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Gastro retentive Drug Delivery Systems: A Review

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ABSTRACT

In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times. Floating tablets are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs. Floating tablets were prepared using directly compression technique using polymers like HPMC K4M HPMC K15M and HPMCK100M for their gel-forming properties.

INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery

system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine).

The identification of new diseases and the resistance shown towards the existing drugs called for the introduction of new therapeutic molecules. In response, a large number of chemical entities have been introduced, of which some have absorption all over the gastrointestinal tract (GIT), some have absorption windows (i.e. absorption sites, especially the upper part of the small intestine) and some drugs have poor solubility in intestinal media. The drugs belonging to the second and third categories, and the drugs which are required for local action in the stomach, require a specialized delivery system. All the above requirements can be met and effective delivery of the drugs to the absorption window, for local action and for the treatment of gastric disorders such as gastro-esophageal reflux, can be achieved by floating drug delivery systems (FDDS).

To date, a number of FDDS involving various technologies, carrying their own advantages and limitations were developed such as, single and multiple unit hydro dynamically balanced systems (HBS), single and multiple unit gas generating systems, hollow micro spheres and raft forming systems.

The hydrodynamic balanced system (HBS) also called Floating drug delivery system (FDDS) is an oral dosage form (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents. Drug dissolution and release from the dosage form retained in the stomach fluids occur at the pH of the stomach under fairly controlled conditions.

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in gastrointestinal tract is to control the gastric residence time(GRT) using *gastro retentive dosage forms (GRDFs)* that offer a new and better option for drug therapy.

Dosage forms that can be retained in stomach are called gastro retentive drug delivery systems **(**GRDDS**).** GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability.

The formulation of the dosage form must comply with three major criteria for HBS.

- It must have sufficient structure to form a cohesive gel barrier.
- It must maintain an overall specific gravity lower than that of gastric contents (1.004 – 1.010)
- It should dissolve slowly enough to serve as a “Reservoir” for the delivery system.

Floating systems are one of the important categories of drug delivery systems with gastric retentive behavior.

Drugs whose solubility is less in the higher pH of the small intestine than the stomach , The drugs prone for degradation in the intestinal pH and the drugs for local action in the stomach can be delivered in the form of dosage forms with gastric retention. Antibiotics, catecholamines,

sedative, analgesics, anticonvulsants, muscle relaxants, antihypertensive and vitamins can be administered in HBS dosage form.

Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, carbopols, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. [1-8]

Drugs reported to be used in the formulation of floating dosage forms are[9]

Floating micro spheres	Aspirin, Griseofulvin, P-nitroaniline,I buprofen, Terfinadine Tranilast
Floating granules	Diclofenac sodium, Indomethacin , Prednisolone
Floating Films	Cinnarizine
Floating capsules	Chlordiazepoxide hydro chloride, Diazepam, Furosemide Misoprostol, L-Dopa, Benserazide, Ursodeoxycholicacid
Floating tablets and pills	Acetaminophen, Acetylsalicylicacid, Ampicillin, Amoxycillin trihydrate ,Atenolol, Diltiazem, Fluorouracil, isosorbide mononitrate, para aminobenzoic acid, theophylline , verapimil hydrochloride, Riboflavin-5'-phosphate etc

Marketed Products

Some of the marketed formulations are listed as follows:

Table → Marketed Products of GRDDS

Brand name	Delivery system	Drug (dose)	Company name
Valrelease	Floating capsule	Diazepam (15mg)	Hoffmann-La Roche, USA
Madopar HBS (Prolopa HBS)	Floating, CR capsule	Benserazide (25mg) L-Dopa (100mg)	Roche Products, USA
Liquid Gaviscon	Effervescent Floating liquid alginate preparations	Al hydroxide(95 mg), Mg Carbonate(358 mg)	GlaxoSmithkline, India
Topalkan	Floating liquid alginate preparation	Al – Mg antacid	Pierre Fabre Drug, France
Almagate Flot coat	Floating dosage form	Al – Mg antacid	----------
Conviron	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India
Cytotech	Bilayer floating capsule	Misoprostol (100µg/200µg)	Pharmacia, USA
Cifran OD	Gas-generating floating form	Ciprofloxacin (1gm)	Ranbaxy, India

Advantages

1. The principle of HBS can be used for any particular medicament or class of medicament.
2. The HBS 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 HBS 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 HBS has been found to be independent of the site of absorption of the particular medicaments.
5. Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolve drug

available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine.
6. 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.
7. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.
8. Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine.
9. Certain types of drugs can benefit from using gastro retentive devices.

These include:
• Drugs acting locally in the stomach
• Drugs those are primarily absorbed in the stomach
• Drugs those are poorly soluble at an alkaline pH;
• Drugs with a narrow window of absorption;
• Drugs absorbed rapidly from the GI tract; and
• Drugs those degrade in the colon.

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 gastro retentive 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.

Requirements for Gastric Retention:
Physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease. [5]

Need For Gastric Retention[10]:
- Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- Drugs that are less soluble or are degraded by the alkaline pH they encounters at the lower part of GIT.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal Small intestine to treat certain conditions.

- Particularly useful for the treatment of peptic ulcers caused by H. Pylori Infections.

Limitations Of the techniques of gastric retention:

More predictable and reproducible floating properties should be achieved in all the extreme gastric conditions.

1. The floating systems in patients with achlorhydria can be questionable in case of swellable systems, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.
2. Bioadhesion in the acidic environment and high turnover of mucus may raise questions about the effectiveness of this technique. Similarly retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.
3. Not suitable for drugs that may cause gastric lesions e.g. Non- steroidal anti inflammatory drugs. Drugs that are unstable in the strong acidic environment, these systems do not offer significant advantages over the conventional dosage forms for drugs, that are absorbed throughout the gastrointestinal tract.
4. The mucus on the walls of the stomach is in a state of constant renewal, resulting in Unpredictable adherence.
5. In all the above systems the physical integrity of the system is very important and Primary requirement for the success of these systems.

Factors Affecting Gastric Retention[11]:

1. Density: GRT is a function of dosage form buoyancy that is dependent on the density.

2. Size: Dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those with a diameter of 9.9mm.

3. 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.

4. Single or multiple unit formulation: Multiple unit formulations show a more Predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

5. Fed or unfed state: under fasting conditions: GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (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.

6. **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.

7. Caloric content: GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

8. Frequency of feed: the GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.

9. Gender: Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
10. Age: Elderly people, especially those over 70, have a significantly longer GRT.
11. Posture: GRT can vary between supine and upright ambulatory states of the patient.
12 Concomitant drug administration: Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.
13. Biological factors: Diabetes and Crohn's disease.

Physiological factors important for oral controlled drug delivery systems[12-14]

1. Gastric emptying

The process of gastric emptying occurs during both fasted state and fed state however, the pattern of motility differs markedly in these two states. In the fasted state, it is characterized by an interdigestive series of electrical events, which propagate both through stomach as well as small intestine every 2-3 hours. This activity is called as interdigestive myoelectric complex (IMC), and is often divided into four consecutive phases. Fig -1 represents these phases.

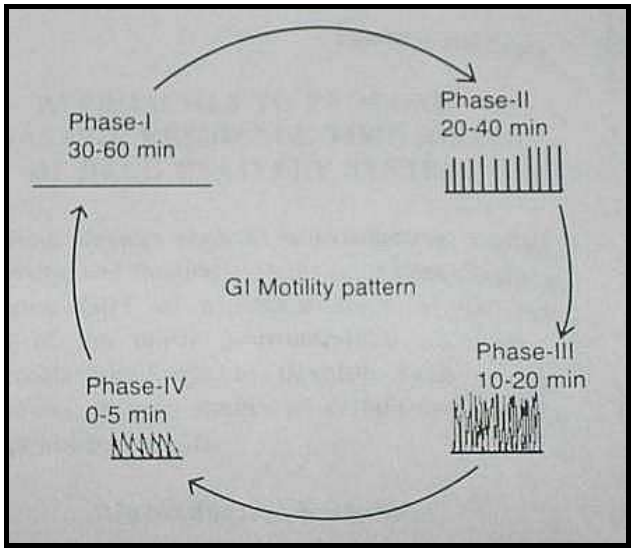


Figure-1: Pictorial representation of the typical GI motility pattern in fasting state

Phase I: *It is a quiet period lasting from 30-60 min. with rare contractions.*
Phase II: *It is a period of similar duration consisting of intermittent action potentials gradually increases an intensity and frequency as phase progresses.*
Phase III : *It is a short period of intense, large regular contractions lasting from 10-20 min. as it serves to sweep undigested materials out of stomach and down in small intestine, it is termed as '**housekeeper waves'.** As the phase III of one cycle reaches the distal part of small intestine, the phase III of next cycle begins in duodenum*
Phase IV: *It is brief transitional phase that occurs between phase III and phase I of two consecutive cycles. In the fed state, the gastric emptying rate is slowed since the onset of IMC is delayed. In other words, feeding results in a lag time prior to onset of gastric emptying.*

Factors affecting gastric emptying time

1. Volume

The resting volume of stomach is about 25-52 ml. This volume is important for dissolution of dosage forms. As the volume is large, emptying is faster. Gastric emptying of small volumes like 100 ml or less is governed by Migrating Myoelectric Complex (MMC) cycle whereas large volumes of liquids like 200 ml or more are emptied out immediately after administration. Fluids at body temperature leave the stomach more rapidly than either warmer or colder fluids.

2. Hormonal effects

Stress conditions increases gastric emptying rate whereas depression slows down gastric emptying time. Generally females have slower gastric emptying rate than males. Age and obesity also affect gastric emptying.

3. Presence of food

Gastric emptying time differs in fasted state and in fed state. The calorific value of food affects the gastric emptying time.

4. Gastric secretions

Acids, pepsin, gastric, mucus and other enzymes are the secretions of stomach. Normal adults produce a basal secretion up to 60ml with approximately 4 mole of hydrogen ions every hour.

Regional variability in intestinal absorption - concept of absorption window[15]

The gastrointestinal tract (GIT) offers a varied environment capable of affecting the absorption of per orally administered drugs. These changes are contributed by anatomical features, physiological phenomenon, and nature of gastrointestinal milieu. This can lead to the variations in intestinal permeability of drug molecules, resulting in the phenomenon of '**absorption window'** wherein the drug is preferentially absorbed only from a particular region of the GIT. Not all drug candidates get uniformly absorbed throughout the GI tract. Drugs exhibiting absorption from only a particular region of GI tract or showing difference in absorption from various regions of GI tract are said to have regional variability in intestinal absorption. Such drugs show 'absorption window' which signifies the region of GI tract from where absorption primarily occurs. Fig-2 gives the various sites in gut from where the drug absorption takes place.

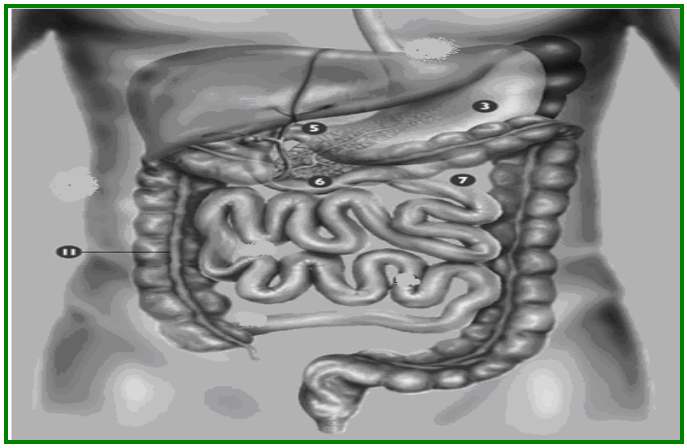


Figure-2: Sites in GI tract for absorption of drug from conventional dosage form stomach, duodenum, and jejunum

This absorption window is observed due to following factors[16,17]

1. Physicochemical factors

a. pH dependent solubility
b. pH dependent stability
c. Degradation due to enzymes

2. Physiological factors

a. Mechanism of absorption
b. Degradation by intestinal micro flora

1. Physico-chemical factors

pH-dependent solubility and stability: A drug experiences a pH range of 1-8 across the GIT and needs to be in solubilised and stable form to successfully cross the biological membranes. Most of the drugs are passively absorbed in their un-ionized form and the extent of ionization at different pH in different regions of GIT can significantly alter the absorption profile. pH dependent solubility, stability and ionization by changing the physical properties of the drug in different portions of the GIT can lead to regional variability in absorption of drugs.

2. Physiological factors

An orally administered drug experiences certain physiological phenomenon which can contribute to absorption window

- **Mechanism of absorption**: Per orally administered drugs are absorbed both by passive diffusion as well as by non-passive means of absorption. Drugs absorbed by active and facilitated transport mechanisms show higher regional specificity due to the prevalence of these mechanisms only in a particular region of GIT.
- **Metabolic enzymes**: Presence of certain enzymes in a particular region of GIT can also lead to regional variability in absorption of drugs that are substrates to those enzymes intestinal metabolic enzymes (majorly, phase one), like cytochrome P-450 (e.g. CYP3A) are abundantly present in the intestinal epithelium.

First-pass metabolism

Hepatic first-pass metabolism is another major contributory factor in reducing the bioavailability of orally administered drugs. A major portion of intestinally absorbed drugs is taken up by the portal veins to liver, a potential site of drug metabolism. On the contrary hepatic first-pass metabolism is of considerable interest in regard of drugs whose therapeutic action is dependent on their hepatic metabolism.

It is a well-accepted fact that it is difficult to predict the real *in vivo* time of release with solid, oral controlled release dosage forms. Thus, drug absorption in the gastrointestinal (GI) tract may be very short and highly variable in certain circumstances.

"The aim of oral controlled release dosage form is not just to prolong the delivery of drugs for more than 12 hrs but to prolong the residence time in absorption region for desired period of time."

It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time

exists today. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT). Dosage forms with a prolonged GRT, i.e. Gastro retentive dosage forms (GRDF), will provide us with new and important therapeutic options. GRDF extend significantly the period of time over which the drugs may be released. Thus, they not only prolong dosing intervals, but also increase patient compliance over the existing controlled release dosage forms.

Formulation Approaches for Gastric Floating Drug Delivery Systems (GFDDS) [13,15,16]

Over last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach, which include

- Floating systems (low density approach)
- Swelling and expanding systems
- Bioadhesive systems
- Modified shape systems
- High density systems and
- Delayed release gastric emptying devices.

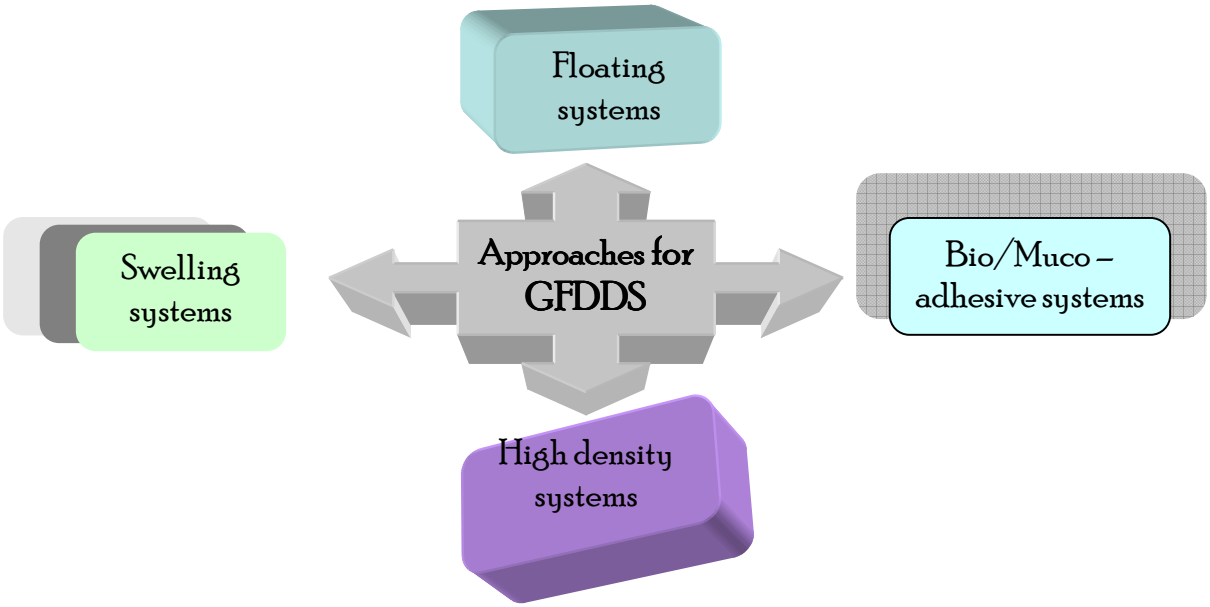


Figure-3: Diagrammatic representation of various approaches for Gastro retentive drug delivery systems

A. Floating system (low density approach)

These systems are also known as hydro dynamically balanced systems (HBS) or floating drug delivery systems (FDDS). They have a bulk density lower than density of gastric fluid, i.e. their bulk density is less than 1. The specific gravity of gastric fluid is approximately 1.004-1.01g/cm^3, thus FDDS remains buoyant in stomach without affecting gastric emptying rate for prolonged period of time, releasing the drug slowly at desired rate.[17]

B. Swelling and Expanding systems

These systems are such that after administration they swell to that extent which prevents their exit from stomach from pyloric sphincter. As a result the dosage form is retained in stomach for long period of time.[18]

C. Bioadhesive Systems

These systems are used to localize a delivery device within the lumen and cavity of body to enhance the drug absorption process in site specific manner. Various bioadhesive polymers are used for achieving the effective bioadhesion.**[**20,21]. These polymers tend to form hydrogen and electrostatic bonds at the mucus membrane polymer boundary. Rapid hydration in contact with the muco-epithelial surface appears to favor adhesion.[22]

D. Modified shape systems

These are non-disintegrating geometric shapes molded from plastic elastomer or extruded from polyethylene blends which extend the GRT depending on the size, shape and flexural modulus of drug delivery system.[23]

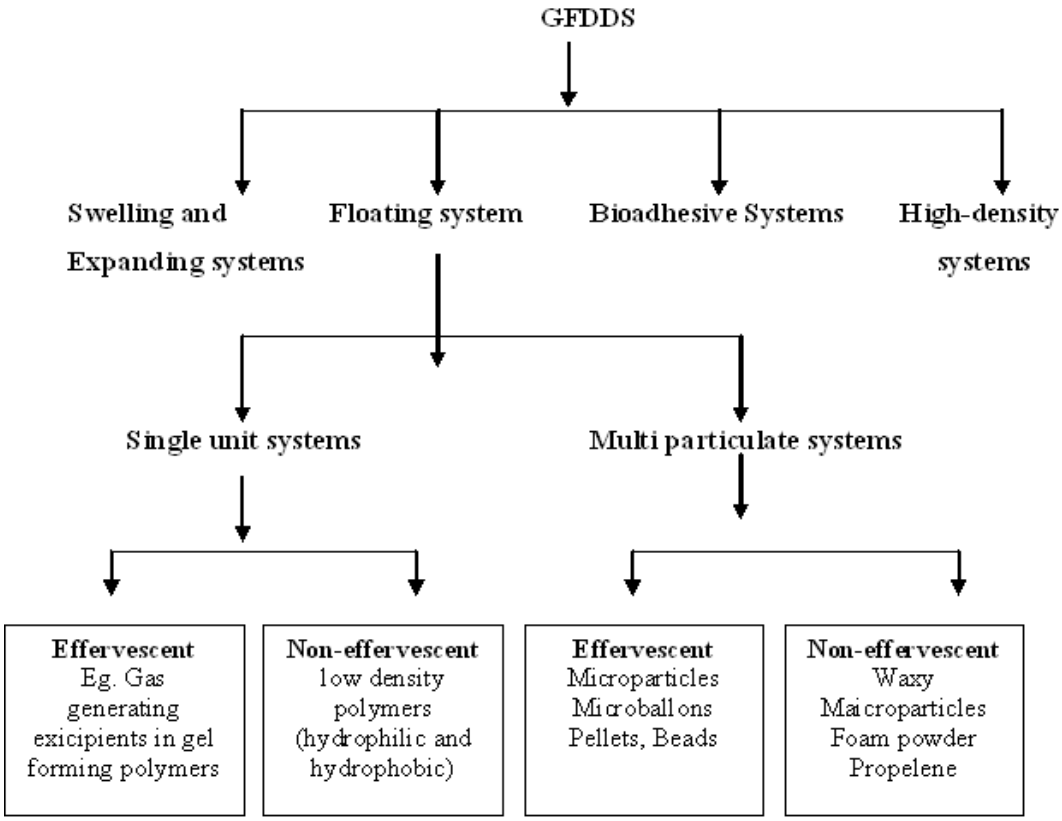


Figure-4: Flowchart enlisting various approaches used for designing floating drug delivery systems.

E. High density formulations
High density formulations have a density greater than that of stomach contents this can be achieved by coating the drug with a heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder.[24]

F. Delayed release gastric emptying approaches
Include feeding of indigestible polymers or fatty acid salts that change the motility pattern of the stomach and decrease the gastric emptying rate

Recent Developments in Floating Drug Delivery Systems (FDDS) [25,26]
The concept of FDDS was described in the literature as early as in 1968 the method was described for overcoming the difficulty of swallowing medicinal pills. The suggested method was providing the pills having a density less than 1.0 g/ml so that pill will float on water surface. Since then several approaches have been used to develop an ideal floating delivery system.

The various buoyant compositions include hollow microspheres (microballoons), granules, powders, capsules, tablets (pills), and laminated films. Most of the floating systems include single unit systems, such as HBS and floating tablets.[27] These systems are unreliable and irreproducible in prolonging residence time in stomach when orally administered due to their 'all or nothing' emptying process. On the other hand, multiple unit dosage forms appear to be effective in reducing inter subject variability and lower the probability of dose dumping. It has been observed that only hydrophilic polymers are not sufficient for floating characteristics and better results are possible with use of some soluble or gas–evolving excipients,[28] the release rate was directly proportional to viscosity and concentration of the polymer used.[29]

Based on mechanism of buoyancy, two distinctly different types of systems have been utilized in the development of FDDS. They are non effervescent and effervescent types of systems. Figure. 6-11 demonstrate these various approaches.

Non effervescent FDDS:
The most commonly used in non effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene.

One of the approaches to the formulation of such floating dosage forms involves intimate mixing of drug with a gel forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. In addition, the gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier.

Sheth and Tossounian [30] postulated that when such dosage forms come in contact with an aqueous medium, the hydrocolloid starts to hydrate by first forming a gel at the surface of the dosage form. The resultant gel structure then controls the rate of diffusion of solvent-in and drug-out of the dosage form. As the exterior surface of the dosage form goes into solution, the gel layer is maintained by the immediate adjacent hydrocolloid layer becoming hydrated. As a result,

the drug dissolves in and diffuses out with the diffusing solvent, creating a 'receding boundary' within the gel structure.

Effervescent FDDS:

These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., Chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature.

The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the jellified hydrocolloid. This produces an upward motion of the dosage form to float on the chyme.

Stockwell et al [31] prepared floating capsules by filling with a mixture of sodium alginate and sodium bicarbonate. The systems were shown to float during *in vitro* tests as a result of the generation of CO_2 that was trapped in the hydrating gel network on exposure to an acidic environment.

The carbonates, in addition to imparting buoyancy to these formulations, provide the initial alkaline microenvironment for polymers to gel. Moreover, the release of CO_2 helps to accelerate the hydration of the floating tablets, which is essential for the formation of a bioadhesive hydrogel. This provides an additional mechanism ('bioadhesion') for retaining the dosage form in the stomach, apart from floatation.

Floating dosage forms with an *in situ* gas generating mechanism are expected to have grater buoyancy and improved drug release characteristics. However, the optimization of the drug release may alter the buoyancy and, therefore, it is sometimes necessary to separate the control of buoyancy from that of drug release kinetics during formulation optimization.

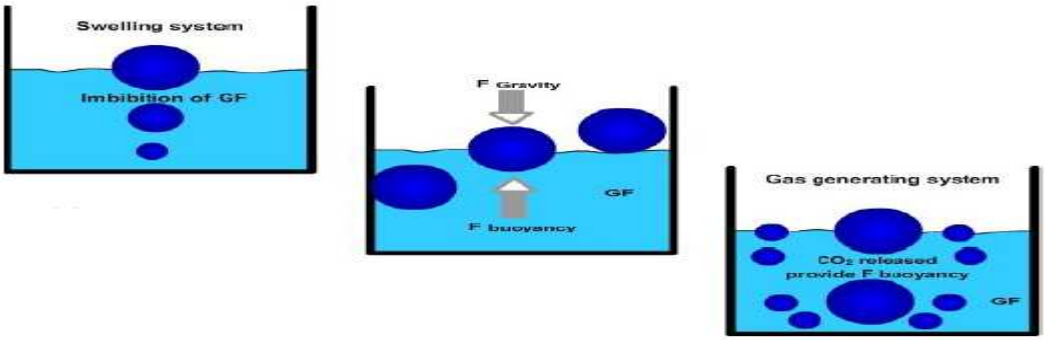


Fig 5: The mechanism of Floating Systems , GF=Gastric fluid

Intra gastric floating tablet employing hydrophilic swellable polymers

Gerogiannis and co-workers have described the floating and swelling characteristics of commonly used excipients. From the results of resultant-weight measurements of various excipients., these authors concluded that higher molecular weight polymers and slower rates of polymer hydration are usually associated with enhanced floating behavior. Hence, the selection

of high molecular weight and less hydrophilic grades of polymers seems to improve floating characteristics.

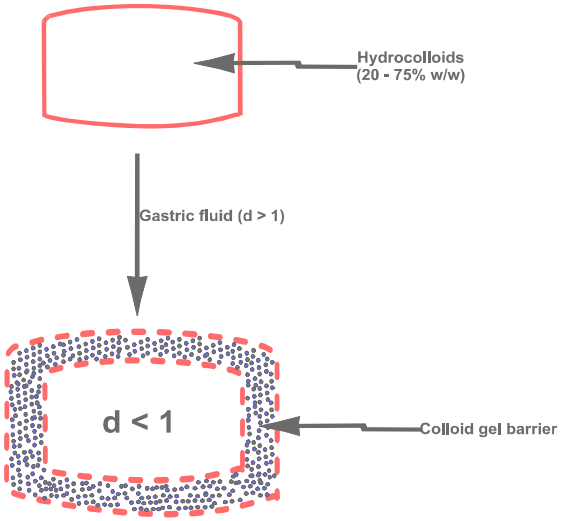


Figure-6: Pictorial diagram for the floating tablet of hydrophilic swellable polymers
Intra gastric floating bi layer tablet containing hydrocolloids in the core

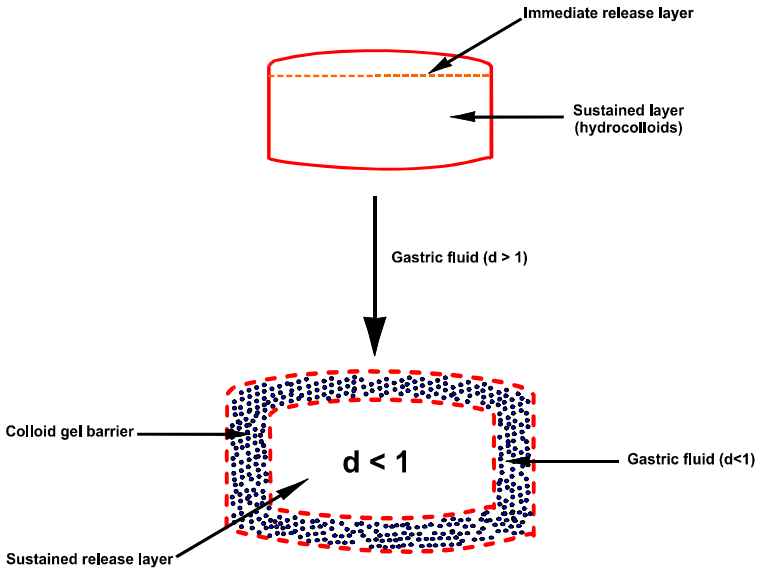


Figure-7: Pictorial diagram for the floating bi layer tablet of hydrocolloids
Intra gastric floating drug delivery device containing micro porous membrane and floatation chamber

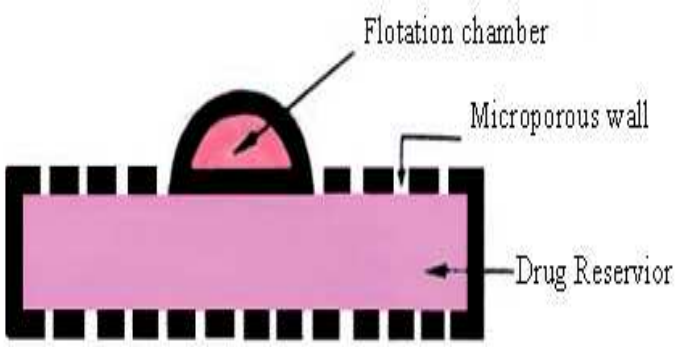


Figure-8: Pictorial diagram for the floating drug delivery device with micro porous membrane and floatation chamber

Multiple-Unit oral floating dosage system

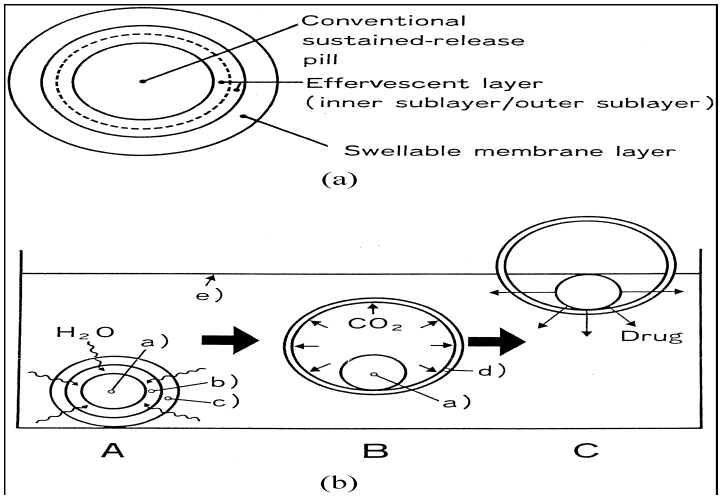
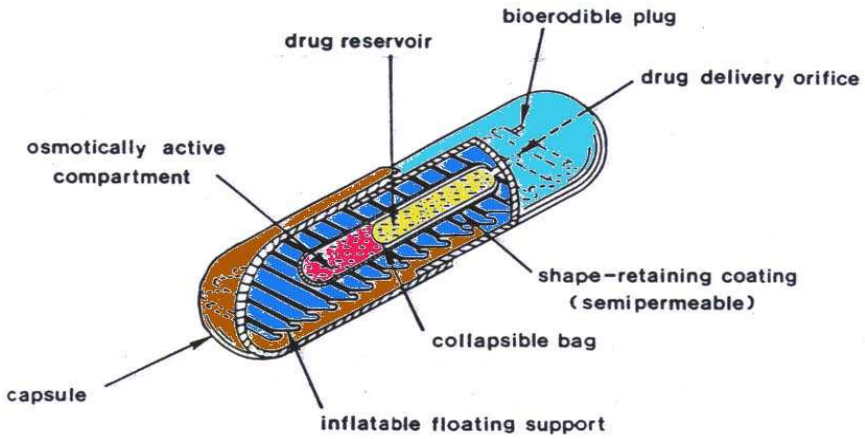


Figure-9: Pictorial diagram for the multiple units floating drug delivery system using gas generation technique



Intra gastric osmosis controlled drug delivery system

Figure-10: Pictorial diagram for the osmosis controlled gastric floating device

Gastro-inflatable drug delivery device

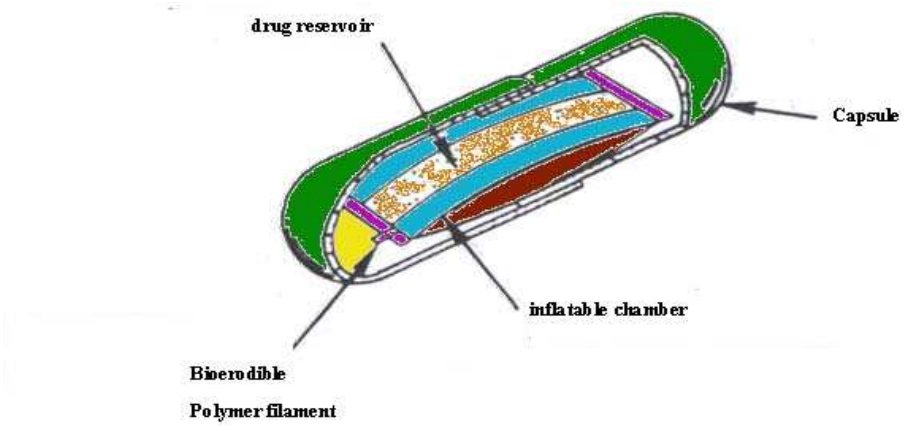


Figure-11: Pictorial diagram of gastro-inflatable drug delivery device

Application of floating drug delivery system

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

Sustained Release Drug Delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.[32]

Site-Specific Drug Delivery

Floating drug delivery system is particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide.[33]

Absorption Enhancement

Drugs that have poor bioavailability because of sites specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. FDDS also serves as an excellent drug delivery system for the eradication of Helicobacter pylori, which causes chronic gastritis and peptic ulcers. The treatment requires high drug concentrations to be maintained at the site of infection that is within the gastric mucosa. By virtue of its floating ability these dosage forms can be retained in the gastric region for a prolonged period so that the drug can be targeted.[34]

Delivery of sparingly soluble and insoluble drugs

Especially effective in delivery of sparingly soluble and insoluble drugs, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit

time becomes a significant factor affecting drug absorption. To address this, oral administration of sparingly soluble drugs is carried out frequently often several times per day.

Pharmacotherapy of the stomach

GRDF's greatly improve the pharmacotherapy of the stomach through local drug release leading to high drug concentrations at the gastric mucosa (eradicating *Helicobacter pylori* from the sub mucosal tissue of the stomach) making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).

Limitations of FDDS

- The residence time in the stomach depends upon the digestive state. Hence, FDDS should be administered after the meal.[35]
- The ability to float lies on the hydration state of the dosage form. In order to keep these tablets floating in vivo, intermittent administration of water (a tumbler full every 2 hours) is beneficial.[35]
- The ability of drug to remain in the stomach depends upon the subject being positioned upright.[36]
- FDDS are not suitable for the drugs that have solubility or stability problems in the gastric fluid.[10]
- Drugs like nifedipine, which is well absorbed along the entire GIT and which undergoes significant first pass metabolism may not be desirable candidates for FDDS since the slow gastric emptying may lead to the reduced systemic bio-availability.[10]

CONCLUSION

Dosage forms with a prolonged GRT will bring about new and important therapeutic options. They will significantly extend the period of time over which drugs may be released and thus prolong dosing intervals and increase patient compliance beyond the compliance level of existing CRDFs. Many of the "Once-a-day" formulations will be replaced by products with release and absorption phases of approximately 24 hrs. Also, GRDFs will greatly improve the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at gastric mucosa which are sustained over a large period. Finally, GRDFs will be used as carriers of drugs with the "absorption window".

Future Prospects:[37]

While the control of drug release profiles has been a major aim of pharmaceutical research and development in the past two decades, the control of GI transit profiles could be the focus of the next two decades and might result in the availability of new products with new therapeutic possibilities and substantial benefits for patients. Soon, the so-called 'once-a-day' formulations may be replaced by novel gastro retentive products with release and absorption phases of approximately 24 hours.

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