

APPROACHES TO INCREASE THE GASTRIC RESIDENCE TIME: FLOATING DRUG DELIVERY SYSTEMS- A REVIEW

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ABSTRACT

The purpose of writing this review was to compile recent literature on pharmaceutical approaches used in enhancing the Gastric Residence Time (GRT). Enhancing the GRT may explore new potentials of stomach as drug-absorbing organ. Several approaches are currently used including Floating Drug Delivery System (FDDS), swelling and expanding system, polymeric bioadhesive systems, modified-shape systems, high density system and other delayed gastric emptying devices. The drugs having absorption window in the upper part of Gastro Intestinal Tract (GIT) have enhanced bioavailability when formulated through these techniques. The recent technological development for enhancing GRT including the physiological and formulation variables affecting gastric retention, patented delivery systems, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. In addition this review also summarizes the in vitro and in vivo studies to evaluate their performance and also their future potential.

Keywords: Floating drug delivery systems, Gastric residence time, single unit, multiple units, in vitro and in vivo.

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability [1].

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastric retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail. In vivo/in vitro evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems. Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems [1,2,3].

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY AND GASTRIC RETENTION

Physiological Consideration

The stomach is situated in the left upper part of the abdominal cavity immediately under the diaphragm. Its size varies according to the amount of distension: up to 1500 ml following a meal; after food has emptied, a collapsed state is obtained with resting volume of 25-50 ml. Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus) [4]. The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions [1, 5].

Gastrointestinal motility & emptying of food

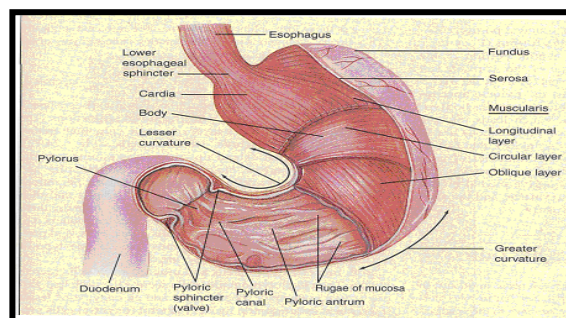


Fig. 1: Location of stomach in human body

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours, this is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC) [6]. It is further divided into following 4 phases.

Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.

Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles [7]. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than

1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate [8]. Figure 2 shows the GIT motility pattern.

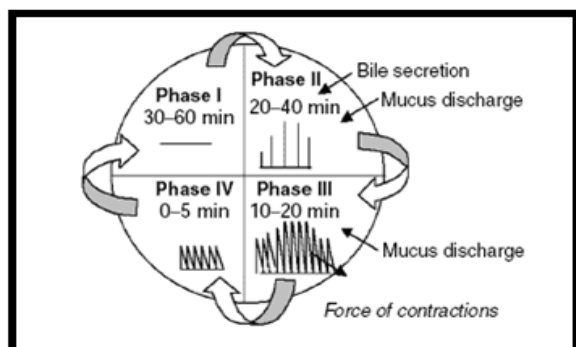


Figure 2: Interdigestive Myoelectric Cycle or Migrating Myoelectric Cycle (MMC)

FACTORS AFFECTING GRT 9

The various factors which influence the efficacy of GRDF's as a gastro-retentive systems are:

Density

GRT is a function of dosage form buoyancy that is dependent on the density. The density of a dosage form also affects the gastric emptying rate. A buoyant dosage form having a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. Drug floatation is a function of time and it could least until hydrodynamic equilibrium is achieved. Dosage forms having larger density then the gastric content sink at the bottom of the atrium where they settle and release the active compound in a controlled manner over a prolonged period of time.

Size

Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm. Larger dosage forms tend to have longer gastric retention time than smaller ones because they are emptied in the digestive phase (weaker MMC) and also because their passage through the pyloric sphincter into the small intestine is hindered.

Shape of dosage form:

Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT = 90% to 100% retention at 24 hours compared with other shapes [10].

Fed or unfed state

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the MMC that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

Nature of meal

Feeding of indigestible polymers or fatty acids salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release. Type of meal and its caloric content, volume, viscosity and co-administered drugs affect gastric secretions and gastric emptying time. The rate of emptying primarily depends on caloric contents of the ingested meal. It does not differ for proteins, fats and carbohydrates as long

as their caloric contents are the same. Generally gastric emptying is slowed down because of increased acidity, osmolarity and calorific values.

Frequency of feed

The GRT can be increased by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender

Mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race matched female counter parts (4.6 ± 1.2 hours) regardless of the weight, height and body surface.

Age

Elderly people, especially those above 70, have a significantly longer GRT.

Posture

GRT can vary between supine and upright ambulatory states of the patient [10, 11, 12, and 13].

Biological factors

Diseases like gastroenteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying. Partial or total gastrectomy, duodenal ulcer and hypothyroidism promote gastric emptying rate [14].

APPROACHES TO INCREASE GRT

Prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc. Over the last few decades, several stomach specific or gastroretentive drug delivery approaches being designed and developed, including:

- High-density systems
- Bioadhesive or Mucoadhesive systems
- Swelling and Expanding Systems
- Superporous Hydrogels
- Ion Exchange Resins
- Bioadhesive Liposomal Systems
- Floating systems
- Raft-forming systems
- Gas-generating systems
- Low-density systems
- Hydrodynamically Balanced Systems (HBS)

High-density systems

These systems, which have a density of ~ 3 g/cm³, are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. Above a threshold density of 2.4–2.8 g/cm³, such systems can be retained in the lower part of the stomach. Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm³) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets. A density close to threshold density seems necessary for significant prolongation of gastric residence time. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–2.4g/cm³ [15,16,17,18].

Bioadhesive or Mucoadhesive Systems

The term 'mucoadhesion' is commonly used to describe an interaction between the mucin layer that lines the entire GIT and a bioadhesive polymer. Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug

absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach [19]. Thus, they prolong the gastric retention time. Bioadhesion can be explained with a number of theories:

- The absorption theory, which suggests that it is due to either of two secondary forces Vander Waal forces and hydrogen bonding.
- The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin net work and the bio adhesive material (polymer).
- The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers, and finally, the diffusion theory proposes physical entanglement of mucin strands and the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.
- The diffusion theory, which proposes physical entanglement of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate [20, 21]. Figure 3 shows the bioadhesive mechanism.

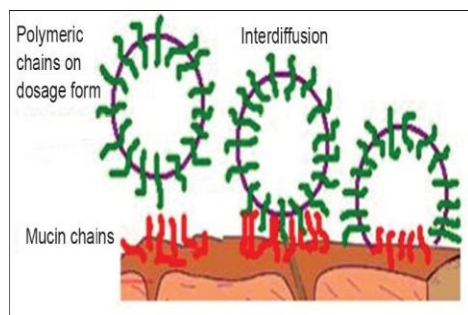


Figure 3: Bioadhesive mechanism

Swelling and Expanding Systems

Swelling and expanding systems are dosage forms that, after swallowing, swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period. These systems may be called 'plug type systems', since they exhibit a tendency to be logged at the pyloric sphincter. Swelling and controlled release of the drug may be achieved on contact of the drug delivery system with gastric fluid; the polymer imbibes water and swells. Extensive swelling of the polymer is the result of the presence of physical-chemical crosslinks in the hydrophilic polymer network. The bulk enables gastric retention and maintains the stomach in a 'fed' state, suppressing housekeeper waves. Medicated polymer sheets or swelling balloon hydrogels are examples of such delivery systems. A balance between the rate and extent of swelling and the rate of erosion of the polymer is crucial to achieve optimum benefit and to avoid adverse effects [22,23].

Super porous Hydrogels

In this approach to improve gastric retention time (GRT) super porous hydrogels of average pore size >100 micro meter, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is achieved by co-processing with a hydrophilic particulate material, croscarmellose sodium. Which forms a dispersed phase within the continuous polymer matrix during the synthesis ('superporous hydrogel composites'). The superporous hydrogel composites stay in the upper GIT for >24 hours. Recent advances in the field have led to 'superporous hydrogel hybrids', which are prepared by adding a hydrophilic or water dispersible polymer that can be cross-linked after the superporous hydrogel is formed. Examples of hybrid agents include

polysaccharides such as sodium alginate, pectin and chitosan [24, 25].

Ion-Exchange Resins

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin, resultant beads were then encapsulated in a semipermeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach and exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in a membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast the uncoated beads, which will sink quickly.

Atyabi *et al* reported the in vivo behavior of the coated and uncoated beads and monitored using a single channel analyzing study in 12 healthy human volunteers by gamma radio scintigraphy. Studies showed that the gastric residence time was prolonged considerably (24 hours) compared with uncoated beads (1 to 3 hours) [26].

Bioadhesive liposomal Systems

Mucoadhesive liposomal systems are formulated by coating a polymer to facilitate enteral absorption of poorly absorbed drugs. Liposomes are generally coated with mucoadhesive polymers such as chitosan, carbopol, Carboxymethyl chitin and carboxymethyl chitosan. The mucoadhesion of the resultant liposomes leads to an enhanced GRT of the dosage form [27, 28].

Floating Drug Delivery Systems

Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability.²⁹ This delivery system is desirable for drugs with an absorption window in the stomach or in the upper small intestine.³⁰ These systems have a bulk density lower than that of gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating in 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. This results in an increase in the gastric retention time and a better control of fluctuations in plasma drug concentration [31].

The major requirements for floating drug delivery system are

- It must maintain specific gravity lower than gastric contents (1.004 gm/cm³).
- It must form a cohesive gel barrier.
- It should release contents slowly to serve as a reservoir [32, 33].

Raft forming systems

Raft forming systems have received much attention for the drug delivery for gastrointestinal infections and disorders. Floating Rafts have been used in the treatment of Gastric esophageal reflux disease (GERD). The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, where in each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO₂. Usually, the system ingredients includes a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO₂ to make the system less dense and float on the gastric fluids. Jorgen *et al* described an antacid raft forming floating system. The system contains a gel forming agent (e.g. sodium alginate), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft), which when comes in contact with gastric fluids, the raft floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus [34,35].

Gas Generating (Effervescent) Systems

In this system floatability can be achieved by the generation of gas bubbles. They are formulated in such a way that when in contact with the acidic gastric contents, CO₂ is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. *In vitro*, the lag time before the unit floats is <1 minute and buoyancy is prolonged for 8-10 hours. Bilayer or multilayer systems have also been designed in which drug and excipients can be formulated independently, and the gas generating unit can be incorporated into any of the layers of multiple unit systems, which avoids the 'all-or-nothing' emptying process encountered in single unit systems [36, 37]. Figure. 4 Shows the mechanism of Gas generating systems.

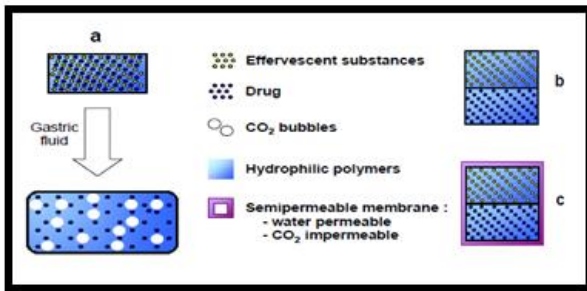


Figure 4 Gas-generating (Effervescent) systems. (a) Bilayer gas-generating systems, with (c) or without (b) semi permeable membrane.

Ichikawa *et al* [38] developed floating capsules composed of a plurality of granules that have different residence times in the stomach and consist of an inner foamable layer of gas generating agents. This layer was further divided into 2 sublayers, the outer containing sodium bicarbonate and the inner containing tartaric acid. This layer was surrounded by an expansive polymeric film (composed of poly vinyl acetate [PVA] and shellac), which allowed gastric juice to pass through, and was found to swell by foam produced by the action between the gastric juices and the gas-generating agents. It was shown that the swellable membrane layer played an important role in maintaining the buoyancy of the pills for an extended period of time. Two parameters were evaluated: the time for the pills to be floating (TPF) and rate of pills floating at 5 hours (FP5h). It was observed that both the TPF and FP5h increased as the percentage of swellable membrane layer coated on pills having an effervescent layer increased. As the percentage of swellable layer was increased from 13% to 25% (wt/wt), the release rate was decreased and the lag time for dissolution also increased. The percentage of swellable layer was fixed at 13% wt/wt and the optimized system showed excellent floating ability *in vitro* (TPF ~10 minutes and FP5h ~80%) independent of pH and viscosity of the medium. Figure 5. Shows the working of Effervescent floating drug delivery systems.

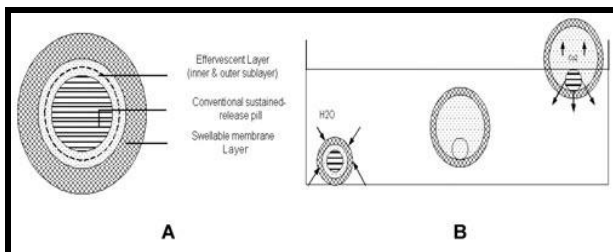


Figure 5. (A) Multiple-unit oral floating drug delivery system. (B) Working principle of effervescent floating drug delivery system

Low Density Systems

Gas-generating systems suffer from a lag time before floating on the stomach contents, during which the dosage form may undergo

premature evacuation through the pyloric sphincter. Low density systems (<1 g/cm³) with immediate buoyancy have therefore been developed. They are made of low-density materials entrapping oil or air. Most examples are multiple unit systems such as hollow microspheres (microballoons), hollow beads, microparticles, emulgel beads or floating pellets. At present, hollow microspheres (figure 6) are considered to be one of the most promising buoyancy systems because they combine the advantages of multiple unit systems and good floating properties [37, 38, 39]

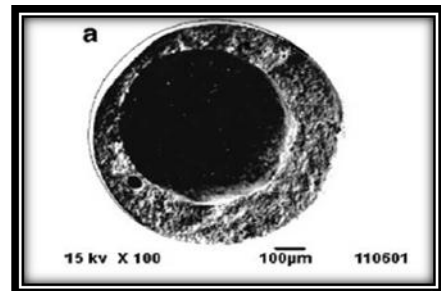


Figure 6: Hollow microsphere

Hollow microspheres loaded with drug in their outer polymer shell were prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40°C. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 h 40.

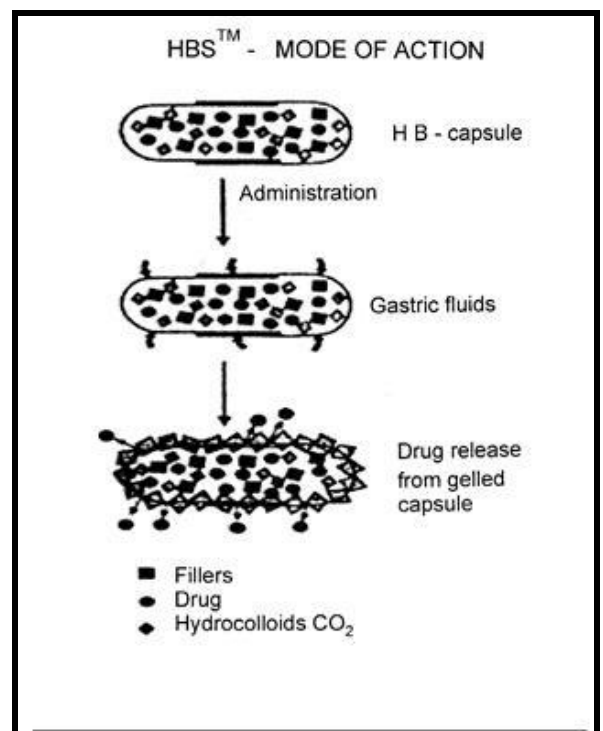


Figure 7: Working principle of the hydrodynamically balanced system within the gel structure (Ushimaru K et al.1987)

Hydrodynamically balanced systems

Hydrodynamically balance systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small

intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. HBS are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems 41,42. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid at body temperature, and hydration

and swelling of the surface polymers produces a floating mass. Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy (Figure 7) [43]. Incorporation of fatty excipients gives low-density formulations and reduced penetration of water, reducing the erosion.

Polymers and other Ingredients

Following types of ingredients can be incorporated into FDDS in addition to the drugs are showed in table 1, and table 2 shows list of available brands.

Table 1: Polymers and other ingredients used for increasing GRT 44

Polymers and other ingredients	Example
Hydrocolloids (20%-75%)	Acacia, Pectin, Chitosan, Agar, Casein, Bentonite, Veegum, HPMC (K4M, K100M and K15M), Gellan gum (Gelrite®), Sodium CMC, MC, Calcium alginate, Eudragit S100, Eudragit RL, Propylene foam, Eudragit RS, ethyl cellulose, poly methyl methacrylate, Polyethylene oxide, β Cyclodextrin, CMC, Polyethylene glycol, polycarbonate, PVA, Polycarbonate, Sodium alginate, HPC-L, CP 934P, HPC, Eudragit S, Metolose S.M. 100, PVP, HPC-H, HPC-M, HPMC K15, Acrylic polymer, E4 M and Carbopol.
Inert fatty materials (5%-75%)	Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.
Effervescent agents	Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate), CG (Citroglycine).
Release rate accelerants (5%-60%)	Lactose, Mannitol
Release rate retardants (5%-60%)	Dicalcium phosphate, Talc, Magnesium stearate
Buoyancy increasing agents (upto80%)	Ethyl cellulose
Low density material	Polypropylene foam powder (Accurel MP 1000®).

Table 2: List of products available with increased GRT: 45

Brand name	Drug (dose)	Company, country	Dosage form
Madopar®	Levodopa(100mg), benserazide(25mg)	Roche Products, US	Floating controlled release capsule
Valrelease®	Diazepam (15mg)	Hoffmann-La Roche, US	Floating capsule
Liquid Gaviscon®	Al. hydroxide (95mg), Mg. carbonate (358mg)	GlaxoSmithKline, India	Raft-forming liquid alginate preparation
Topalkan®	Aluminium-magnesium antacid	Pierre Fabre Drug, France	Floating liquid alginate preparation
Conviro®	Ferrous sulphate	Ranbaxy, India	gel-forming floating system
Cifran OD®	Ciprofloxacin (500mg & 1g)	Ranbaxy, India	Gas-generating floating tablet
Oflin OD®	Ofloxacin (400mg)	Ranbaxy, India	Gas-generating floating tablet
Cytotec®	Misoprostol (100ng/200 .ig)	Pharmacia, US	Bilayer floating capsule

Advantages of Increasing GRT

Increasing the GRT with either of the approaches offers several advantages such as:

- Acidic drug substances like aspirin cause irritation on the stomach wall when come in to contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
- The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts, Antacids. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
- Controlled delivery of drugs. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
- The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.
- Administration of prolongs release floating dosage forms, tablet or capsules, will results in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be

available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from the floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

- When there is vigorous intestinal movement and a shorted 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.
- As sustained release systems, floating dosage forms offer various potential advantages. Drugs that have poor bioavailability because their absorption is limited to upper GI tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability.
- Floating dosage forms with SR characteristics can also be expected to reduce the variability in transit performance. In addition, it might provide a beneficial strategy for gastric and duodenal cancer treatment.
- The concept of FDDS has also been utilized in the development of various anti- reflux formulations [46, 47].

Limitations/Disadvantages of system having prolonged GRT

- One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently.
- Not suitable for drugs that have solubility or stability problem in GIT.
- Drugs such as Nifedipine, which is well absorbed along the entire GI tract and also undergo significant first-pass metabolism, may not be suitable candidates for increasing the GRT since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.
- The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.

- The dosage form should be administered with a full glass of water (200-250 ml).
- These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.
- The use of large single-unit dosage forms sometimes poses a problem of permanent retention of rigid large-sized single-unit forms especially in patients with bowel obstruction, intestinal adhesion, gastropathy, or a narrow pyloric opening (mean resting pyloric diameter 12.8 ± 7.0 mm) [48].

POTENTIAL DRUG CANDIDATE FOR FDDS [49]

FDDS is beneficial for drug candidate which have stability problems at alkaline pH, having absorption window in stomach, or upper part of small intestine. Table 3 shows the potential candidates.

Table 3: Potential Candidate for FDDS

Formulation	Drug candidates
Floating microspheres	Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen, Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol, Trilast and Terfinadine
Floating granules	Diclofenac sodium, Indomethacin and Prednisolone
Films	Cinnarizine, Albendazole
Floating tablets and Pills	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Fluorouracil, Isosorbide mononitrate, Para-aminobenzoic acid, Piretanide, Theophylline, Verapamil hydrochloride, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol, pentoxifylline and Diltiazem HCl, Atenolol, ciprofloxacin.
Floating Capsules	Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid and Pepstatin, and Propranolol

EVALUATION OF FLOATING DOSAGE FORMS

For Single Unit Dosage Forms: (Ex: Tablets, Capsules) [50]

PRECOMPRESSION PARAMETERS

Angle of repose

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The height (h) of the heap formed is measured with a cathetometer, and the radius (r) of the cone base is also determined. The angle of repose (θ) can be calculated from:

$$\theta = \tan^{-1} [h/r]$$

Where θ is angle of repose.

The relation between angle of repose (θ) and flow characteristic of powder has been tabulated, Table 4.

Table 4: Powder flow characteristics in relation to Angle of repose

Angle of Repose	Powder flow characteristic
< 25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Carr's Compressibility Index

An accurate weight of formula blend is poured into a volumetric cylinder to occupy a volume (V0) and then subjected to a standard tapping procedure onto a solid surface until a constant volume is achieved (Vf) Carr's "percent compressibility" calculated using the equation:

$$\text{Compressibility Index, (CI)} = \frac{V_0 - V_f}{V_0} \times 100$$

POST COMPRESSION PARAMETERS

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets can be determined using Monsanto hardness tester. It is expressed in kg/cm².

Friability

The friability of tablets is determined by using Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (Winitial) and transferred into Friabilator. The Friabilator is operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets are weighed again (Wfinal). The % friability is then calculated by -

$$F (\%) = \left(1 - \frac{W_0}{W}\right) \times 100$$

Where, W₀ is weight of the tablets before the test.

W is the weight of the tablets after test

Tablet density

Tablet density is an important parameter for floating tablets. The tablet would float only when its density is less than that of gastric fluid (1.004). The density is determined using following relationship 51.

$$V = r^2 h d = \frac{m}{\rho}$$

v = volume of tablet (cc)

r = radius of tablet (cm)

h = crown thickness of tablet (g/cc)

m = mass of tablet

Tablet weight variation

The weight variation test is performed as per specified in official monograph. The limits as per U.S.P has been tabulated in the table 5:

Table 5: Tablet weights and the deviation permissible

Average Weight of Tablet	Percent Deviation
130 mg or less	10
>130 mg but < 324 mg	7.5
324 mg or more	5

Floating Lag Time / Total Floating Time

The time between the introduction of the tablet into the medium and its rise to upper one third of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats is termed as the floating / flotation time/ Total floating time. These tests are usually performed in Simulated Gastric Fluid (SGF) or 0.1 N HCl (900ml) maintained at 37°C, by using USP dissolution apparatus as the dissolution medium [52].

Tablet swelling indices

Tablet are weighed (W1) and placed in a glass beaker, containing 200 mL of 0.1 N HCl, maintained in a water bath at 37 ± 0.5° C. At regular time intervals, the tablet are removed and the excess surface liquid was carefully removed by a filter paper. The swollen tablet are then reweighed (W2). The swelling index (SI) is calculated using the formula:

$$SI = \frac{W2 - W1}{W1}$$

Where,

W2 = Final Weight, W1 = Initial Weight

In vitro drug release

This is determined by using USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at 37 ± 0.2 °C in simulated gastric fluid (pH 1.2 without pepsin). Aliquots of the samples are collected and analyzed for the drug content. Recent methodology as described in USP XXIII states that the dosage unit is allowed to sink to the bottom of the vessel before rotation of blade is started. A small, loose piece of non reactive material such as not more than a few turns of wire helix may be attached to the dosage units that would otherwise float.

In vivo evaluation for gastro-retention

This is carried out by means of X-ray or Gamma scintigraphic monitoring of the dosage form transition in the GIT.

Kawashima et al 53 prepared Tranilast Eudragit S (BaSO₄) Isardipine (HPMC) system and for in vivo studies two healthy male volunteers administered hard gelatin capsules packed with microballons (1000 mg) with 100 mL water. X-ray photographs at suitable intervals were taken.

Two phases: Phase I (fasted conditions): Five healthy volunteers (3 males and 2 females) in an open randomized crossover design, capsules ingested in sitting position with 100 mL of tap water. Phase II (fed states): Four subjects received normal or MR capsules in a crossover design after standard breakfast. Venous blood samples were taken in heparinized tubes at predetermined time intervals after dosing.

Atyabi et al 54 prepared floating beads and used Gamma scintigraphy: In vivo behavior of coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers of mean age 34 yrs. (22–49).

FOR MULTIPLE UNIT DOSAGE FORMS (EX: MICROSPHERES) 55

In case of multiparticulate drug delivery systems, differential scanning calorimeter (DSC), particle size analysis, flow properties, surface morphology, mechanical properties and x-ray diffraction studies are performed.

Size and shape evaluation

The particle size and shape plays a major role in determining solubility rate of the drugs and thus potentially its bioavailability. The particle size of the formulation can be determined using Sieve analysis, Air elutriation analysis, Photo analysis, Optical microscope, Electro resistance counting methods, Sedimentation techniques, Laser diffraction methods [26, 57].

Morphology and surface topography

The surface topography and structures were determined using scanning electron microscope (SEM) operated with an acceleration voltage of 10k.v, Contact angle meter, Atomic force microscopy (AFM), Contact profilometer [57].

Percentage drug entrapment

Percentage entrapment efficiency was reliable for quantifying the phase distribution of drug in the pre-pared formulations. The drug is extracted by a suitable method, analyzed and is calculated from:

$$PDE = \frac{\text{Practical drug loading}}{\text{Theoretical drug loading}} \times 100$$

In vitro floating ability (Buoyancy %):

A known quantity of microspheres are spread over the surface of a USP (Type II) dissolution apparatus filled with 900 ml of 0.1 N HCl and agitated at 100 rpm for 12 hours. After 12 hours, the floating and settled layers are separated, dried in a dessicator and weighed. The buoyancy is calculated from the following formula 56.

$$\text{Buoyancy (\%)} = \frac{W_f}{(W_f + W_s)} \times 100$$

Where,

W_f and W_s are the weights of floating and settled microspheres respectively.

Drug-excipient (DE) interactions

This is done using FTIR. Appearance of a new peak, and/or disappearance of original drug or excipient peak indicate the DE interaction. Apart from the above mentioned evaluation parameters, for the effect of ageing with the help of Differential Scanning Calorimeter or Hot stage polarizing microscopy [57, 58].

FUTURE POTENTIAL

FDDS approach may be used for various potential active agents with narrow absorption window, e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines) which are absorbed from very specific regions of GI tract and whose development has been halted due to the lack of appropriate pharmaceutical technologies. The quantitative efficiency of floating delivery systems in the fasted and fed states and the correlation between prolonged GRT and SR/PK characteristics. Floating Drug Delivery Systems (FDDS) have been developed in order to increase the gastric residence time (GRT).

CONCLUSION

FDDS promises to be a potential approach for gastric retention. Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption.

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