Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

Advancements in Gastroretentive Drug Delivery : Floating *In Situ* Gel Systems - An Overview

Akhila Shaji*, Dr. Prasanth M. S.

College of Pharmaceutical Sciences, Government Medical College, Thiruvananthapuram, Kerala, India.

ARTICLE HISTORY

Received: 11.02.2024

Accepted: 20.02.2024

Available online: 30.06.2024

DOI:

10.5530/ajphs.2024.14.64

KEYWORDS:

Floating, *In situ* gel

***Corresponding author:**

Email : akhilavarsha31@gmail.com
Phone : +91 - 6282376877

ABSTRACT

Conventional oral dosage forms often encounter challenges with low bioavailability due to their rapid transit through the stomach, especially for drugs which are less soluble in the alkaline environment of intestine. Additionally, drugs intended for activity in the stomach are quickly emptied, limiting their residence time. To address these issues, various strategies have been explored to prolong drug retention in the stomach. In recent years, significant attention has been directed towards the development of *in situ gel* systems. *In situ* gel-forming drug delivery systems are designed to release drugs in a sustained manner, maintaining a consistent and steady level of the drug in the bloodstream over a prolonged period. Initially liquid, these dosage forms undergo gelation upon interaction with gastric fluids, thereby floating on the surface. Gel formation occurs in response to stimuli such as pH change, temperature modulation, or ionic crosslinking, resulting in prolonged residence and sustained release. This approach allows for easy and precise application of the drug exactly where it needs to be absorbed, streamlining the delivery process and enhancing its efficacy. This overview provides insight into floating oral *in situ* gel formation and summarizes various approaches, advantages, disadvantages, major polymers used and applications of floating *in situ* gel.

INTRODUCTION

The oral route is still preferred for administering therapeutic drugs because it is easier to administer and results in lower therapy costs and more patient compliance. Despite significant improvements in the last few decades, oral controlled drug delivery has limited effectiveness when it comes to medications whose absorption window is narrow throughout the gastrointestinal tract. One of the biggest obstacles to the development of an oral controlled drug delivery system is the modification of the gastrointestinal transit time. Drugs gastric emptying varies greatly and is influenced by the dosage form as well as the fed or fasted condition in the stomach. The rate at which the stomach empties a dosage form is highly unpredictable and variable process. Limiting the dosage form to the appropriate region of the gastrointestinal tract is one of the major challenges. Many drug delivery methods with extended gastric retention times have been researched as a solution to this physiological issue. By delivering drugs in a controlled and consistent way that are less soluble in high pH environments, efforts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations, thereby reducing the frequency of dosing and minimising fluctuations in plasma drug concentration at steady state. The process of mucoadhesion, flotation, sedimentation, expansion, altered shape systems, or the administration of pharmacological drugs that delay stomach emptying can all be used to produce controlled gastric retention of solid dosage forms. These methods suggest that floating drug delivery systems are the most promising for controlled drug release[1].

FLOATING DRUG DELIVERY SYSTEM[2]

The floating drug delivery system (FDDS) is a useful tool for increasing the duration of the gastrointestinal residence period, which enhances the drug bioavailability. FDDS are low-density systems with enough buoyancy to float over the contents of the stomach and stay there for a longer period of time. Because stomach fluids are low in density, floating drug delivery technology intended for gastric retention float on the surface of them and produces a sustained impact. For drugs that are absorbed

from the upper portion of the stomach, this kind of delivery mechanism is quite beneficial.

However, immediate floating of the delivery system is only possible only when the density of the system is low. Higher density delivery systems first sink to the stomach where they absorb water, then swells, and eventually float. However, with such a system, it is possible that the stomach will empty the system before the floating begins. Low density system, which causes floating, can be caused by adding low density excipients or by creating a mechanism that traps air inside the system, but each has its own set of drawbacks.

FACTORS AFFECTING FLOATING DRUG DELIVERY SYSTEMS

The factors includes:

Formulation Factors and Idiosyncratic Factors [3].

FORMULATION FACTORS

Density

Gastric emptying rate is also influenced by the density of dosage forms. A dosage form that is buoyant and has a density lower than the gastrointestinal fluid floats. This distance from the pyloric sphincter keeps the dosage unit in the stomach for an extended period of time. Drug floatation is time dependent and may not occur until hydrodynamic equilibrium is reached. Larger dosage forms that are heavier than the stomach content sink to the bottom of the stomach, where they remain for a longer period of time and release the active ingredient gradually.

Size

It has been reported that dosage form with a diameter larger than 7.5 mm had a higher Gastric Retention Time (GRT) when compared to those with a diameter of 9.9 mm.

Shape of dosage form

Tetrahedron and ring-shaped devices are said to have a better Gastric Residence Time (GRT) at 24 hours compared to other shapes, with flexural moduli of 48 and 22.5 kilo pounds per square inch, respectively.

Fed or unfed state

Periods of intensive motor activity that last for 1.5 to 2 hours while fasting are indication of gastro intestinal motility. If the formulation is administered at the same time as the MMC, the GRT should be extremely short. But under the fed state, GRT is much longer and MMC is delay.

Viscosity Grade of Polymer

The viscosity of the polymers and their interactions have a significant impact on the drug release and floating properties of gastro retentive floating drug delivery system. When it came to enhancing floating qualities, low viscosity polymers like HPMC K100 LV were found to be more advantageous than high viscosity polymers like HPMC K4M. Additionally, it was found that when polymer viscosity increased, the release rate decreased.

Nature of meal

Drug release can be prolonged and the pace of gastric emptying reduced by the intake of fatty acid salts, which alter the stomach motility pattern to a fed state. Gastric secretions and emptying time are influenced by the type of food, as well as its caloric content, volume, viscosity, and co-administered medications. The caloric content of the food consumed mostly determines the rate of emptying. As long as the calories in proteins, lipids, and carbohydrates are the same, there is no difference in regards to this. Because of the higher osmolarity, acidity, and calorific values, stomach emptying is generally delayed. It has been observed that a meal high in fats and proteins causes a GRT of 4 to 10 hours.

Feed frequency

As MMC occurs rarely, giving multiple meals instead of just one can enhance GRT by more than 400 minutes.

IDIOSYNCRATIC FACTORS

An abnormal response to a chemical that is determined by genetics is called an idiosyncrasy. The medication interacts with a specific characteristic of the person that is absent from most individuals, leading to the unusual effect. This kind of response is limited to people who have a specific genotype. Additionally, it might rely on:

Gender

Compared to men, regardless of weight, height, or body surface, the mean ambulatory GRT in males (3.4 ± 0.6 hours) is lower than that of female (4.6 ± 1.2 hours).

Age

Compared to younger subjects, elderly individuals exhibit a lower gastric emptying time. Intestinal and stomach transit times are also found to vary within and between subjects. A much longer GRT is seen in the elderly, particularly in individuals over 70.

Posture

When a patient is in an upright ambulatory or supine position, their GRT may change.

Upright Position: Floating forms, regardless of size, are protected from postprandial emptying when they are in an upright position because they stay above the stomach contents. While conventional dosage forms sink to the bottom part of the distal stomach and are then evacuated by the pylorus by astral peristaltic movements, floating dosage forms exhibit longer and more consistent GRTs.

Supine Position: There is no consistent defence against irregular and early emptying in this position. Both floating and conventional large dosage formulations have longer retention in supine patients. Between the stomach lower and greater curvatures, the gastric retention of floating forms seems to stay buoyant. When these units travel distally, they could be carried away by the peristaltic motions that push the stomach contents in the direction of the pylorus, which would significantly lower GRT in comparison to patients who remain upright.

Concomitant intake of Drugs

Prokinetic drugs are one type of drug that may have an impact on Gastro Retentive Floating Drug Delivery System (GRFDDS) performance. Gastric emptying time may lengthen if GI motility reducing medications are used concurrently.

Example: Metoclopramide, Cisapride, Atropine

Biological factors

Gastritis, Gastric ulcers, Pyloric stenosis, Hypothyroidism, and Diabetes are among the illnesses that cause the stomach to empty slowly. Gastric emptying rate is accelerated by duodenal

ulcers, hypothyroidism, and partial or complete gastrectomy.

ADVANTAGES OF FDDS[4]

- Long term maintenance of a steady therapeutic level.
- Improved drug bioavailability.

  For example. Improved bioavailability of Riboflavin in Controlled Release Gastro Retentive Dosage Forms (CR-GRDF) compared to non-CR-GRDF polymeric formulation.
- The gastro retentive dosage form reduces the frequency of doses, which increases patient compliance.
- Treatment for gastrointestinal conditions such as Helicobacter pylori infection and gastroesophageal reflux ailments.
- For medications with restricted intestinal absorption, a floating drug delivery system is a better solution.

DISADVANTAGES OF FDDS[5]

- It work effectively when there is an adequate amount of fluid in the stomach.
- In supine position, the gastric emptying of floating dosage form is greatly dependent on the diameter size. As a result, patients should not take these formulations right before bed.
- It is necessary for dosage forms in swellable systems to remain bigger than the pylorus aperture.
- The limitations of the floating drug delivery system include the production of violent gas, the disintegration of dosage forms, burst release, dose dumping, and an alkaline microenvironment.

INTRODUCTION TO ORAL FLOATING *IN SITU* GEL[6]

Oral *in situ* gel forming system, have provided a suitable way for the controlled drug delivery within the stomach with enhanced gastric retention. The tablet/capsule floating dosage forms are stable as compared to liquids, but the problem with them is, they are needed to swallow as a whole unit. In such cases, these cannot be broken in halves as these are designed for controlled release and floating ability also depends on dimensions of tablets. Elderly patients, children, some adult persons and patient with certain disease conditions have difficulties to swallow tablet/capsule dosage forms. In addition, these floating solid dosage forms needed to be available in various strengths to accommodate different dosing requirements, allowing for flexible dosage adjustments. When an environment specific gel forming solution, converts to low- density gel that floats on the surface of the gastric fluids. This solution initially having a thin consistency, undergoes transformation in its polymer structure upon contact with gastric fluids, resulting in thick and buoyant gel. The technique leverages smart solution that adapts to the gastric environment, changing its viscosity and density to form a gel that stays afloat, allowing for targeted and controlled drug release.

APPROACHES TO PRODUCE *IN SITU* GEL

There are various methods and mechanisms employed to achieve *in situ* gel formation, including: [7]

1. Physiological stimuli

   A. Temperature

   B. pH

2. Physical changes in biomaterials

   A. Swelling

   B. Diffusion

3. Chemical reactions

   A. Enzymatic cross - linking

   B. Ionic cross linking

   C. Photo-initiated polymerization.

1. Physiological stimuli

- *In situ* gel formation depending on changes in temperature

This approach utilizes temperature sensitive polymers that undergo a phase transition from a low viscosity solution to high viscosity gel in response to temperature changes. As the temperature shifts, the polymers solubility changes abruptly, leading to polymer-polymer interaction that form hydrophobic, solvated macromolecules. This temperature dependent mechanism is widely studied and exploited to create *in situ* gel characteristics, making temperature sensitive polymers a popular choice for this purpose. E.g. Polyacrylic acid, Polyacrylamide, etc.

- *In situ* gel formation due to change in pH of the system

Certain polymers, like polyacrylic acid and its derivative, polymethacrylate form gels in response to pH changes. This is due to the presence of ionizable groups in their chemical structure. Polymers with anionic (negative) groups swell more as pH increases, whereas polymers with cationic (positive) groups shrink as pH increases.

2. Physical changes in biomaterials

- Swelling

This process is also known as “solvent activated” or “water-activated” gel formation, where the materials absorbs water and expands to form a gel like structure. Myverol 18-99 (glycerol mono-oleate), type of polar 1400 lipid that can absorb water and spontaneously form gel like structure, making it a useful component for in situ gel formation applications. It also exhibit bio adhesive properties, allowing it to bind to biological tissues, and can be broken down in the body by enzymes, making it biodegradable.

- Diffusion

This process involves the diffusion of a solvent from polymer solution into surrounding tissue, causing the polymer matrix to precipitate or solidify. N- Methyl-Pyrrolidone (NMP) has been identified as a suitable solvent for this system, facilitating the diffusion and precipitation process.

C. Photo-initiated polymerization.

- Ionic cross linking

Polymers can undergo a change in phase in response to the presence of different ions, this phenomenon is known as ion triggered phase transition. This means that the properties of the polymer, such as its solubility or viscosity, can change when it comes into contact with specific ions, leading to a transformation from one phase to another. (e.g., from a liquid to gel). K-

carrageenan forms rigid, brittle gels, i-carrageenan forms elastic gels mainly in the presence of Ca2+. Gellan gum is an anionic polysaccharide that undergoes *in situ* gelling in the presence of mono- and divalent cations, including $Ca2^{+}$, Mg^{+}, K^{+} and Na^{+}. Likewise, alginic acid, a type of polymer, forms a gel like structure in the presence of divalent or polyvalent cations, such as calcium or magnesium ions, through an ion triggered gelation process.

- Enzymatic cross-linking

While research on enzyme catalysed *in situ* formation is limited, it offers several advantages over chemical and photochemical methods. Enzymatic processes can efficiently occur under physiological conditions, eliminating the need for potentially harmful chemicals like monomers and initiators. For instance, researchers have explored the development of stimulus responsive delivery systems using hydrogels that can release insulin, showcasing the potential of enzymatic approaches in biomedical applications.

- Photo Polymerization

Photo-polymerisation is a widely utilized technique for the in situ formation of biomaterials, where light is used to initiate the polymerization process, creating solid material from a liquid precursor. A solution containing monomers or reactive macromers and an initiator can be injected into a tissues site, and then exposed to electromagnetic radiation, such as light radiation, to initiate the polymerization process and forms a gel like structure.

IN SITU GELATION MECHANISM[8]

These are fluids before administration and forms gel under physiological conditions. *In situ* formation of gels can be achieved through various mechanism, including ionic cross-linkage, pH change and temperature regulation. Polymers that contain divalent particles e.g. sodium alginate can shape a complex with sodium citrate, in this way breakdown of complex happens in acidic condition to discharge $Ca2^{+}$ which prompts *in situ* gelation. Complexation with cations and hydrogen holding with water prompts *in situ* gelation.

CRITERIA FOR THE SELECTION OF DRUG CANDIDATE FOR FLOATING

IN-SITU GEL[9]

- Drugs, which undergo significant first pass metabolism may not be a desirable candidate.
- Drugs having solubility or stability problems in the highly acidic gastric environment or which are irritant to gastric mucosa cannot be formulated as FDDS.
- Absorption from upper GIT: Drugs have a particular site for maximum absorption.

  Example: Ciprofloxacin
- Drug having low pKa, which remains unionized in stomach for better absorption.
- Drugs that are less soluble in alkaline environments.

  Example: Captopril.
- Drugs works directly in the stomach, without being absorbed into the body, to provide quick relief from heart burn, acid reflux, and bacterial infections like ulcers.

  Example: Antacids, Antibiotics.

ADVANTAGES OF FLOATING *IN SITU* GEL [10]

- To decrease the wastage of drug.
- Ease of administration.
- It helps to extended or prolonged release of drugs.
- It allows more patient comfort and compliance.
- Due to the low dose, there will be no drug accumulation and minimize the drug toxicity.
- It offers more bioavailability.
- By using natural polymers, it offers the advantages of biocompatibility and biodegradability, ensuring that the material is non-toxic and can easily decompose, reducing the risk of adverse reactions and environmental harm.
- It can adhere to the mucous membranes in the body, allowing to deliver drugs directly to the target site, making it ideal for non invasive drug delivery methods like pills, nasal sprays or eye drops.

DISADVANTAGES OF FLOATING *IN SITU* GEL[11]

A larger volume of fluid is required.

- The drug solution form is more prone to degradation, making it less stable.
- Chemical degradation can lead to stability issues, potentially compromising the drug's efficacy and shelf life.
- Eating and drinking restricted for a few hours after administering the drug.
- Only small doses have to be administered.
- Due to low mechanical strength, it may dissolve faster, which leads to variable results.
- Hydrogels may have difficulty in loading and distributing hydrophobic drugs evenly, which can limit the effectiveness of the drug delivery systems.

COMMONLY USED NATURAL POLYMERS IN THE PREPARATION OF *IN SITU* GEL[12]

SODIUM ALGINATE

Sodium alginate is commonly used natural polymer for the formulation of *in situ* gels. It is chemically a salt of alginic acid which comprises of residues of L-glucuronic acid and D-mannuronic acid connected by 1, 4 glycosidic linkages.

XANTHAN GUM

Xanthan gum is obtained from gram negative bacterium Xanthomonas campestris by fermentation process. Due to the presence of both glucuronic acid and pyruvic acid group in the side chain, it exhibits an anionic character.

PECTIN

Pectin is an anionic polysaccharides which is obtained from

the cell wall of plants. Pectin comprised of (1-4)-D-galacturonic acid residue in its structure. It forms stiff gel in the presence of medium.

GELLAN GUM

Gellan gum is chemically anionic deacetylated polysaccharide (1 unit) and -D-glucuronic acid (2 units). Gellan gum is obtained from Sphingomonas elodeae. Due to presence of cations (e.g. Na^+, K^+, Ca_2^+) or change in temperature, gellan gum forms gel in the medium.

CARBAPOL

The well-known pH-dependent polymer carbopol forms a low viscosity gel at alkaline pH levels but remains in solution at acidic pH levels. When used in conjunction with carbopol, HPMC gives the solution a viscous quality while lowering its acidity.

XYLOGLUCAN

It is a plant-based polysaccharide that is extracted from tamarind seeds. Although xyloglucan itself does not produce gels, diluted solutions that have been partially broken down by galactosidase shows gelling property when heated up to a certain temperature. It is employed not just for oral drug delivery but also for drug delivery via the eyes and the rectal tract. Xyloglucan has demonstrated an extremely short gelation time, only for few minutes.

CHITOSAN

It is obtained by alkaline deacetylation of a natural component called chitin. Chitosan is a biodegradable, thermosensitive and polycationic polymer.

APPLICATION OF FLOATING *IN SITU* DRUG DELIVERY SYSTEMS[13]

Floating *in situ* drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It keeps the drug in place at the site where it is absorbed, allowing the body to absorb more of the drug and making it more effective. These are summarized as follows.

- **Sustained Drug Delivery:** The general problem of short gastric residence time encountered with an oral controlled release formulation can be overcome with these systems. Hydrodynamically balanced systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. These systems have a bulk density of less than 1. As a result they can float on the gastric contents. These systems are relatively large in size when it swells and passing from the pyloric opening is restricted.

- **Increased absorption:** Drugs absorbed in the upper stomach stay in contact with the absorption site for longer period, which can lead to improved absorption and bioavailability.

- **Improved bioavailability:** As the absorption of the drug from stomach is increased, bioavailability of the drug enhanced, remarkably. Increase in the gastric transit time also causes an increase in the bioavailability of drug

- **Less adverse effect of drug:** As drug remains in the stomach till the complete release, frequency of the adverse effect on the colon decreases to greater extent.

- **Site specific drug delivery:** Drugs which are absorbed from the stomach get enough residence time for absorption, hence increase in the absorption rate occurs. Furthermore, local action of the drug in stomach is prolonged, so less amount of dose is required.

CONCLUSION

The exploration of floating *in situ* gel systems for gastro retentive drug delivery presents a promising avenue for overcoming challenges associated with low bioavailability and rapid transit through the stomach. By leveraging stimuli such as pH change, temperature modulation, and ionic crosslinking to induce gel formation, these systems offer sustained drug release and prolonged residence time in the stomach. The ability of *in situ* gel systems to float on the surface of gastric fluids, forming a low-density gel matrix known as a raft, not only facilitates extended drug contact but also enables continuous and controlled drug release. With a focus on enhancing drug absorption and maintaining consistent plasma profiles, floating *in situ* gel systems represent a valuable approach in oral controlled drug delivery. Further research and development in this area hold great potential for optimizing therapeutic outcomes and improving patient compliance in the realm of pharmaceutical formulations.

REFERENCE

1. Hirtz J. The GIT absorption of drugs in man: a review of current concepts and methods of investigation. BJCP., 1985; 19: 77-83.
2. P. N. Murthy, Anjan K. Mahapatra, Tapan Kumar Nayak and DiptanuDey. Formulation, characterization and drug release kinetics of floating drug delivery systems. J. Chem. Pharm. Res., 2015, 7(6):781-792.
3. Chaturvedi Shashank, KumariPrabha, Singh Sunil, AgrawalVipinKumar. Approaches to increase the gastric residence time: floating drug delivery systems- a review. Asian j pharm clin res, 2013; 6(3):1-9.
4. Jain NK. Progress in controlled and novel drug delivery systems Delhi, CBS Publishers. 2003; 76-97.
5. Srividya B, Cardoza RM & Amin PD. Sustained ophthalmic delivery of ofloxacin from a pH triggered in-situ gelling system. Journal of Controlled Release, 2001; 73: 205-211.
6. Miyazaki S, Suzuki S, Kawasaki N, Endo K, Takahashi A & Attwood D. In-situ gelling xyloglucan formulations for sustained release ocular delivery of Pilocarpine hydrochloride. International Journal of Pharmaceutics, 2001; 229:2.
7. Bhardwaj L, Sharma PK & Malviya R. A Short Review on Gastro Retentive Formulations for Stomach Specific Drug Delivery: Special Emphasis on Floating In-situ Gel Systems. African Journal of Basic & Applied Sciences, 2011; 3(6): 300-312.
8. Bhalerao KK. A short Review on Stomach Specific Floating in-situ gel. Journal of Biomedical and Pharmaceutical Research. 2012; 1(3): 01-04.
9. Jain NK. Progress in controlled and novel drug delivery systems Delhi, CBS Publishers. 2003; 76 - 97.
10. Langmaier F, Mokrejs P, Kolomaznik K, Mladek M. Biodegradable packing materials from hydrolysates of collagen waste proteins. Waste Management 2008;28:549-56.

11. Kempe S, Mader K. In situ forming implants-an attractive formulation principle for parenteral depot formulations. J Controlled Release 2012;161:668-79.

12. Rathod, H., V. Patel and M. Modasia, 2010. In situ gel as a novel approach of gastroretentive drug delivery. International Journal Of Pharmacy and Life Sciences, 1(8): 440-447.

13. Bhardwaj L, Sharma PK, Malviya R. A short review on gastro retentive formulations for stomach specific drug delivery: special emphasis on floating in situ gel systems. African journal of basic & applied sciences, 2011; 3(6): 300-12.

Cite this article : Akhila Shaji, Dr. Prasanth M. S.
Advancements in Gastroretentive Drug Delivery : Floating in *Situ Gel* Systems - An Overview
Asian J. Pharm. Hea. Sci.. 2024;14(2):2970-2975. DOI : 10.5530/ajphs.2024.14.64