



A NOVEL APPROACH TO COMBAT REGIONAL VARIABILITY: FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

Success of oral drug delivery system depends on its degree of absorption through GIT. Thus, the idea of enhancing drug absorption in the GIT pioneered the idea of development of Gastroretentive drug delivery system. To design and evaluate the performance of GRDDS, it is important to understand the relevant anatomy and physiology of the GI tract. To achieve gastric retention, the dosage form should satisfy certain requirements; primarily, the dosage form must be able to withstand the forceful peristaltic waves in the stomach and the constant contractions, grinding and churning. To function as a gastric retention device, it must resist premature gastric emptying. Once the purpose has been served, the device should be removed from the stomach with ease. Floating DDS or hydrodynamically balanced systems (HBS) have a bulk density lower than the gastric fluids ($<-1.004 \text{ g/cm}^3$), and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Using FDDS one can easily increase the absorption of gastric secretion-labile drugs.

Keywords: oral drug delivery, floating drug delivery, gastric retention.

INTRODUCTION

Oral route of administration is one of the most reliable methods of drug administration. It is due to its ease of intake that it increases patient compliance, be it fast disintegrating or sustained release type of dosage form. Oral drug delivery system can be classified into: fast release & prolonged release forms. fast release forms lead to fluctuations in plasma drug levels and require multiple dosing whereas, prolonged release are most commonly used for 1) delayed release (e.g., by using an enteric coating); 2) extended release (e.g., zero-order, first-order, biphasic release, etc.); 3) programmed release (e.g., pulsatile, triggered, etc.) and 4) site specific or timed release (e.g., for colonic delivery or gastric retention). Extended, sustained or prolonged release drug delivery systems are terms used synonymously to describe this group of controlled drug delivery devices, with predictability and reproducibility in the drug release kinetics.¹

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PHYSIOLOGY OF STOMACH

Role in GRDDS development

To design and evaluate the performance of GRDDS, it is important to understand the relevant anatomy and physiology of the GI tract.² The wall of the GI tract is made of the same structure from oesophagus to anus, with some local variation in each region.³ The stomach is a J-shaped dilated portion of the alimentary tract situated in the epigastric, umbilical and left hypochondriac regions of

the abdominal cavity. Its size varies with the amount of food it contains. The volume is 1.5 l or more in adult⁴ and after food has emptied a 'collapsed state' is obtained with a resting volume of only 25-30 ml.⁵ The stomach consists of fundus, body and antrum; pylorus is a sphincter present in between the most terminal antrum and duodenum.⁶ The fundus and body store food temporarily, secrete digestive juices and propels chimes, a milky mixture of food with gastric juices, to the antrum. The antrum grinds and triturates food particles and regulates the secretion of the hydrochloric acid as well as the emptying of food.⁷

In the fasted state, the process of gastric emptying is characterized by an inter-digestive series of electrical events, which cycle both through the stomach and small intestine every 2-3 h.⁸ This activity is called the inter-digestive myoelectric cycle or inter-digestive migration myoelectric complex (IMMC), which is divided into four consecutive phases.⁹

Phase I: A period lasting from 40-60 min with rare contractions.

Phase II: A period consisting of intermittent action potentials and contractions that gradually increases in intensity and frequency as the phase progress. It lasts for the same time of 40-60 min.

Phase III: A period of intense, large regular contractions lasting from 4 to 6 min, also called "house keeper" wave, undigested materials are swept out of the stomach, down the small intestine in this phase.

Phase IV: A phase that occurs between phase III and phase I of two consecutive cycles.



In the fed state, the onset of IMMC is delayed and therefore the gastric emptying rate is slowed.¹⁰ In other words, feeding results in a lag time prior to the onset of gastric emptying.

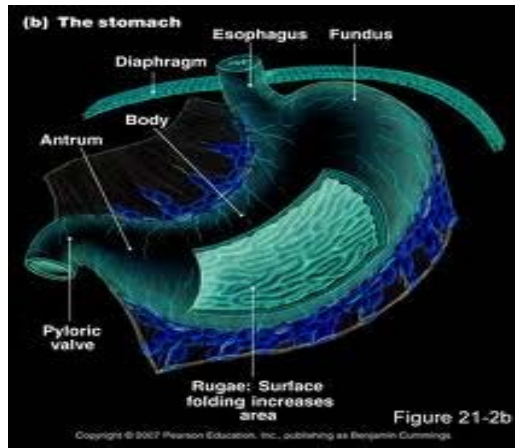


Figure 1: Gross anatomy of stomach

Requirement for gastric retention

To achieve gastric retention, the dosage form should satisfy certain requirements; primarily, the dosage form must be able to withstand the forceful peristaltic waves in the stomach and the constant contractions, grinding and churning. To function as a gastric retention device, it must resist premature gastric emptying. Once the purpose has been served, the device should be removed from the stomach with ease.

Factors affecting the gastric emptying and hence the gastric retention time of an oral dosage form

- i. Size, shape and density of the dosage form.¹¹
- ii. Concomitant ingestion of food, its nature, caloric content and frequency of intake. Interestingly, most studies related to effects of food on gastric residence time of floating systems share a common viewpoint that food intake is the main determinant of gastric emptying, while specific gravity has only a minor effect on the emptying process, or not have an effect at all.
- iii. Drugs such as anticholinergic agents (e.g. atropine, propantheline); opiates (e.g. codeine) and prokinetic agents (e.g. metoclopramide, cisapride).¹²
- iv. Biological factors such as gender, posture, age, sleep, body mass index, physical activity and disease states e.g. diabetes and Crohn's disease¹⁵ Many factors could lead to alterations in gastric emptying process, which may seriously affect the release of a drug from its delivery system; it is therefore, desirable to develop a DDS that exhibits an extended GI residence and a drug release profile independent of patient related variables.^{10, 12}

GASTRORETENTIVE DRUG DELIVERY SYSTEM

This drug delivery system aims at enhancing bioavailability of drugs by prolonging their retention in the stomach. Various approaches have been procured by

experiments aiming at formulating gastroretentive drug delivery systems.

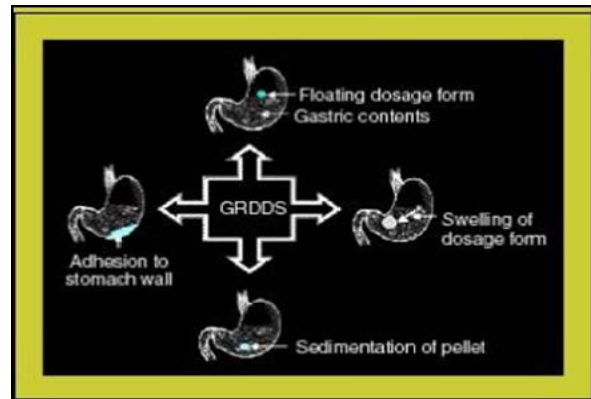


Figure 2: Approaches to gastric retention

1. Floating gastroretentive drug delivery system

- ❖ Hydrodynamically balanced systems (HBS)

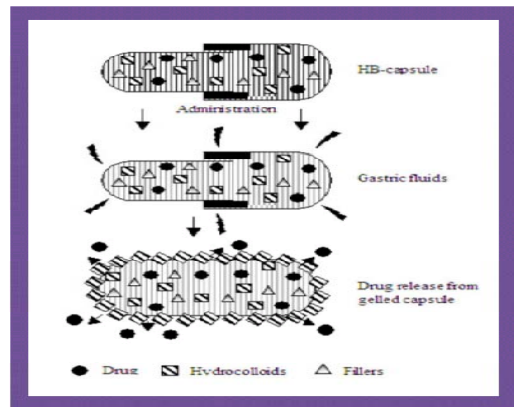


Figure 3

- ❖ Raft systems incorporate alginate gels

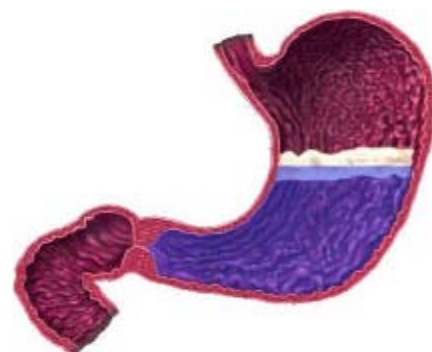


Figure 4: Barrier formed by a raft-forming system¹³

- ❖ Swelling type of dosage form

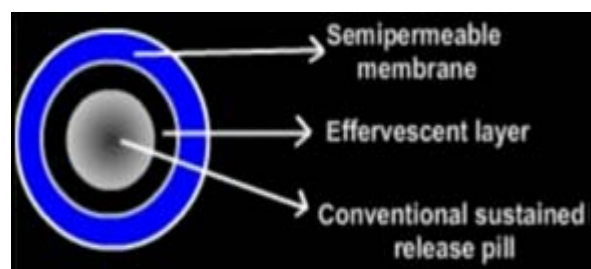


Figure 5

2. Bioadhesive or mucoadhesive systems

These systems are used to localize a delivery device within the lumen and cavity of the body in order to enhance site-specific drug absorption process. In this, bioadhesive polymers are used that can be adhere to the epithelial surface of the GIT.

3. Modified shape systems

These are non-disintegrating geometric shapes molded from silastic elastomer or exuded from polyethylene blends to extend to the GIT depending on the size, shape and flexural modulus of the drug delivery device.

4. High density formulations

These include coated pellets, and have density greater than that of the stomach content (1.004 gm/cm³). This is accomplishing by coating the drug with a heavy inert material such as barium sulphate, ZnO, titanium dioxide. This formulation of high-density pellet is based on assumption that heavy pellets might remain longer in the stomach, since they are position in the lower part of the antrum.¹⁴

FLOATING DRUG DELIVERY SYSTEM

Floating DDS or hydrodynamically balanced systems (HBS) have a bulk density lower than the gastric fluids (<-1.004 g/cm³), and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach.

The HBS systems are unreliable and irreproducible in prolonging residence time in the stomach when orally administered due to their all or nothing emptying process.¹⁵ On the other hand, multiple unit dosage forms, such as hollow microsphere (microballoons), granules, powder, and pellets, are more suitable since they are claimed to reduce the inter- and intra-subject variability in absorption and reduce the probability of dose dumping.¹⁶

Classification

The floating drug delivery systems are classified into two categories on the basis of formulation variables:

- (1) Effervescent system
- (2) Noneffervescent system

Effervescent floating dosage form

These are matrix types of systems prepared using swellable polymer such as methylcellulose and effervescent compounds like sodium bicarbonate, tartaric acid. When effervescent compounds come in contact with the acidic gastric contents, carbon dioxide is liberated which gets entrapped in the swollen hydrocolloids. This provides buoyancy to the dosage forms.

Ichikawa *et al.*, developed a new multiple type of floating dosage form composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agent containing sodium bicarbonate and tartaric acid was divided into two sublayers to avoid direct contact between the two agents. These sublayers were surrounded by swellable polymer membrane. When this system was immersed in buffer at 37 OC the solution permeated into effervescent layers.²⁰

Yang *et al.*, developed a swellable asymmetric triplet layer floating tablet to prolong the gastric residence time of triplet drug regimen (tetracycline, metronidazole and clarithromycin) in H.pylori associated peptic ulcer. HPMC and polyethylene oxide polymer were the major rate controlling excipients. Tetracycline and metronidazole were incorporated into the core layer of triple layer matrix for controlled delivery, while bismuth salts were included in one of the outer layer for instant release. The floatation was accomplished by incorporating a gas generating layer consisting of sodium bicarbonate, calcium carbonate (1:2) along with the polymer. This resulted in the sustained delivery of the drug.²¹

Non-effervescent floating dosage form

Systems with initially low density are highly desired, since they prevent the risk of premature emptying from the stomach. One of the approaches involves mixing of the drug with a gel forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and bulk density of less than the unity, within the outer gelatinous barrier.²¹ The air trapped by the swollen polymer imparts buoyancy to these dosage forms. Thus, the drug is released by controlled diffusion.

Sheth and Toussounian et al developed a HBS capsule containing a mixture of a drug and hydrocolloids.¹⁷ Upon contact with gastric fluids, the capsule shell dissolves and the mixture swells and forms a gelatinous barrier thereby remaining buoyant in the gastric juice for an extended period of time. Pharmaceutical products, using the same principle, containing APIs have been developed, containing L-DOPA, combined with a decarboxylase inhibitor.¹⁹

FACTORS AFFECTING FLOATING AND FLOATING TIME

1. **Density:** Density of a dosage form plays a vital role in determining its buoyancy and henceforth, its floating efficiency.
2. **Shape of dosage form:** Compared to other shapes, devices with tetrahedron and ring shape have better floating potential. They have 90-98% better retention for 24 hrs.
3. **Single or multiple unit formulation:** Multiple unit formulations permit a larger margin of safety against dosage form failure compared with single unit dosage forms.



Multiple unit formulations show a more predictable release profile and negligible impairing of performance due to failure of units.

4. **Fed or unfed state:** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours.¹⁸

5. **Nature of meal:** Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.²³

6. **Caloric content:** A meal rich in protein and fat content can increase floating by 4-10 hrs. 7. **Frequency of feed:** - The floating can increase by over 400 minutes when successive meals are given compared with a single meal.

8. **Age:** Elderly people, above the age of 60, have a significantly longer floating.

9. **Posture:** Floating varies considerably between supine and upright ambulatory states of the patient.

10. **Concomitant drug administration:** Anticholinergics like atropine, opiates like codeine and prokinetic agents like metoclopramide and cisapride affect floating time.

11. **Biological factors:** floating may vary as per health conditions or physiological status of a person.eg. Diabetes and Crohn's disease alters floating time.

EVALUATION TECHNIQUES

1. **For powder blends-** Evaluation of powder blenders can be done by considering angle of repose, bulk density and percentage porosity.
2. **For tablets** - Evaluation of powder blenders can be done by considering Buoyancy, *in-vitro* floating & dissolution behaviour, Weight variation, Hardness & friability, Particle size analysis, X-ray/gamma scintigraphy and Pharmacokinetic parameters.

ADVANTAGES

1. The principle of HBS of FODDS can be used for any particular medicament or class of medicament.
2. The FODDS 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.
3. The FODDS 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.
4. The efficacy of the medicaments administered utilizing the sustained release principle of FODDS has been found

to be independent of the site of absorption of the particular medicaments.

5. When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, 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.

6. FODDS provides advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.

7. Certain types of drugs can benefit from using FODDS. These include:

- a) Drugs acting locally in the stomach.
- b) Drugs those are primarily absorbed in the stomach.
- c) Drugs those are poorly soluble at an alkaline pH.
- d) Drugs with a narrow window of absorption.
- e) Drugs absorbed rapidly from the GI tract.
- f) Drugs those degrade in the colon.²²

DISADVANTAGES

1. There are certain situations where gastric retention is not desirable.

Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.

2. Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.

3. 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.²²

LIMITATIONS

1. The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach.
2. Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.
3. The dosage form should be administered with a minimum of glass full of water (200-250 ml).
4. The drugs, which are absorbed throughout gastrointestinal tract, which under go first-pass metabolism (nifedipine, propranolol etc.), are not desirable candidate.
5. Some drugs present in the floating system causes irritation to gastric mucosa.



CONCLUSION

From the enlisted drugs, dosage forms and the patented number of drugs, it can be easily inferred that FDDS is gaining popularity at a fast pace. This is due to its novel

technique of gastric retention of drugs thereby increasing their bioavailability and maintaining its blood-plasma levels. Using FDDS one can easily increase the absorption of gastric secretion-labile drugs.

Table 1: List of drugs under testing for formulation of FDDS

Type of dosage forms	Drugs used
Floating microspheres	Aspirin, griseofulvin, p-Nitroaniline, ibuprofen, terfenadine & tranilast
Floating granules	Diclofenac sodium, indomethacin, prednisolone
Floating capsules	Verapamil HCl, chlordiazepoxide HCl, diazepam, furosemide, levodopa, benserazide, misoprostol, propranolol HCl, nicardipine. ²⁸
Floating tablets and capsules	Acetaminophen, acetylsalicylic acid, ampicillin, amoxicillin trihydrate, atenolol, diltiazem, fluorouracil, isosorbide mononitrate, theophylline, verapamil HCl
Floating In-situ Gel	Aluminium hydroxide or calcium carbonate

Table 2: List of drugs patent under FDDS²⁴

Drugs	Dosage forms	Patent appln no.
Azithromycin	Swelling type oral CR table	US patent Appl 2007196396
Metformin HCl	Swelling type oral CR table	US patent US6488962
Rosiglitazone	Swelling type tablet	EP Patent 1732513
Heparin & insulin	Bilayered SR tablet	US Patent Appln 2008153779
Levodopa & Carbidopa	Swelling Tablet	EP Patent 1560569
Bupropion HBr	Swelling Tablet	US Patent 7241805
Valsartan	Swelling Tablet	WO PCT Appln 2008027945
Gabapentin	Swelling Tablet	US Patent Appln 2007092565
Ranitidine HCl	Swelling Tablet	US Patent 6340475
Theophylline	Multi-layered tablet	US Patent 5783212
Ciprofloxacin, Acyclovir, Ofloxacin	Buoyant bilayer tablet	US Patent Appln 2006013876
Diltiazem HCl	Buoyant CR tablet	WOPCT Appln 02102415
Glipizide, Nifedipine, Verapamil	Pellets, beads, granules or capsules	WOPCT Appln 0110405
Amoxicillin	SR floating capsule form	US Patent Appln 2006121106
Theophylline, Ampicillin, Captopril	Non-compressed SR floating tablets	US Patent 4814179
Riboflavin, Chlordiazepoxide, Diazepam	HBS of SR Tablet	US Patent 4451260
Misoprostol+Aspirin, Diclofenac, Piroxicam, Ibuprofen or Naproxen	HBS of bilayer capsule	US Patent 5232704
Cimetidine, Ranitidine & Omeprazole	Antacid powders, tablets	US Patent 5288506
Methotrexate	SR Tablet	US Patent Appln 2008268045
Ofloxacin, Acyclovir, Simvastatin, Carbamazepine, Niacin, Cefixime	SR Tablet	Indian Patent IN2002MU00769

Table 3: Marketed products of FDDS

Brand name	Drug	Company	Remarks
Madopar	Levodopa, benserazide	Roche products, USA	Floating, CR capsule
Cifran OD	Ciprofloxacin	Ranbaxy, India	Gas generating floating form
Valrelease	Diazepam	Hoffman-laroche, USA	Floating capsule
Topalkan	Al-mg antacid	Pierrefibre drug, france	Floating liquid alginate
Convion	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
Cytotec	Misoprostol	Pharmaacia, USA	Bilayer floating capsule



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