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An overview of gastric floating *in-situ* gelling systems

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ABSTRACT

Oral dosage forms designed to act in the stomach are often limited by poor bioavailability due to incomplete drug release and short gastric residence time (GRT). To overcome these issues, novel gastric drug delivery systems have been developed such as gastroretentive floating systems, mucoadhesive systems, and viscosity-increasing systems. These platforms are specifically indicated for drugs requiring localized therapeutic action in the gastric mucosa - such as in the eradication of *H. pylori* - and for active ingredients with pH-dependent solubility that are poorly soluble in the alkaline environment of the lower intestine. By anchoring the dosage form in the stomach, these systems maximize drug dissolution and prolong the absorption phase within the narrow absorption window. Liquid oral dosage forms generally exhibit lower bioavailability because they are rapidly pushed out of the stomach. Floating *in-situ* gels can effectively overcome the drawbacks of standard liquid oral forms. *In-situ* gels exist as a low-viscosity liquid under storage conditions but upon administration, they transform into a floating gel within the gastric fluid environment. This gel transition allows the system to be retained in the stomach and provides sustained and controlled drug release compared to conventional drug delivery systems. This article provides an overview of the characteristics of floating *in-situ* gels and highlights recent research demonstrating the potential of this innovative dosage form.

1. INTRODUCTION

Oral dosage forms consistently remain the most widely used due to their convenience of use,

flexibility in drug design and low cost. However, for drugs that require absorption or local action in the stomach, traditional dosage forms like tablets and capsules face a major obstacle due to the gastric emptying mechanism, which often causes the drug to fail to achieve therapeutic concentrations (Banu et al., 2021). To increase the gastric residence time, certain conditions must be met: The active ingredient is best absorbed in the stomach (e.g., aspirin, phenylbutazone). The gastric fluid environment facilitates improved drug disintegration and dissolution. Drug dissolution and absorption can be enhanced by food (e.g., griseofulvin). The drug is slowly soluble and intended for local action within the stomach. However, some active ingredients that meet these criteria may cause gastric irritation (e.g., diclofenac sodium, ibuprofen, aspirin), while others are unstable in the acidic gastric fluid environment (e.g., macrolide antibiotics) (Banu et al., 2021).

To overcome these obstacles and enhance efficacy in the stomach, gastroretentive floating drug delivery systems (GDDS) were developed and have received significant attention in recent years. A floating GDDS is a dosage form utilized to increase the gastric residence time of the active ingredient. The system floats on the gastric fluid surface due to its low density, thereby providing a prolonged-release action achieved through slow drug release and long retention on the gastric surface (Banu et al., 2021). Floating GDDS have been developed based on two principal mechanisms: effervescent and non-effervescent systems.

Effervescent system: This is a dosage form that achieves buoyancy in an organ system through gas generation. Carbon dioxide (CO₂) is

formed via the chemical reaction of carbonate and bicarbonate ions upon contact with gastric acid. The active ingredient is formulated alongside the effervescent system, which typically includes swelling polymers (e.g., Methocel, chitosan) and bicarbonate combined with citric acid or tartaric acid. This entire unit is then coated with a hydrophobic polymer, such as ethyl cellulose. This coating acts as a semi-permeable membrane, helping to regulate the influx of gastric fluid and maintain the system's integrity throughout the gastric residence time (Banu et al., 2021).

Volatile liquid containing system: This is a floating system designed to increase the gastric residence time and prolong the drug release process. The system's structure features a deformable hollow unit capable of expanding its volume and returning to its original state after an extended period. This unit comprises two chambers separated by a water-impermeable, movable membrane. The first chamber contains the drug, and the second chamber holds a volatile liquid (Padhan et al., 2019).

Low-density system: This system was developed to address a major drawback of the effervescent system, where the dosage form might be carried to the duodenum before successfully floating on the gastric fluid surface. Consequently, research has focused on reducing the density of non-effervescent systems (to less than 1g/cm³) so that the dosage form can float and release the active ingredient immediately after ingestion. These formulations typically utilize low-density excipients by trapping air or oil (Bardonnet et al., 2006).

Floating *in-situ* gelling system: Upon contact with gastric fluid, this dosage form swells and

forms a highly viscous gel layer. The gel layer achieves a very low density due to CO₂ effervescence, allowing the system to float on the gastric fluid surface. The gelling polymer, belonging to the alginate group such as alginic acid, is formulated together with CO₂ generating agents like bicarbonate and carbonate (Yanadaiah, 2023).

2. GASTRIC FLOATING *IN-SITU* GELLING SYSTEMS

A gastric floating *in-situ* gel is a low-viscosity solution that is administered in a liquid state. It undergoes a phase transition into a semi-solid floating gel within the gastric lumen upon contact with the gastric fluid environment. This mechanism allows the drug to be retained in the stomach longer and prolongs drug release. The *in-situ* gelling is achieved through the use of gelling polymers, such as gellan gum, alginic acid, xyloglucan and chitosan. The floating capability is formed and maintained by effervescent excipients (gas-generating agents) like bicarbonate or carbonate salts, which may be combined with acids such as citric acid or tartaric acid. The resulting CO₂ gas makes the gel lighter and allows it to float on the gastric fluid surface (Banu et al., 2021).

Floating *in-situ* gelling systems offer several significant clinical and biopharmaceutical advantages (Thomas, 2014):

- Enhanced patient compliance: The liquid nature of the formulation ensures ease of oral administration, particularly for geriatric and pediatric populations.
- Modified release profile: These systems provide controlled drug release and prolonged therapeutic action compared to

conventional immediate-release dosage forms.

- Optimized surface area for absorption: The resulting gel layer exhibits low density and high viscosity, providing a larger effective surface area than solid tablets. This architecture facilitates a more efficient release rate and significantly improves oral bioavailability.
- Rapid buoyancy: The system achieves gastric buoyancy more rapidly than floating tablets, reducing the risk of premature gastric emptying.
- Targeted delivery and safety: By retaining the drug within the stomach, the system minimizes drug exposure to the colon, thereby reducing localized adverse effects in the lower gastrointestinal tract (Banu et al., 2021).

However, despite these therapeutic benefits, floating *in-situ* gels present certain pharmaceutical and stability challenges. Due to their preparation in a liquid state, they generally exhibit lower physicochemical stability than solid dosage forms. The integrity of the system is highly sensitive to environmental factors; specifically, fluctuations in pH or inappropriate storage temperatures can lead to product instability or phase separation. Moreover, exposure to various forms of radiation, such as ultraviolet, visible light, or electromagnetic fields, may trigger premature sol-to-gel transition within the primary packaging, rendering the preparation unusable before administration (Banu et al., 2021).

2.1 Mechanisms of *in-situ* gel formation

The formation of *in-situ* gels is triggered by one or more external stimuli. Three main

mechanisms of *in-situ* gel formation are commonly utilized: Physiological triggers (temperature and pH), physical changes (solvent exchange and swelling), and chemical changes (Dumotier et al., 2006).

Physiological triggers:

Temperature-induced gelation: Phase transition occurs as the temperature changes, converting the low-viscosity solution into a high-viscosity gel. This temperature change causes an abrupt alteration in the polymer's solubility, simultaneously triggering polymer-polymer interactions to form solvated macromolecules. Temperature variation is relatively easy to control and readily applicable both *in vitro* and *in vivo*.

pH-induced gelation: Due to the presence of ionizable functional groups, polymers such as polyacrylic acid and its derivatives and polymethacrylates, are capable of gel formation when the pH changes. Polymers with anionic functional groups show increased swelling as the pH rises, while those with cationic groups exhibit decreased swelling (Banu et al., 2021).

Chemical changes:

Ionic cross-linking: Ion-sensitive polysaccharides such as sodium alginate, gellan gum, and pectin undergo a phase transition in the presence of ions like K^+ , Ca^{2+} , Mg^{2+} and Na^+ due to cross-link formation. A typical example of this mechanism is the gel formation of sodium alginate in an environment containing calcium ions. The free Ca^{2+} ions are attracted to the polymer chains, causing cross-linking to form a polymer matrix structure that initiates local gelation of the polymer solution. The polymer network aggregates double-helix segments that complex with the cations and hydrogen bond with water. During floating retention in the stomach,

the drug is gradually released at the desired rate. The remaining polymer framework is subsequently eliminated from the stomach after drug release (Padhan et al., 2019).

Enzymatic cross-linking: Enzymes present in body fluids have the ability to form cross-links to create a polymer network (Banu et al., 2021). For example, pH-sensitive cationic polymers containing insulin will swell upon association with glucose oxidase to release insulin when blood glucose levels increase. Therefore, adjusting the enzyme concentration controls the rate of gelation, allowing the drug mixture to be injected before the gel fully forms.

Physical changes:

Swelling mechanism: The system's polymer absorbs water from the surrounding environment and swells into a gel; glycerol monooleate is an example of such a polymer. This polymer exhibits bioadhesive properties and is biodegradable *in vivo* under the influence of gastric enzymes (Padhan et al., 2019).

Diffusion mechanism (Solvent exchange): The solvent used to dissolve or disperse the active ingredient and the polymer diffuses into the surrounding tissues, leading to the precipitation of the polymer to form a gel. N-methyl pyrrolidone is a commonly used solvent for this system (Banu et al., 2021).

2.2 Polymers commonly used for floating *in-situ* gels

Sodium alginate

Sodium alginate is a commonly used natural polymer due to its biodegradability, non-toxicity, and bioadhesive properties. Its chemical structure consists of two molecules, β -D-mannuronic acid (M) and α -L-glucuronic acid (G), linked together by 1-4 glycosidic bonds. Alginates with a high

gulfuronic acid (G) content enhance gelling characteristics and reduce the required polymer amount. The interaction between the G units and Ca^{2+} ions allows alginate to form a stable gel. The ion exchange between Na^+ and Ca^{2+} ions induces swelling in the gastric fluid and the subsequent degradation of sodium alginate in the colon. The characteristics of the resulting gel depend on the G:M ratio, the type of cross-linking ion, and the initial concentration and viscosity of the alginate solution (Nanjawade et al., 2007).

Pectin

Pectin is a plant-derived polysaccharide isolated from cell walls. Pectin is structurally composed of a chain of α -(1-4)-D-galacturonic acid units. Pectin forms a gel in the presence of divalent ions, which induce cross-linking of the galacturonic acid units, as well as in the presence of H^+ ions.

Gellan gum

Gellan gum is an anion-degrading polysaccharide with repeating tetrasaccharide units consisting of β -D-glucuronic acid, α -L-rhamnose, and two β -D-glucuronic acid units. In an ion-free aqueous environment, the polymer chains form double helices, creating a liquid solution with a viscosity close to that of water. In the presence of cations (Na^+ , K^+ , Ca^{2+} , Mg^{2+}), portions of the helices link with the intermediate cations to form a gel network. The resulting gel rapidly exhibits mucoadhesive properties even at low polymer concentrations and small amounts of cations. Gellan gum is used as a potential carrier for oral drug delivery systems.

Carrageenan

Carrageenan is a sulfated linear polysaccharide composed of D-galactose and 3,6-anhydro-D-galactose, obtained by extracting

various types of red seaweed belonging to the class Rhodophyceae. Carrageenans are divided into three types: λ -carrageenan, i-carrageenan, and k-carrageenan. Among these, k-carrageenan is a strong gelling polymer with a helical secondary structure. Carrageenan is utilized as a matrix-forming polymer in oral extended-release tablets. Additionally, carrageenan is employed as an excipient to induce gelation or increase viscosity to ensure controlled and prolonged drug release (Padhan et al., 2019).

2.3 Quality evaluation parameters for floating *in-situ* gels

In accordance with the general evaluation principles described in the United States Pharmacopeia (USP) and the British Pharmacopoeia (BP), the quality assessment of floating *in-situ* gels typically includes parameters such as:

Appearance: Evaluation of the organoleptic properties of the formed gel in pH 1.2 buffer. the formulation should be clear, homogeneous, and free of visible particles; after gelation in simulated gastric fluid (pH 1.2), the gel must remain uniform without precipitation.

Gelation time: Measurement of the time required for the formulation to transition from a low-viscosity liquid state to a semi-solid gel state in pH 1.2 buffer medium. The formulation must achieve a semi-solid gel state within 60 seconds of contact with the pH 1.2 buffer to ensure immediate gastroretention.

pH: The pH should ideally be maintained within the range of 6.0 to 8.0 to ensure compatibility with the oral mucosa and prevent premature gelation during storage.

Viscosity: Viscosity is determined using devices such as the Brookfield viscometer or the Ostwald

viscometer at the appropriate temperature. The viscosity of the formulation must be suitable to prevent difficulties during the administration of the drug.

FTIR Analysis: Evaluation of physicochemical interactions between the drug substance and the excipients. The FTIR spectra of the formulation should show no significant changes or disappearance of the characteristic functional group peaks of the drug, indicating the absence of chemical interactions and confirming drug-excipient compatibility.

In vitro floating ability: Evaluation of the lag time before floating and the total duration of continuous floating in pH 1.2 buffer medium at 37 °C. Floating lag time is calculated from the moment the gel contacts the medium until the gel begins to float on the surface of the test medium (Banu et al., 2021).

Assay: Verification that the content of the active ingredient meets the required standard for the studied formulation.

In vitro drug release: Performed using the USP dissolution apparatus (Type II) at 50 rpm in 900 mL of HCl buffer pH 1.2 at 37 °C. Appropriate samples are withdrawn at predetermined time intervals and replaced with an equivalent volume of fresh buffer medium. The active ingredient in the samples is quantified to calculate the amount of drug released after each interval. The drug release data obtained allows for the prediction of the appropriate kinetic model for the study.

Antimicrobial activity: Assessment of the gel's ability to inhibit microorganisms, typically used when the formulation targets bacterial infections like *H. pylori* (Modasiya et al., 2010).

3. STUDIES ON FLOATING *IN-SITU* GELS

Helicobacter pylori is the leading cause of gastrointestinal diseases such as gastritis, peptic ulcers, and gastric cancer. Antibiotics used in *H. pylori* eradication regimens require a long gastric residence time to effectively eliminate the bacteria. Consequently, in recent years, the floating *in-situ* gelling system has attracted significant attention for the treatment of *H. pylori* infection.

Rajinikanth et al. (2007) investigated floating *in-situ* gel formulations containing amoxicillin for treating *H. pylori* infection. The formulations utilized gellan gum as the gelling polymer and calcium carbonate as the effervescent agent. *In vivo* results showed that the required amoxicillin concentration for bacterial eradication in this dosage form was 10 times lower than that of a comparable suspension (Rajinikanth et al., 2007).

In 2008, the same authors further studied a floating *in-situ* gel formulation using gellan gum and calcium carbonate, this time containing clarithromycin. *In vivo* activity against *H. pylori* was tested in rats using PCR and bacterial culture techniques. The results indicated that the *in-situ* gel formulation containing sucralfate was more effective at eradicating *H. pylori* than the formulation without sucralfate. The clarithromycin concentration required for eradication was lower than that of the corresponding clarithromycin suspension, suggesting that this dosage form has the potential for better therapeutic action against *H. pylori* infection (Rajinikanth et al., 2008).

In 2013, Pandya et al. researched a floating *in-situ* gel containing ranitidine hydrochloride. The formulations utilized sodium alginate as the gelling polymer and calcium carbonate as the

cross-linking agent upon contact with gastric fluid. The results showed that the formulation containing 2 % sodium alginate was able to control the release of the active ingredient over a prolonged period and met all evaluation criteria for viscosity, drug assay, pH, *in vitro* gelation ability, *in vitro* floating ability, and stable drug release (Pandya et al., 2013).

Thomas (2014) developed a floating *in-situ* gel formulation containing 2.5 % metronidazole to increase its GRT and thereby enhance its efficacy against *H. pylori*. The study investigated various concentrations of viscosity-enhancing polymers (methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), or carboxymethyl cellulose (Na CMC) combined with a 2 % sodium alginate base and effervescent agents (calcium carbonate and/ or sodium bicarbonate) at different ratios. The results indicated that all formulations formed a gel immediately upon contact with the pH 1.2 acidic buffer and had a floating duration exceeding 12 hours. The *in vitro* drug release profile differed among the polymers, decreasing in the order: HPMC > MC > Na CMC. An increase in the concentration of calcium carbonate reduced the drug release rate due to the formation of a rigid and stable gel structure through cross-linking, which hindered active ingredient release (Thomas, 2014).

The research group of Abou Youssef (2015) investigated formulations containing various ratios of sodium alginate and gellan gum in a metronidazole floating *in-situ* gel system. The optimal formulation, containing 4 % sodium alginate and 2 % calcium carbonate, exhibited immediate gelation, a floating lag time of approximately 1 minute, a floating duration exceeding 24 hours, and stable drug release with

reliable results. These studies are promising for developing formulations capable of maintaining antibacterial concentrations for the necessary duration to treat *H. pylori* infection, while simultaneously reducing cost and minimizing adverse effects associated with immediate-release dosage forms (Abou Youssef et al., 2015).

4. CONCLUSION

The floating *in-situ* gelling system offers significant advantages and promise for active pharmaceutical ingredients characterized by poor bioavailability and a narrow absorption window in the stomach. The efficacy of the drug in the gastric compartment is improved due to the formulation's ability to achieve high active pharmaceutical ingredients concentrations at the gastric mucosa and maintain them over a prolonged period via local drug release. To date, the *in-situ* gel drug delivery system continues to receive considerable research attention and represents a potential dosage form for treating conditions such as chronic gastritis and *H. pylori*-induced peptic ulcers. Since the gel is prepared as a liquid for oral administration, it is convenient for both pediatric and geriatric patients who may experience difficulty swallowing. Research into *in-situ* gels using water-swallowable and biodegradable polymers to control drug release holds many benefits compared to conventional oral dosage forms. The application of the floating *in-situ* gelling system to deliver natural product-derived drugs will also be a promising area for future research.

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