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REVIEW ON: GASTRO-RETENTIVE FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

Oral administration of medicines with a narrow absorption window in the gastrointestinal tract (GIT) is frequently hampered by poor bioavailability with conventional dosage forms due to inadequate drug release and a short residence time at the absorption site. To address this issue and maximize oral absorption of these medications, gastro-retentive systems, namely floating and mucoadhesive systems, have been developed. These devices allow regulated drug delivery with extended stomach residence duration. Some floating drug delivery systems have demonstrated the ability to accommodate these fluctuations while maintaining medication release. This review focuses on GRDDS applications, physiological consideration development, and future prospects. This review describes in detail the floating drug delivery system, its classification, and the formulation parameters that influence FDDS stomach retention. In addition, this review summarises the in vitro methodologies used to assess the performance, advantages, and applications of floating systems. Floating drug delivery systems are promising solutions for controlled drug release because they eliminate the difficulties that are often encountered during the creation of pharmaceutical dosage forms.

KEYWORDS: Floating Drug Delivery Systems, Bioavailability, Gastric residence time, Narrow absorption window.

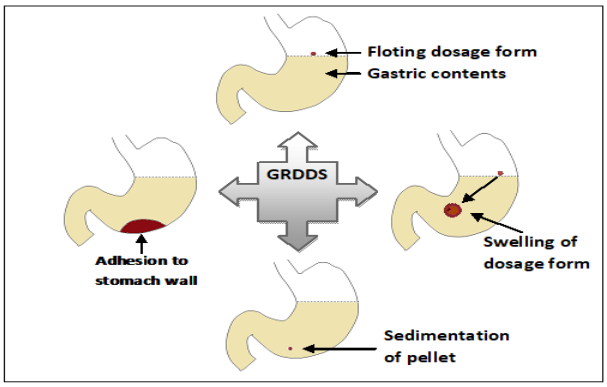
INTRODUCTION

Oral dosage forms have been a popular choice for drug delivery for over four decades due to their ease of administration, patient compliance, and formulation flexibility. However,

traditional dosage forms have limitations in achieving controlled drug delivery as drug absorption can vary significantly between individuals due to physiological variability, including gastrointestinal transit and gastric residence time.[1,2]

To address these challenges, gastroretentive drug delivery systems (GRDDS) have emerged as an advanced approach to drug delivery. GRDDS aims to retain the drug in the stomach for a prolonged period, making it particularly suitable for drugs with narrow absorption windows, those that act locally in the gastrointestinal tract, those that are unstable in intestinal fluids, and those that exhibit poor solubility in the intestinal tract.[3,4]

Floating drug delivery system (FDDS) is a prominent approach in GRDDS characterized by the ability of the formulation to float in and over the gastric contents. FDDS has been effectively used to design sustained drug delivery systems and improve overall oral bioavailability of drugs.[5-7] Effervescent systems are commonly employed in the development of FDDS based on the mechanism of buoyancy, where carbon dioxide gas production occurs due to the reaction of carbonates and bicarbonates with gastric fluid. The gas entrapped in the polymers enables the system to remain buoyant.



Application of GRDDS

Table 1 introduces potential GRDDS medication candidates. Despite the fact that numerous types of GRDDS have been recorded in the literature, floating and mucoadhesive systems are the most commonly used gastroretentive dosage forms in pharmaceutical businesses and contribute the most to the market. The commercially available gastroretentive dose forms are shown in Table 2.

Table 1: Suitable drug candidates for gastroretentive drug delivery systems (GRDDS).

Bioavailability Challenges	Drug	Therapeutic Indications	References
Local activity	Ranitidine, Amoxicillin, Levofloxacin, metronidazole	Peptic ulcer and reflux esophagitis, eradication of H. pylori	[8,15,20–23]
Plasma fluctuations	Ciprofloxacin, Clarithromycin	Urinary tract, respiratory, and GI infections	[8,24–27]
Low solubility at alkaline pH	Ofloxacin	Urinary tract, respiratory, and GI infections	[8,13]
	Cinnarizine	Nausea, vertigo, and motion sickness	[17]
Narrow absorption window	Riboflavin	Essential nutrients, mouth ulcer and sore throat	[28,29]
	Cilostazol	Inhibit platelet aggregaration	[9]
	Pregabalin	Fibromyalgia, diabetic peripheral neuropathy, post-herpetic neuralgia, and adjunctive therapy for partial onset seizures	[10,30]
Short half-life, narrow absorption window	Levodopa	Parkinson's disease	[31]
	Metformin	Type II diabetes mellitus	[11,12,32,33]
Poor absorption from lower GIT	Atenolol	Hypertension	[8]
	Lafutidine	Gastric and duodenal ulcers	[34]
Unstable at alkaline PH	Verapamil, Captopril	Hypertension	[8,14,16]

Table 2: Various gastroretentive products available in the market.[8,18,35,36]

Delivery systems	Brand name	Active ingredient	Manufacturing company
Bioadhesive tablets	Xifaxan®	Rifampicin	Lupin, India
Bilayer floating capsule	Cytotec®	Misoprostol	Pfizer, UK
Coated multi-layer & swelling system	Baclofen GRS®	Baclofen	Sun Pharma, India
Colloidal gel forming floating system	Conviron®	Ferrous sulphate	Ranbaxy, India
Effervescent floating system	Zanocin OD®	Ofloxacin	Ranbaxy, India
	Riomet OD®	Metformin hydrochloride	Ranbaxy, India
	Cifran OD®	Ciprofloxacin	Ranbaxy, India
Effervescent floating liquid alginate preparation	Liquid Gaviscon®	Alginic acid and sodium bicarbonate	Reckitt Benckiser Healthcare, UK
Effervescent and swelling based	Prazopress XL®	Prazosin hydrochloride	Sun Pharma, Japan

floating system			
Erodible matrix based system	Cipro XR®	Ciprofloxacin hydrochloride and betaine	Bayer, USA
Expandable system (unfolding)	Accordion Pill®	Carbidopa/levodopa	Intec Pharma, Israel
Raft forming system	Topalkan®	Aluminum magnesium	Pierre Fabre Medicament, France
	Almagate FlatCoat®	Aluminium-magnesium antacid	Pierre Fabre Medicament, France
Floating system—controlled release capsule	Madopar HBS®	Levodopa and benserzide	Roche, UK
	Prolopa HBS®	Levodopa and benserzide hydrochloride	Roche, UK
	Valrelease®	Diazepam	Roche, UK
Foam based floating system	Inon Ace Tables®	Simethicone	Sato Pharma, Japan
Gastroretention with osmotic system	Coreg CR®	Carvedilol	GlaxoSmithKline, UK
Minextab Floating®—floating and swelling system	Metformin HCl	Metformin hydrochloride	Galanix, France
	Cafeclor LP	Cefaclor	Galanix, France
	Tramadol LP	Tramadol	Galanix, France
Polymer based swelling technology: AcuFormTM	Gabapentin GR	Gabapentin	Depomed, USA
	proQuin XR	Ciprofloxacin	Depomed, USA
	Glumetza	Metformin hydrochloride	Depomed, USA
	Metfromin GRTM	Metformin hydrochloride	Depomed, USA

Classification of floating drug delivery systems

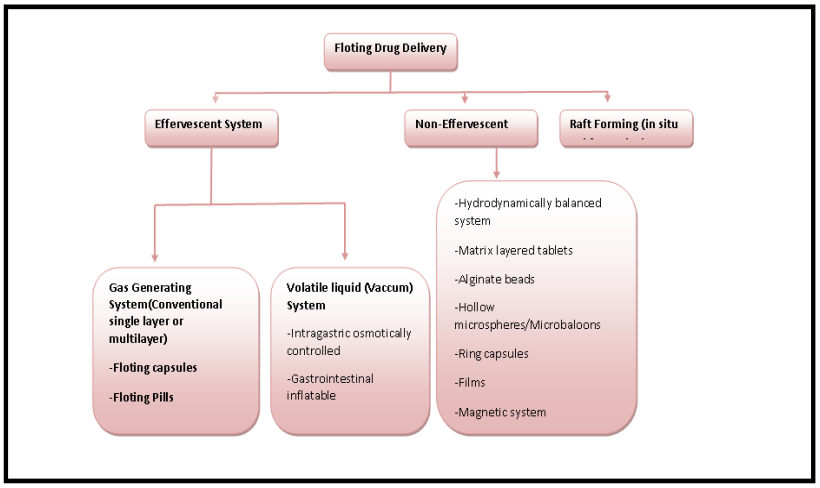
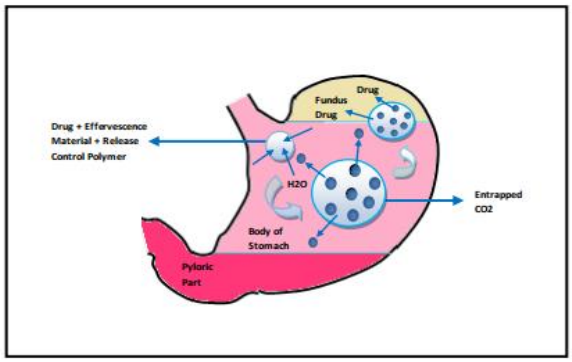


Fig.: Classification of floating drug delivery system (FDDS)

The two formulation variables Effervescent and Non-effervescent systems are used to classify floating drug delivery systems.

Effervescent floating dosage forms

These are matrix systems made from swellable polymers such as methylcellulose, HPMC, and chitosan, as well as effervescent substances such as sodium carbonate, calcium carbonate, tartaric acid, and citric acid. They are designed in such a way that when they come into touch with the acidic gastric contents, CO2 is liberated and captured in the swelling hydrocolloids, providing buoyancy to the dosage forms such as Famotidine, Amlodipine besylate.[37]



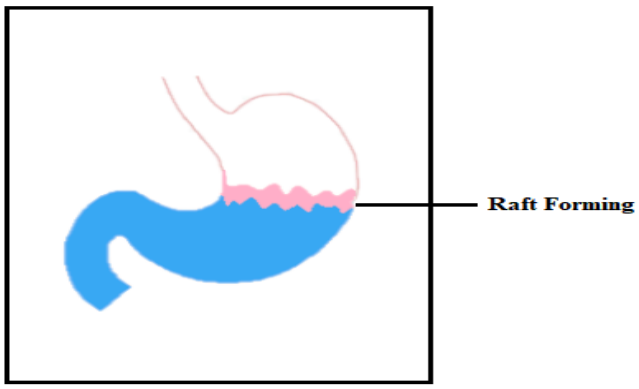
Non-effervestive floating dosage forms

These dosage forms contain gel-forming or swellable cellulose hydrocolloids, polysaccharides, and matrix-forming polymers such as polycarbonates, polymethaacrylate, and polystyrene. The formulation is created by combining the drug and the gel-forming hydrocolloid following oral administration of this dosage form swells in contact with gastric juices and achieves a bulk density of 1. The buoyancy of the dosage form was achieved through air trapping in the swelling gel-like structure, which acts as a reservoir and enables for continuous drug release through the gelatinous mass. Famotidine[38] and Levodopa[39] are two examples of medications.

Raft-forming systems

Another type of GRDDS is raft-forming systems, which are prepared with effervescent excipients and gel-forming polymers to achieve prolonged drug delivery. Figure 5 depicts the principle of these systems, which focuses on achieving localized effects due to floating rafts acting as blockades between the esophagus and the stomach. As a result, they can be utilized to effectively control gastroesophageal reflux disease. When raft-forming systems come into

contact with stomach fluid, they swell and create a viscous cohesive gel, resulting in the development of rafts.[41,42] The antacid raft-forming floating mechanism was described by Fabregas et al.[44] The gel-forming polymer utilized by the authors was sodium alginate, while the gas-generating agents were sodium bicarbonate and acid neutralizer. As a result, CO2 gas is produced, which lowers the system's bulk density and causes the raft to float on the gastric fluid. Nabarawi et al.[42] created a mebeverine hydrochloride controlled release floating raft system and evaluated various excipients for their floating behavior and in vitro controlled-release. When it swells and entraps CO2 bubbles produced by the interaction of carbonates with stomach juice, it produces a viscous and cohesive gel.[40] The created raft can stay intact in the stomach for several hours, encouraging continuous medication release. These rafts are especially beneficial for delivering antacid medications such aluminum hydroxide, calcium carbonate, and simethicone.[45] However, the mechanical strength of the systems is low and readily damaged.



Merits[46]

- Drug delivery with a restricted absorption window in the small intestine.
- A longer residence period in the stomach may be beneficial for local action in the upper region of the small intestine, such as treating peptic ulcer disease.
- Improved bioavailability is anticipated for medications that are easily absorbed in the GI tract, such as cyclosporine, ciprofloxacin, ranitidine, amoxycillin, captopril, and others.
- Improve patient compliance by instituting once-daily therapy.
- Greater therapeutic efficacy.
- Reduces dosing frequency.
- Targeted treatment for upper GI tract problems.

- When compared to non-gastroretentive drug delivery, this gastroretentive drug delivery strategy can dramatically increase the bioavailability of therapeutic drugs, particularly those that are metabolised in the upper GIT.
- Gastro retentive medication administration can result in prolonged and sustained drug release from dosage forms that provide local therapy in the stomach and small intestine. As a result, they are useful in the treatment of stomach and small intestinal problems.
- Gastro retentive medication administration can reduce body counter-activity, resulting in improved drug efficiency.
- Increases the dose form's residence duration at the site of absorption.
- To prevent first-pass metabolism
- High accessibility.
- Rapid absorption due to abundant blood supply and high blood flow rates.
- First-pass metabolism increases medication bioavailability.
- Site-specific medication administration.
- Drugs that release slowly and at a controlled rate reduce mucosal irritation.
- Drugs that release slowly and at a controlled rate reduce mucosal irritation.

Demerits[46]

- One disadvantage of floating devices is that they require a high level of fluids in the stomach in order to float and perform efficiently. With this dosage form, increased water intake is advised.
- In supine (sleeping) posture, contractile waves may sweep away floating dose form (if not of greater size). As a result, the patient should not take the floating dose form right before going to bed.
- Pharmaceuticals that have a problem with stability in high acidic environments, pharmaceuticals with very low solubility in acidic environments, and drugs that irritate the stomach mucosa cannot be included into GRDDS.
- High turnover rate of mucus layer, thick mucus layer, and soluble mucus related restrictions plague bio/muco adhesives systems.
- Swellable dosage forms must be able to swell quickly before exiting the stomach and acquire a size bigger than the pylorus aperture. It must be able to withstand the housekeeping waves of MMC Phase III.

- Many factors influence gastric retention, including stomach motility, pH, and the presence of food. Because these variables are never consistent, buoyancy cannot be anticipated.
- The high turnover rate of stomach mucus is a major problem for a bioadhesive system.
- There is also the possibility of esophageal binding with bio adhesive drug delivery systems.
- Drugs with GIT stability and solubility issues are not ideal candidates for these systems.

Physiological considerations for grdds development

Fundamental GIT Physiology[47-50]

The stomach plays a crucial role in the digestive process, and its anatomical structure and function are essential considerations in the design of controlled drug delivery systems. The stomach is divided into three regions, the fundus, body, and antrum, and is composed of different types of cells that secrete various digestive enzymes and fluids. The contraction forces of the stomach mix the chyme and propel it towards the antrum, where it undergoes further grinding and trituration. The antrum also regulates gastric emptying by its propelling actions and acts as a pump to move the food particles towards the pylorus.

The pylorus is a sphincter that separates the antrum from the duodenum and acts as a mechanical stricture and a sieve for the passage of large particles. The size of particles that can pass through the pyloric valve is between 1 to 2 mm in size. Therefore, to prolong gastric retention and prevent premature gastric emptying, controlled drug delivery systems should use drug-particle sizes larger than the pyloric diameter.

In conclusion, understanding the anatomy and physiology of the stomach is crucial for the development of effective controlled drug delivery systems, especially those designed for gastro retentive drug delivery. By using larger particles or other techniques to prolong gastric retention, drug absorption can be improved, and therapeutic benefits can be enhanced.

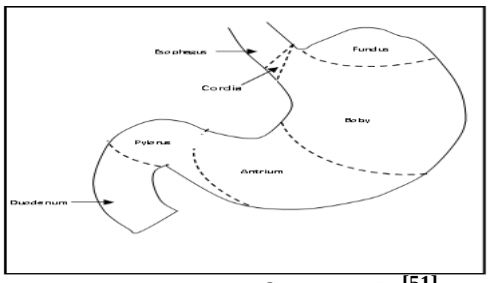


Fig: Anatomy of stomach.[51]

Gastric pH[47,52,53 and 54]

The pH of the stomach in humans varies across different parts of the gastrointestinal tract and is not constant. Large intra- and inter-subject variability can occur due to differences in the state of the stomach during measurement, as well as other physiological and biological factors. In fasted healthy subjects, the mean gastric pH is reported to be 1.1 ± 0.15, while in healthy males in the fed state, the mean pH is reported to be 3.6 ± 0.4, initially falling below 5.0 and gradually reaching fasting state values over several hours. Physiological changes in the elderly can lead to hypochlorhydria or achlorhydria, increasing their basal pH value to more than 5. Pathological conditions like pernicious anemia and AIDS, as well as the presence of drugs like H2-receptor antagonists and proton-pump inhibitors, can significantly reduce gastric acid secretion and increase gastric pH. Due to the large variability in gastric pH, clinical trials involving GRDDS should have strict screening protocols to identify such factors and implement appropriate controls to reduce bias and obtain more reliable results.

Gastric emptying[55-60]

The human gastric pH is subject to variation across different sections of the gastrointestinal tract and is influenced by various physiological and biological factors, causing intra- and inter-subject variability. In fasted healthy subjects, the mean value of gastric pH is reported to be 1.1 ± 0.15, while in the fed state, the mean pH in healthy males is reported to be 3.6 ± 0.4. Pathological conditions and drugs such as H2-receptor antagonists and proton-pump inhibitors can increase the basal pH value to more than 5, reducing gastric acid secretion and increasing the gastric pH. To ensure reliable results in clinical trials involving GRDDS, screening protocols should be in place to identify such factors and adapt appropriate controls to reduce bias.

Gastric emptying is an essential process in drug delivery that determines the length of time the dosage form remains in the stomach, particularly for drugs with a narrow absorption window. It affects the time that the drug remains in contact with the target site and oral bioavailability. Factors that affect gastric emptying influence the drug's absorption and its ability to control or regulate the process. The motility pattern of the stomach is mostly contractile, including grinding food, mixing it with gastric juices, and emptying it into the small intestine. The inter-digestive migrating myoelectric cycle (MMC) clears the stomach and intestine of undigested food. Feeding disrupts this cycle, resulting in a period of irregular contractile activity that may last for 3 to 4 hours. In the fed state, the onset of MMC is

delayed due to the lag time for the onset of gastric emptying, resulting in a slowing down of the gastric-emptying rate. Therefore, frequent feeding may delay the onset of gastric emptying and offer the advantage of prolonged retention of the dosage form.

Gastric motility is affected by various biological factors and pathological conditions in humans, such as age, gender, posture, mental stress, and disease states with intestinal involvement, such as gastroesophageal reflux, congenital heart disease, diabetes, and respiratory distress syndrome. Formulation factors such as density, shape, and size of the device also affect the gastric retention of dosage forms. Researchers aim to develop successful GRDDS to provide controlled delivery of the drug at the target site and better control over fluctuations in peak plasma concentrations. Formulation factors affecting gastric retention of dosage forms have been exploited to design different types of GRDDS, including high-density, low-density/flotation, mucoadhesion, and swelling/unfoldable systems.

Factors Influencing FDDS Gastric Retention

1. **Formulation factors:** GRT of gastro retentive FDDS can be affected by formulation characteristics such as shape and size.

A. Shape

Cadwill et. al. evaluated the influence of form on the gastric-retention capability of FDDS in an in vivo study of healthy human participants. Their findings revealed that the tetrahedron- and ring-shaped devices provided greater retention and longer GRTs than the other shapes (cloverleaf, string, pellet, and disc) due to their ability to achieve a size large enough to be retained in the stomach and their flexibility to resist premature emptying by the stomach's strong propulsive forces.[61-62]

B. Size

To summarize, the size of a dosage form can affect its gastric retention time. The human pylorus, which functions as a sieve for the emptying of gastric contents, has a critical value for the diameter of dosage forms. Small-sized tablets are usually emptied from the stomach during the digestive phase, while large ones are emptied during the "housekeeping" waves. Floating dosage forms, by virtue of their density, can float over the gastric contents and position themselves away from the pyloric sphincter, allowing them to avoid premature emptying and prolong gastric retention in the stomach. Research has shown that the buoyancy of dosage forms can prolong gastric retention time, especially for small- and medium-sized

floating units, but there is a cut-off size over which flotation does not significantly improve gastric retention.[63-64]

2. Patient posture

Timmermans et al.120 discovered that patients that were given floating units supine had extended retention of the dose form. However, the size of the dose form primarily influenced this prolonged retention, and buoyancy no longer remained an advantage for stomach retention.121 This is because the floating dosage form is close to the pyloric sphincter in the supine position, which preferentially empties the particles based on their size. Wilson et al.27 have also shown that posture influences stomach emptying in patients lying on their backs to sleep after consuming floating dosage forms. They discovered that when patients were resting on their backs on their right side, an alginate floating raft emptied more slowly than food. The raft was positioned in the greater curvature of the stomach as a result of this posture, which prolonged its gastric retention. In contrast, while the patients were lying on their left sides, the raft was given to the pylorus ahead of the meal and thus emptied faster.[64-66]

3. Effect of food

In vivo, multi particulate drug delivery systems distribute throughout the gastrointestinal tract and empty in a consistent manner in the presence of food. Conversely, single-unit systems empty in an "all-or-nothing" fashion. The use of multi-unit formulations instead of single-unit ones often leads to more reliable gastric-emptying patterns, less variability in absorption between individuals, and a lower likelihood of dose dumping. Studies have explored the effects of stomach state, food type, and frequency of intake on the performance of these systems. In several studies, gastric residence times of non-disintegrating dosage forms were correlated with the caloric intake of subjects. Therefore, most studies support the view that food, not buoyancy, is the most important factor affecting gastric residence time and that floating does not necessarily increase it. In a study comparing floating and non-floating capsules, both types of capsules had shorter gastric-emptying times in fasted subjects (less than 2 hours) compared to subjects who had eaten, with emptying times of 4 hours or more. Studies have also shown that a gastric residence time of 4 to 10 hours can be achieved after a meal of fat and protein. Gastric emptying depends on the onset of the migrating motor complex, which is delayed under fed conditions, leading to a prolonged gastric residence time. This delay can increase drug absorption from floating systems due to increased drug dissolution and longer residence at sites of absorption. However, an ideal floating drug

delivery system should be able to provide gastro retentive properties independent of meal size and be suitable for patients with varying eating habits. In summary, while floating drug delivery systems possess an inherent ability to facilitate gastric retention, they rely more on the presence of a meal to retard their emptying.[56,67-73]

Characterization of multiparticulate floating drug delivery system

Characterization of the micro particulate carrier is an important phenomenon that aids in the development of an appropriate carrier for protein, medication, or antigen delivery.[74,75]

Particle Size and Shape

In comparison to the LM, the SEM gives higher resolution. The most common methods for visualizing micro particles are conventional light microscopy (LM) and scanning electron microscopy (SEM). (SEM). Both can be used to determine the shape and exterior structure of multi particulate materials.

Capture efficiency

Allowing washed microspheres to lyse can be used to estimate the capture efficiency or percent entrapment. The lysate is then tested for active components in accordance with the monograph requirements. The following equation is used to compute the percent encapsulation efficiency:

% Entrapment = Actual content/Theoretical content x 100

Floating behavior

A suitable amount of floating micro particles was mixed with 100 ml of simulated stomach fluid (SGF, pH 2.0) and swirled with a magnetic stirrer. Filtration was used to remove the layer of buoyant micro particles. Filtration was used to separate particles from the sinking particulate layer. Both sorts of particles were dried in a desiccator until they reached a consistent weight. The weight ratio of floating particles to the sum of floating and sinking particles was used to calculate buoyancy for both fractions of microspheres.

(%) buoyancy = Wf / Wf + Ws

Wf and Ws are the weights of the floating and settled micro particles, respectively.

Bulk and Tapped density

The bulk and tapped densities were determined using a 10 ml graduated cylinder. The sample put into the cylinder was mechanically tapped 100 times, and the tapped volume, bulk density, and tapped density were calculated.

Carr's compressibility index

The compressibility index (C.I.) or Carr's index value of micro particles was calculated using the equation:

Carr's index = [Tapped density – Bulk density/Tapped density] X 100

A score less than 15% suggests a powder with good flow properties, whereas a value greater than 25% indicates a powder with poor flow capabilities.

Hausner ratio

Hausner's micro particle ratio was calculated by comparing the tapped density to the bulk density using the following equation:

Hausner ratio = Tapped density/Bulk density.

Angle of repose (θ)

The fixed funnel and free standing cone methods use a funnel with its tip fastened at a set height, h, which was held 2 cm above graph paper on a flat horizontal surface. The angle of repose can be calculated using the following equation, where r is the radius of the base of the conical pile:

$\theta = \tan^{-1}(h/r)$

In this equation, is the angle of repose, h is the height, and r is the radius.

Moisture content

Karl Fisher titration is used to determine moisture content.

Content uniformity

Each batch's content uniformity (assay) is carried out in accordance with the protocol outlined in the official pharmacopoeia.

In-Vitro release studies

In vitro drug release from the floating multi particulate is complicated because the multi particulate float and adhere to the inner surfaces of dissolution basket, which leads to the non-participation of multi particulate or their surface in release study. The release rate of floating

multi particulate was determined in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus. A weighed amount of floating multi particulate equivalent to 50 mg drug was filled into a hard gelatin capsule (No. 0) and placed in the basket of dissolution rate apparatus. The dissolution fluid was maintained at 37 ± 1° at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. 5ml samples were withdrawn at each 30 min interval, passed through a 0.25 µm membrane filter (Millipore), and analyzed using LC/MS/MS method to determine the concentration present in the dissolution medium.

The future of gastro retentive medication delivery systems

The future of gastro retentive drug delivery systems with industrial applications includes the development of innovative gastro retentive drug delivery formulations that overcome the disadvantages associated with oral medication delivery. During development methods, pharmacotherapy of disease states, as well as assessment of fed and fasted conditions, should be considered. Scaling up the technology should also be studied in order to improve the marketability of gastro retentive medication delivery formulations.

CONCLUSION

In recent years, gastrointestinal medication delivery systems have received a lot of attention. The most favored systems in which FDDS promises to be a promising strategy for stomach retention are gastro retentive drug delivery systems. The number of commercial goods and patents issued in various sectors attest to this. The goal is to optimize drug bioavailability in the gastrointestinal tract region with a restricted absorption window. Prolonging the drug's residence time in the GI area enhances the solubility of drugs that are less soluble in high pH, decreases drug waste, and reduces plasma level variability. Although there are a lot of challenges to overcome in order to achieve prolonged gastric retention, a huge number of companies are working to commercialise this technology.

REFERENCES

1. Srikanth M, Janaki B, Sunil S, Sreenivasa R, Ramana M. Gastroretentive drug delivery systems: Novel approaches and its evaluation: A Review. Int J Pharm Sci Rev Res, 2011; 10: 203-16.
2. Srikananth M, Dharmanlingam S, Kolapalli V. Formulation of gastroretentive floating drug delivery system using hydrophilic polymers and its *in vitro* characterization. Braz J Pharm Sci, 2014; 50: 431-9.

3. Singh B, Kim K. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. J Control Release, 2000; 63: 235-59.
4. Lopes C, Bettencourt C, Rossi A, Buttini F, Barata P. Overview on gastroretentive drug delivery systems for improving drug bioavailability. Int J Pharma, 2016; 510: 144-58.
5. Sharma A, Khan A. Gastroretentive drug delivery system: An approach to enhance gastric retention for prolonged drug release. Int J Pharma Sci Res, 2014; 5: 1095-106.
6. Narang N. An updated review on: Floating drug delivery system (FDDS). Int J Appl Pharm, 2011; 3: 1-7.
7. Thahera P, Latha K, Shailaja T, Nyamathulla S, Uhumwangho M. Formulation and evaluation ofnorfloxacin gastro retentive drug delivery systems using natural polymers. Int Curr Pharma J, 2012; 1: 155-64.
8. Lopes, C.M.; Bettencourt, C.; Rossi, A.; Buttini, F.; Barata, P. Overview on gastroretentive drug delivery systems for improving drug bioavailability. *Int. J. Pharm*, 2016; *510*: 144–158.
9. Hwang, K.-M.; Cho, C.-H.; Tung, N.-T.; Kim, J.-Y.; Rhee, Y.-S.; Park, E.-S. Release kinetics of highly porous floating tablets containing cilostazol. *Eur. J. Pharm. Biopharm*, 2017; *115*: 39–51.
10. Kim, S.; Hwang, K.-M.; Park, Y.S.; Nguyen, T.-T.; Park, E.-S. Preparation and evaluation of non-effffervescent gastroretentive tablets containing pregabalin for once-daily administration and dose proportional pharmacokinetics. *Int. J. Pharm*, 2018; *550*: 160–169.
11. Sarkar, D.; Nandi, G.; Changder, A.; Hudati, P.; Sarkar, S.; Ghosh, L.K. Sustained release gastroretentive tablet of metformin hydrochloride based on poly (acrylic acid)-grafted-gellan. *Int. J. Biol. Macromol*, 2017; *96*: 137–148.
12. Thapa, P.; Jeong, S. Effffects of Formulation and Process Variables on Gastroretentive Floating Tablets with A High-Dose Soluble Drug and Experimental Design Approach. *Pharmaceutics*, 2018; *10*: 161 10.
13. Chavanpatil, M.D.; Jain, P.; Chaudhari, S.; Shear, R.; Vavia, P.R. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for oflfloxacin. *Int. J. Pharm*, 2006; *316*: 86–92.
14. Sawicki, W. Pharmacokinetics of verapamil and norverapamil from controlled release flfloating pellets in humans. *Eur. J. Pharm. Biopharm*, 2002; *53*: 29–35.

15. El-Zahaby, S.A.; Kassem, A.A.; El-Kamel, A.H. Design and evaluation of gastroretentive levoflfloxacin flfloating mini-tablets-in-capsule system for eradication of Helicobacter pylori. *Saudi Pharm. J*, 2014; *22*: 570–579.
16. Jiménez-Martínez, I.; Quirino-Barreda, T.; Villafuerte-Robles, L. Sustained delivery of captopril from flfloating matrix tablets. *Int. J. Pharm*, 2008; *362*: 37–43.
17. Sethi, S.; Mangla, B.; Kamboj, S.; Rana, V. A QbD approach for the fabrication of immediate and prolong buoyant cinnarizine tablet using polyacrylamide-g-corn fifibre gum. *Int. J. Biol. Macromol*, 2018; *117*: 350–361.
18. Mandal, U.K.; Chatterjee, B.; Senjoti, F.G. Gastro-retentive drug delivery systems and their in vivo success: A recent update. *Asian J. Pharm. Sci*, 2016; *11*: 575–584.
19. Prinderre, P.; Sauzet, C.; Fuxen, C. Advances in gastro retentive drug-delivery systems. *Expert Opin. Drug Deliv*, 2011; *8*: 1189–1203.
20. Cvijic, S.; Ibric, S.; Parojcic, J.; Djuris, J. An in vitro—In silico approach for the formulation and characterization of ranitidine gastroretentive delivery systems. *J. Drug Deliv. Sci. Technol*, 2018; *45*: 1–10.
21. Hooda, A.; Nanda, A.; Jain, M.; Kumar, V.; Rathee, P. Optimization and evaluation of gastroretentive ranitidine HCl microspheres by using design expert software. *Int. J. Biol. Macromol*, 2012; *51*: 691–700.
22. Odeku, O.; Aderogba, A.; Ajala, T.; Akin-Anjani, O.; Okunlola, A. Formulation of flfloating metronidazole microspheres using cassava starch *(Manihot esculenta)* as polymer. *J. Pharm. Investig*, 2017; *47*: 445–451.
23. Diós, P.; Nagy, S.; Pál, S.; Pernecker, T.; Kocsis, B.; Budán, F.; Horváth, I.; Szigeti, K.; Bölcskei, K.; Máthé, D.; et al. Preformulation studies and optimization of sodium alginate based flfloating drug delivery system for eradication of Helicobacter pylori. *Eur. J. Pharm. Biopharm*, 2015; *96*: 196–206.
24. Jain, S.K.; Jangdey, M.S. Lectin conjugated gastroretentive multiparticulate delivery system of clarithromycin for the effffective treatment of Helicobacter pylori. *Mol. Pharm*, 2008; *6*: 295–304.
25. Hardikar, S.; Bhosale, A. Formulation and evaluation of gastro retentive tablets of clarithromycin prepared by using novel polymer blend. *Bull. Fac. Pharm. Cairo Univ*, 2018; *56*: 147–157.
26. Inukai, K.; Takiyama, K.; Noguchi, S.; Iwao, Y.; Itai, S. Effffect of gel formation on the dissolution behavior of clarithromycin tablets. *Int. J. Pharm*, 2017; *521*: 33–39.

27. Mostafavi, A.; Emami, J.; Varshosaz, J.; Davies, N.M.; Rezazadeh, M. Development of a prolonged-release gastroretentive tablet formulation of ciproflfloxacin hydrochloride: Pharmacokinetic characterization in healthy human volunteers. *Int. J. Pharm*, 2011; *409*: 128–136.
28. Fu, J.; Yin, H.; Yu, X.; Xie, C.; Jiang, H.; Jin, Y.; Sheng, F. Combination of 3D printing technologies and compressed tablets for preparation of riboflflavin flfloating tablet-in-device (TiD) systems. *Int. J. Pharm*, 2018; *549*: 370–379.
29. Kagan, L.; Lapidot, N.; Afargan, M.; Kirmayer, D.; Moor, E.; Mardor, Y.; Friedman, M.; Hoffffman, A. Gastroretentive Accordion Pill: Enhancement of riboflflavin bioavailability in humans. *J. Control. Release*, 2006; *113*: 208–215.
30. Qin, C.; Wu, M.; Xu, S.; Wang, X.; Shi, W.; Dong, Y.; Yang, L.; He, W.; Han, X.; Yin, L. Design and optimization of gastro-flfloating sustained-release tablet of pregabalin: In vitro and in vivo evaluation. *Int. J. Pharm*, 2018; *545*: 37–44.
31. Ngwuluka, N.C.; Choonara, Y.E.; Kumar, P.; du Toit, L.C.; Modi, G.; Pillay, V. An optimized gastroretentive nanosystem for the delivery of levodopa. *Int. J. Pharm*, 2015; *494*: 49–65.
32. Oh, T.-O.; Kim, J.-Y.; Ha, J.-M.; Chi, S.-C.; Rhee, Y.-S.; Park, C.-W.; Park, E.-S. Preparation of highly porous gastroretentive metformin tablets using a sublimation method. *Eur. J. Pharm. Biopharm*, 2013; *83*: 460–467.
33. He, W.; Li, Y.; Zhang, R.; Wu, Z.; Yin, L. Gastro-flfloating bilayer tablets for the sustained release of metformin and immediate release of pioglitazone: Preparation and in vitro/in vivo evaluation. *Int. J. Pharm*, 2014; *476*: 223–231.
34. Patil, S.; Talele, G.S. Gastroretentive mucoadhesive tablet of lafutidine for controlled release and enhanced bioavailability. *Durg Deliv*, 2015; *22*: 312–319.
35. Pawar, V.K.; Kansal, S.; Garg, G.; Awasthi, R.; Singodia, D.; Kulkarni, G.T. Gastroretentive dosage forms: A review with special emphasis on flfloating drug delivery systems. *Durg Deliv*, 2011; *18*: 97–110.
36. Kotreka, U.; Adeyeye, M.C. Gastroretentive flfloating drug-delivery systems: A critical review. *Crit. Rev. Ther. Drug*, 2011; *28*.
37. Pare A, Yadav SK and Patil UK, Formulation and Evaluation of Effervescent Floating Tablet of Amlodipine besylate , Research J. Pharm. and Tech, 2008; 1(4*)*.
38. Ramana Murhy, K. V. Shailaja1, P. Naresh, N. Shiva Kumar, M. Development and Characterization of Non-Effervescent Gastric Floating Drug Delivery Systems (GFDDS) of Famotidine using Compritol® 888 ATO.

39. Goole, J. Vanderbist, F. Amighi, K. Development and evaluation of new multiple unit levodopa sustained-release floating dosage forms, International Journal of Pharmaceutics, 2007; 334: 35–41.
40. Bardonnet, P.; Faivre, V.; Pugh, W.; Piffffaretti, J.; Falson, F. Gastroretentive dosage forms: Overview and special case of Helicobacter pylori. *J. Control. Release,* 2006; *111*: 1–18.
41. Prajapati, V.D.; Jani, G.K.; Khutliwala, T.A.; Zala, B.S. Raft forming system—An upcoming approach of gastroretentive drug delivery system. *J. Control. Release,* 2013; *168*: 151–165.
42. Abouelatta, S.M.; Aboelwafa, A.A.; El-Gazayerly, O.N. Gastroretentive raft liquid delivery system as a new approach to release extension for carrier-mediated drug. *Durg Deliv,* 2018; *25*: 1161–1174.
43. Youssef, N.A.H.A.; Kassem, A.A.; El-Massik, M.A.E.; Boraie, N.A. Development of gastroretentive metronidazole flfloating raft system for targeting Helicobacter pylori. *Int. J. Pharm,* 2015; *486*: 297–305.
44. Fabregas, J.; Claramunt, J.; Cucala, J.; Pous, R.; Siles, A. "In-Vitro" Testing of an Antacid Formulation with Prolonged Gastric Residence Time (Almagate Flot-Coat®). *Drug Dev. Ind. Pharm,* 1994; *20*: 1199–1212.
45. Hampson, F.C.; Jolliffffe, I.G.; Bakhtyari, A.; Taylor, G.; Sykes, J.; Johnstone, L.M.; Dettmar, P.W. Alginate–antacid combinations: Raft formation and gastric retention studies. *Drug Dev. Ind. Pharm,* 2010; *36*: 614–623.
46. Joseph R. Robinson and Vincent H. L. Lee, Controlled Drug Delivery, Fundamentals and Applications, Revised and Expanded, Marcell. Dekker Inc., New York, 2009; 2.
47. Dressman JB, Berardi RR, Dermentzoglou LC, Russell TL, Schmaltz SP, Barnett JL, Jarvenpaa KM. Upper gastrointestinal (GI) pH in young, healthy men and women. Pharm Res, 1990; 7(7): 756–61.
48. Talukder R, Fassihi R. Gastroretentive delivery systems: a mini review. Drug Dev Ind Pharm, 2004; 30(10): 1019–28.
49. Timmermans J, Moes AJ. The cutoff size for gastric-emptying of dosage forms. J Pharm Sci, 1993; 82(8): 854.
50. Wilson CG, Washington N, Washington C. The stomach. In: Wilson CG, Washington N, Washington C, editors. Physiological pharmaceutics: biological barriers to drug absorption. New York: Taylor and Francis Inc, 2000; 75–108.

51. Ashford M. The gastrointestinal tract: physiology and drug absorption. In: Aulton ME. Pharmaceutics: The science of dosage form design. Philadelphia: Churchill Livingstone, 2002; 217–33.
52. Davies B, Morris T. Physiological parameters in laboratory animals and humans. Pharm Res, 1993; 10(7): 1093–5.
53. Johannesson E, Magnusson PO, Sjoberg NO, Skov-Jensen A. Intragastric pH evaluation with radiotelemetry. Scand J Gastroenterol, 1973; 8(1): 65–9.
54. Varis K, Ihamaki T, Harkonen M, Samloff I, Siurala M. Gastric morphology, function, and immunology in fifi rst-degree relatives of probands with pernicious anemia and controls. Scand J Gastroenterol, 1979; 14(2): 129–39.
55. Klausner E, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. J Control Release, 2003; 90(2): 143–62.
56. Desai S, Bolton S. A flfl oating controlled-release drug delivery system: in vitro-in vivo evaluation. Pharm Res, 1993; 10(9): 1321–5.
57. Besunder JB, Reed MD, Blumer JL. Principles of drug biodisposition in the neonate - a critical evaluation of the pharmacokinetic-pharmacodynamic interface (part I). Clinical Pharmacokinetics, 1988; 14(4): 189–216.
58. Read N, Sugden K. Gastrointestinal dynamics and pharmacology for the optimum design of controlled-release oral dosage forms. Crit Rev Ther Drug Carrier Syst, 1988; 4(3): 221–63.
59. Ali J, Arora S, Ahuja A, Babbar AK, Sharma RK, Khar RK, Baboota S. Formulation and development of hydrodynamically balanced system for metformin: In vitro and in vivo evaluation. Eur JPharm Biopharm, 2007; 67(1): 196–201.
60. Sheth P, Tossounian J, inventors; Hoffman-La Roche Inc., assignee. Sustained –release pharmaceutical capsules. United States patent US 4126672, 1978; 21.
61. Garg S, Sharma S. Gastroretentive drug delivery systems. Business Briefifi ng, Pharmatech, 2003; 160–6.
62. Marathe P, Wen Y, Norton J, Greene D, Barbhaiya R, Wilding I. Effect of altered gastric emptying and gastrointestinal motility on metformin absorption. Br J Clin Pharmacol, 2000; 50(4): 325–32.
63. Khosla R, Davis S. The effect of tablet size on the gastric emptying of non-disintegrating tablets. Int J Pharm, 1990; 62: R9–11.
64. Timmermans J, Gansbeke V, Moes A. Assessing by gamma scintigraphy the in vivo buoyancy of dosage forms having known size and flfl oating force profifi les as a function

of time. Proceedings of the APGI International Conference on Pharmaceutical Technology, 1989; 5, 1: 42–51.

65. Wilson CG, Washington N, Washington C. The stomach. In: Wilson CG, Washington N, Washington C, editors. Physiological pharmaceutics: biological barriers to drug absorption. New York:Taylor and Francis Inc, 2000; 75–108.
66. Van Gansbeke B, Timmermans J, Schoutens A, Moes A. Intragastric positioning of two concurrentlyingested pharmaceutical matrix dosage forms. Int J Rad Appl Instrum B, 1991; 18(7): 711–8.
67. Muller-Lissner S, Blum A. The effect of specififi c gravity and eating on gastric emptying of slow release capsules. N Engl J Med, 1981; 304(22): 1365–6.
68. Sangekar S, Vadino W, Chaudry I, Parr A, Beihn R, Digenis G. Evaluation of the effect of food and specififi c gravity of tablets on gastric retention time. Int J Pharm, 1987; 35: 187–91.
69. Waterman KC. A critical review of gastric retentive controlled drug delivery. Pharm Dev Technol, 2007; 12(1): 1–10.
70. Iannuccelli V, Coppi G, Sansone R, Ferolla G. Air compartment multiple-unit system for prolonged gastric residence. Part II. In vivo evaluation. Int J Pharm, 1998; 174: 55–62.
71. Muller-Lissner S, Will N, Muller-Duysing W, Heinzel F, Blum A. A flfl oating capsule with slow release of drugs: a new method of oral drug medication [Article in German]. Dtsch Med Wochenschr, 1981; 106(36): 1143–7.
72. Mazer N, Abisch E, Gfeller J, Laplanche R, Bauerfeind P, Cucala M, Lukachich M., Blum A., Intragastric behavior and absorption kinetics of a normal and ‘flfl oating’ modififi ed-release capsule of isradipine under fasted and fed conditions. J Pharm Sci, 1988; 77(8): 647–57.
73. Oth M, Franz M, Timmermans J, Moes A. The bilayer flfl oating capsule--a stomach-directed drug delivery system for misoprostol. Pharm Res, 1992; 9(3): 298–302.
74. Joshi P and Shah M. Single and Multiparticulate Floating Drug Delivery System: An Updated Review. International Journal of Universal Pharmacy and Bio Sciences, 2013; 2(1): 102-88.
75. Ganesh NS, Bharathi G and Joshi H. Buoyant Multiparticulate Drug Delivery: A Focus on Hydrogel Beads. World Journal of Pharmacy and Pharmaceutical Sciences, 2013; 2(2): 464-450.