal Drug Delivery System

Thermally reversible gel of Pluronic F127 was evaluated as vehicle for the percutaneous administration of Indomethacin. In-vivo studies suggest that 20% w/w aqueous gel may be of practical use as a base for topical administration of the drug.
Poloxamer 407 gel has demonstrated suitability for transdermal delivery of insulin. [20] The combination of chemical enhancers and iontophoresis resulted in synergistic enhancement of insulin permeation.

7. Various approaches to produce in situ gelation [21]

In-situ gelation can occur through mechanisms such as physical changes (e.g., solvent diffusion and swelling), chemical reactions (e.g., ionic and enzymatic crosslinking), and physiological stimuli (e.g., temperature and pH variations).

a) By Physical Change (Swelling and Diffusion)

By this approach physical change like swelling or diffusion may take place. During swelling, the polymer absorbs surrounding fluid, leading to expansion and formation of a viscous gel structure. In diffusion, solvent in which the drug and polymer is dissolved or dispersed, diffuse into the surrounding tissues causing the precipitation of the polymer to form gel.

b) By Chemical Change

Change in chemical environment leads to polymeric cross linking thereby formation of gel. Ion sensitive polymer (sodium alginate, calcium alginate, gellan gum, pectin) undergo phase transition in present of various monovalent and divalent cation (ca+2, mg+2, Na+, k+) for the formation of gel.

For e.g.: gelation of low methoxy pectin in present of divalent cation (ca+2). Alginate contain molecule (sodium alginate) undergo gelation in presence of di/polyvalent cation e.g. ca+2 interact with guluronic acid block in alginate side chain.

c) By Physiologically Changes

(i) pH Dependent Gelling:

Another formation of in situ gel based on pH dependent. For these purpose various pH sensitive polymers are use such as PAA (carbomer) or its derivatives, polyvinyl acetyl dimethyl amino acetate (AEA), mixture of poly (methyl acrylic acid) (PMA), and poly (ethylene glycol) (PEG) shows change from sol to gel when changes in pH. At higher pH levels, weakly acidic groups promote gel formation, whereas the reverse occurs at lower pH. This principle is applied in pH-triggered in-situ gels such as levetiracetam formulations.

(ii) Temperature Dependent Gelling:

Dosage form is solution at room temperature (20 – 25 ˚C) but when in contact with body temperature (35 – 37°C) they convert into gel. Certain polymers exhibit significant solubility changes with increasing temperature, particularly at their lower critical solution temperature (LCST). At the LCST the interaction between polymer and water is unfavourable as compared to polymer-polymer and water-water. So, molecule becomes dehydrated and produce hydrophobic structure polymer such as pluronic (poly (ethylene oxide)-poly (propylene oxide poly (ethylene oxide) (PEO-PPO-PEO) triblock), polymer network of poly (acrylic acid) (PAA) and poly acryl amine (PAAM) or poly (acrylamide-co-butyl methacrylate).

Below the upper critical solution temperature (UCST), hydrogels contract upon cooling, forming what are known as positive temperature-sensitive hydrogels. Polymer used such as poly acrylic acid, poly acryl amide and co-butyl methacrylate. Eg: In situ gelling formulation based on the methylcellulose / pectin systems for oral sustain drug release to dysphagia patient.

d) Dilution-Sensitive

In this approach, a polymer that undergoes phase transition in presence of higher amount of water may lead to formation of gel. E.g. Lutrol.

e) Electrical Signal Sensitive Hydrogels

Hydrogels sensitive to electric current undergo shrinking or swelling in the presence of an applied electric field.

f) Light-Sensitive Hydrogels

Light-sensitive hydrogels can be used in the development of in situ forming gels for cartilage tissue engineering. E.g. Quinone can be injected into a tissue and applied electromagnetic radiation

is used to form a gel by enzymatic processes. For that long ultraviolet wavelengths are used.

g) Glucose-Sensitive Hydrogels

Delivery systems which are responsive to stimuli using hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can respond to glucose levels by swelling and releasing insulin in a pulsatile manner. Another approach is based on competitive binding of insulin or insulin and glucose to a fixed number of binding sites in concanavalin A, where insulin is displaced in response to glucose stimuli, so it will be functioning as a self-regulating insulin delivery system.

8. Advantages and disadvantages

8.1 Advantages of Floating Drug Delivery System [22-25]

Floating drug delivery systems have numerous advantages listed below: The principle of HBS can be used for any particular medicament or class of medicament.

a) The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.

b) The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.

c) The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.

d) Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After gastric emptying, the dissolved drug becomes available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine.

e) When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption is expected under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

f) Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.

g) Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended-release development challenging. Designing systems with prolonged gastric retention can extend the duration available for drug absorption in the small intestine.

h) Certain types of drugs can benefit from using gastro retentive devices. These include: Drugs acting locally in the stomach; Drugs those are primarily absorbed in the stomach; Drugs those are poorly soluble at an alkaline pH; Drugs with a narrow window of absorption; Drugs absorbed rapidly from the GI tract; and Drugs those degrade in the colon.

8.2 Advantages of In Situ Forming Polymeric Delivery [23]

Ease of administration
To increase local bioavailability
Reduced dose frequency
Improved patient compliance
Its production is less complex and so lowers the investment

8.3 Disadvantages of Floating Drug Delivery Systems [22-24]

There are certain situations where gastric retention is not desirable. Aspirin and nonsteroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted. Drugs that irritate the gastric mucosa or are unstable in acidic conditions are not suitable candidates for gastroretentive systems. Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.

9. Evaluation of in situ gelling system [26-28]

9.1 Determination of Drug Content

Certain weight of formulation equivalent to an amount of drug has to be dissolved in a suitable medium, stirred for required time, filtered and analysed for drug content.

9.2 pH Determination

The pH of solution can be determined using digital pH meter and the favourable conditions that facilitate in situ gelling can be identified The effect of pH on sol-to-gel transition can be assessed using media of varying pH conditions.

9.3 *In-vitro* Gelling Capacity

In general, the gelling capacity of an in-situ gel forming system can be determined by formulating a color solution of in situ gelling system for visual observation. By introducing the in-situ gelling formulation into simulated gastric fluid, parameters such as gelation time, gel strength, and duration of stability can be evaluated.

9.4 *In*-vitro Buoyancy Studies

After adding a fixed volume of in situ gelling formulation to a medium (simulating gastric fluid), the parameters like the time taken for the system to float over the surface of medium (floating lag time) and the time the formed gel constantly float over the surface of the dissolution medium (floating time) can be estimated.

9.5 In-vitro Drug Release Studies

The release rate of drug from in situ gel can be determined using USP dissolution rate testing apparatus I (basket covered with muslin cloth) at 50 rpm. 900 ml of 0.1 N HCl can be used as dissolution medium and temperature of 37+0.5°C can be maintained. 5 ml samples can be withdrawn at various time points for estimating the drug release using UV-Visible spectrophotometer. Same volume of fresh medium has to be replaced every time the sample is withdrawn. The drug release studies from in situ gel can also be done using plastic dialysis cell.

9.6 Measurement of Rheological Property of Sol and Gel

Viscosity of the solution prepared using various concentrations of gelling agents can be determined by viscometers like Brookfield viscometer, Cone & plate viscometer etc. Viscosity of the formed gel can also be determined to estimate the gel strength. Effect of pH, concentration of gelling agent/cross linking agent on viscosity, in-situ gelation character, floating ability and drug release can be studied for in-situ gelling type of floating formulations.

9.7 Water Uptake Study

Once the sol is converted to gel, it is collected from the medium and the excess medium was blotted using a tissue paper. The initial weight of thus formed gel has to be noted. Again the gel has to be exposed to the medium/distilled water and the

same process is repeated for every 30 min to note down the weights of the gel at each interval after removing the excess amount of medium/distilled water, using filter paper. The weight gain due to water uptake has to be noted from time to time.

9.8 Gel Strength

Gel strength is determined using a rheometer, where a specified quantity of gel is prepared in a beaker and the resistance encountered by the probe as it penetrates the gel is measured. This beaker is raised so pushing the probe of rheometer through the gel. The change in the load on the probe can be measured as a function depth of merge of the probe below the gel surface.

9.9 Spreadability

For the determination of spread ability, excess of sample was applied between the two glass slides and was compressed to uniform thickness by placing 1000 g weight for 5 min. Weight (50 g) was added to the pan and the time required for separating the two slides, i.e. the time in which the upper glass slide moves over the lower plate was taken as measure of spread ability (S).

Spreadability (g.cm/s) (S) = M × L / T

Where M represents the weight applied to the upper slide, L denotes the distance travelled on the glass slide, and T indicates the time required.

9.10 Sol-Gel Transition Temperature and Gelling Time

Sol-gel transition temperature is the temperature at which the phase transition of sol meniscus is first noted when it kept in a sample tube at a specific temperature and then heated at a specified rate Gel formation is confirmed when the meniscus shows no movement upon tilting the tube. Gelling time is the required for first detection of gel formation of sol formulation.

CONCLUSION

In situ gelling systems have emerged as a highly promising and innovative approach within gastro-retentive drug delivery systems, offering significant advantages over conventional oral dosage forms. These systems are uniquely designed to undergo a sol-to-gel transition upon exposure to physiological conditions such as pH, temperature, or ionic interactions, thereby ensuring prolonged gastric residence time and sustained drug release. This characteristic is particularly beneficial for drugs with narrow absorption windows, poor solubility at intestinal pH, or instability in the lower gastrointestinal tract. The use of natural and synthetic polymers such as sodium alginate, gellan gum, pectin, and poloxamers plays a crucial role in achieving effective gelation and controlled drug release. The versatility of these polymers allows the development of formulations with desirable rheological properties, improved bioavailability, and enhanced patient compliance. Moreover, the ability of in situ gels to float on gastric fluids further contributes to their effectiveness in maintaining the drug in the stomach for an extended duration.

Despite their numerous advantages, certain limitations such as variability in gastric conditions, potential dose dumping, and unsuitability for gastric irritant drugs must be carefully considered during formulation development. However, continuous advancements in polymer science and drug delivery technologies are expected to overcome these challenges.

Overall, in situ gelling systems represent a valuable and efficient platform for gastro-retentive drug delivery, with wide-ranging applications across oral, ocular, nasal, and other routes. Future research should focus on optimizing formulation parameters, exploring novel polymers, and conducting extensive in vivo studies to further

enhance their clinical applicability and therapeutic effectiveness.

ACKNOWLEDGEMENT

The authors are very much grateful to the management of Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Hyderabad for encouraging to write the review article.

Conflict of Interests

Declared none

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HOW TO CITE: Salma Sulthana, Sana Farheen, Konda Shravan Kumar, In Situ Gel for Gastro-Retentive Drug Delivery -A Comprehensive Review, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 9, 1977-1989, https://doi.org/10.5281/zenodo.22793279