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A Review Gastroretentive (Flotting) Drug Delivary System

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Abstract
Because of its flexibility in formulation, ease of administration, and patient compliance, the oral route of drug administration is the most preferred route. However, this route has some limitations, such as a limited gastric residence time (GRT) for sustained drug delivery systems and drugs that are absorbed from a specific region of the gastrointestinal tract (GIT). To overcome these limitations, various approaches to increasing the gastric retention time of the delivery system in the upper gastrointestinal tract have been proposed. The gastroretentive dosage form (GRDF) extends the GRT by directing drug release to the upper part of the GIT. GRDFs enable continuous and prolonged drug release and improve bioavailability of drugs with a narrow therapeutic window, thereby extending dosing intervals and increasing patient compliance. This article's goal is to compile the various gastroretentive approaches. We have summarized important factors controlling gastric retention in order to understand the various physiological difficulties in achieving gastric retention. Finally, the parameters for evaluating gastroretentive drug delivery systems are discussed. The current review briefly discusses the current state of various leading Until now, gastroretentive drug delivery technologies such as high density (sinking), floating, bio- or mucoadhesive, expandable, unfoldable, super porous hydrogel, magnetic systems, and so on have been developed. Furthermore, important factors controlling gastroretention, benefits, and future potential are discussed.

Keywords: Gastro retentive system, Floating Delivery

INTRODUCTION

The oral route of administration has been more successful despite significant advancements in drug delivery because the gastrointestinal physiology allows for greater design flexibility in dosage form creation than other routes. Therefore, efforts to provide medications with a well-controlled release profile over a longer period of time are ongoing. The process of gastric emptying a dose form can be very changeable, with the capacity to extend and regulate the emptying duration. A useful feature for dosage forms that stay in the stomach longer than traditional dosage forms is the gastric transit time. Oral dose forms that are conventional, like tablets and capsules, induce significant changes in plasma drug levels

and supply a precise drug concentration in the systemic circulation without allowing for any control over administration. Sustained release formulations with longer-lasting clinical effects and lower dosage frequency have been the subject of numerous attempts to create. The inability to lengthen the sustained release dosage form's half-life in the stomach and the lack of control over drug administration are two issues that commonly arise with these forms, causing variations in the drug's plasma level.One Both in fed and fasting conditions, gastric emptying takes place. But there are differences in the motility patterns between the two states. During a fast, an electrical sequence of interstitial events takes place in the stomach and intestine every two to three hours. The inter-digestive myloelectric cycle, also known as the migrating myloelectric cycle (MMC), is further subdivided into the following 4 phases (fig. 1), as Wilson and Washington have explicated.[1] [2]

a. The 40–60 minute phase I, or basal phase, is punctuated by sporadic contractions.
b. There are sporadic contractions and action potentials during the 40–60 minute pre-burst phase (phase II). Both frequency and intensity gradually rise as the phase goes on. Phase III (burst phase)
c. Takes 4–6 minutes to complete. It involves brief, frequent, and strong contractions. This wave is responsible for pushing all of the undigested material down the small intestine and out of the stomach. The housekeeping wave is another name for it.[3]
d. Phase IV occurs between phases III and I of two consecutive cycles 2 and lasts 0 to 5 minutes.
e. The dosage form should be administered with a full glass of water (200-250 ml). f) These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.

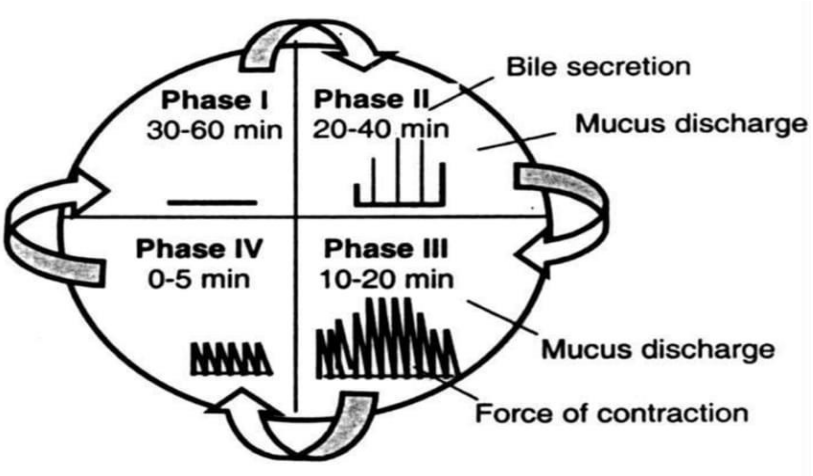


Fig. 1: Different Phases Of Mmc Cycle

After consuming a mixed meal, the pattern of contractions shifts from fasted to fed state. This is also known as the digestive motility pattern and consists of continuous contractions as in fasted phase II.

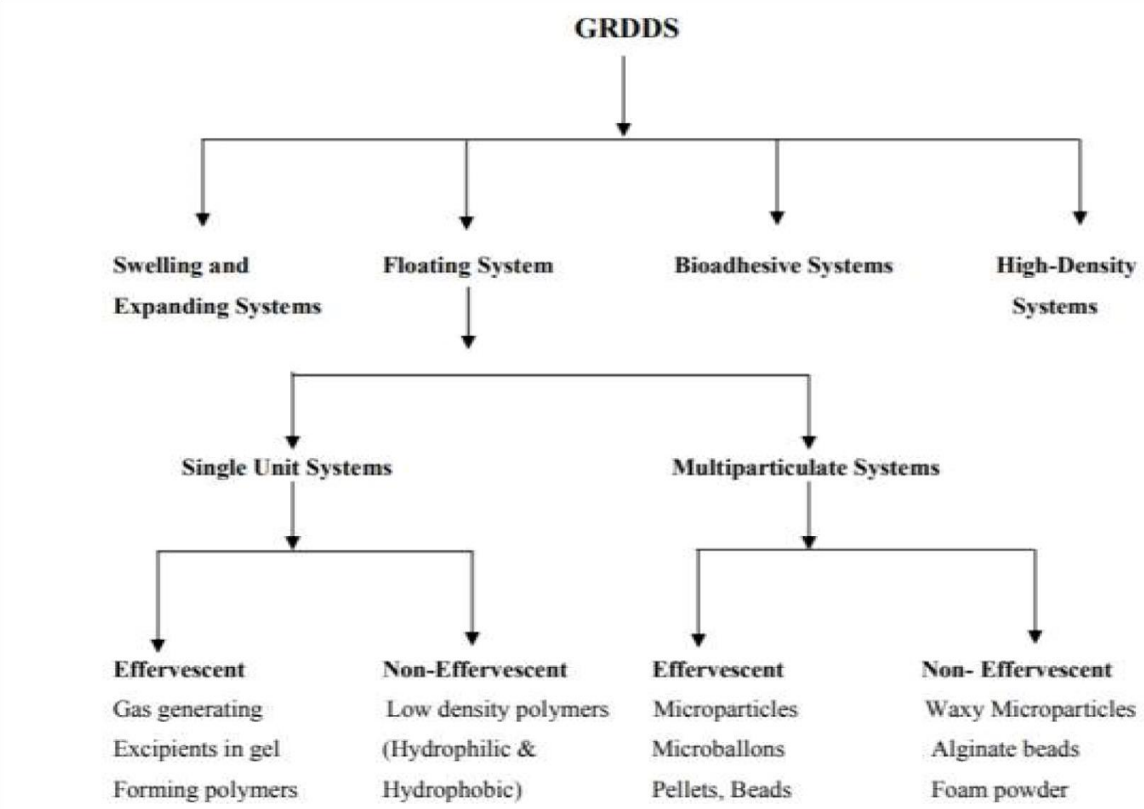
These contractions reduce the size of food particles (to less than 1 mm), which are propelled in suspension toward the pylorus. The onset of MMC is delayed during the fed state, resulting in a slowing of the gastric emptying rate 3.[4][5]

Gastro retentive systems can remain in the gastric region for several hours, significantly extending drug gastric residence time. Prolonged gastric retention improves bioavailability, decreases drug waste, and increases solubility for drugs that are less soluble in high pH environments.

Gastric retention may improve bioavailability by increasing solubility of drugs that are poorly soluble in the intestine due to alkaline pH before they are emptied. These systems are also useful for improving GIT

absorption of drugs with narrow absorption windows and controlling the release of drugs with site-specific absorption limitations.

From the standpoint of formulation and technology, floating drug delivery system (FDDS) is a significantly simple and logical approach in the development of gastroretentive drug delivery system (GRDDS). [6]



Approaches to GRDDS

Over the last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach, including (**fig. 2**);

- Floating system,
- Swelling and expanding systems,
- Bioadhesive systems,
- Modified-shape systems,
- High-density systems and;
- Other delayed gastric emptying devices.

a) Hydrodynamically Balanced Systems (HBS):

HBS have a lower bulk density than gastric fluids and thus remain buoyant in the stomach for a longer period of time without affecting the gastric emptying rate. The drug is slowly released from the system while the system is floating on the gastric contents at the desired rate. The residual system is emptied from the stomach after the drug is released. In some cases, thi s results in an increase in GRT and better control of fluctuations in plasma drug concentrations.[7] The buoyant materials used in the device allow it to float

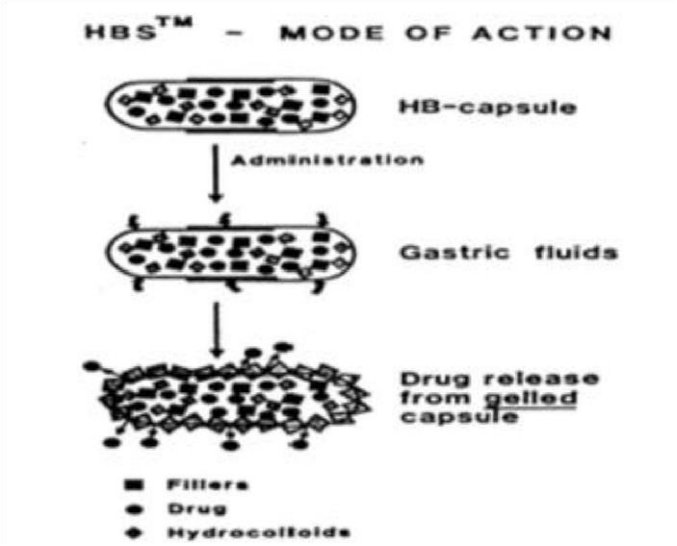


Fig. 3: Hydro-Dynamically Balanced System (Capsule System)

b) Raft Systems Incorporating Alginate Gels:

These contain a carbonate component, and when exposed to gastric acid, bubbles form in the gel, allowing it to float.

c) Bioadhesive Or Mucoadhesive Systems:

These systems are used to localize a delivery device within the body's lumen and cavity in order to increase drug absorption on a site-specific basis (fig. 4). In these approaches, bioadhesive polymers that can adhere to the epithelial surface of the GIT are used. [8]The proposed bioadhesive mechanism is hydrogen and electrostatic bonding at the mucus polymer boundary. The basis of adhesion is that a dosage form can adhere to the mucosal surface through various mechanisms.

The wetting theory, which is based on bioadhesive polymers' ability to spread and form intimate contact with the mucous layers.

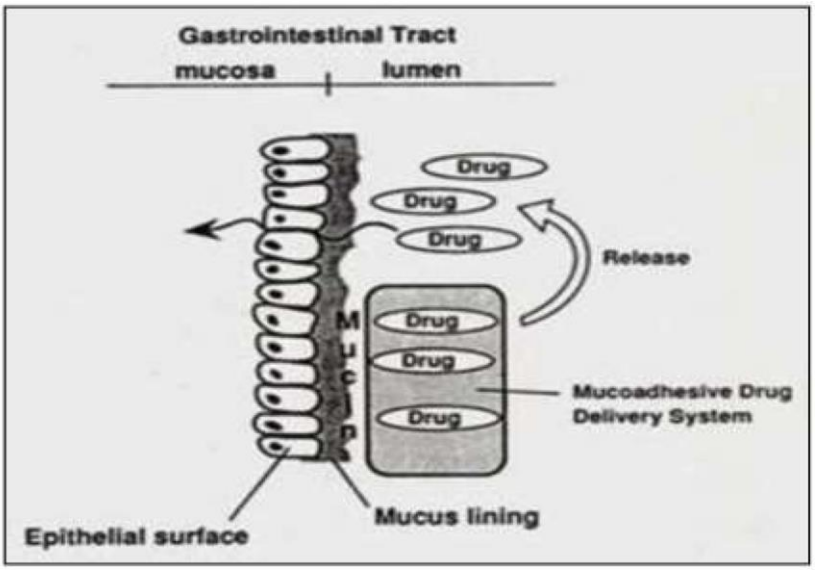


Fig. 4: Mucoadhesive Drug Delivery System

d) High Density Systems:

They include coated pallets and have a denser density than stomach content (1.004 gm/cm). The drug is coated with a heavy inert material such as barium sulphate, ZnO, or titanium dioxide to achieve this goal. This high-density pellet formulation is based on the assumption that heavy pellets may stay in the stomach longer due to their location in the lower part of the antrum.[9]

e) Swelling System:

These products swell to such an extent that they are unable to exit the stomach via the pylorus. Swelling delivery systems can swell to the point where they can no longer pass through the pylorus. When the polymer comes into contact with gastric fluid, it absorbs water and swells, allowing the dosage form to stay in the stomach for a longer period of time.[10] This dosage form is referred to as a "Plug type system" because it tends to remain logged in the pyloric sphincters for a longer period of time**.**

f) Magnetic Systems:

These are the systems that use external stimuli such as a magnetic field to deliver drugs to specific locations. To achieve site specificity, some magnetically active compounds are included in the dosage form.

g) Floating Drug Delivery Systems:

to float over gastric contents and remain in the stomach for an extended period of time. The drug is slowly released Floating systems are low density systems with enough buoyancy at the desired rate while the system floats over the gastric contents, resulting in increased gastro-retention time and reduced fluctuation. [11]

FDDS is classified as either non-effervescent or gas-generating (effervescent)

Type Of System

Non-effervescent Systems

After swallowing, this type of system swells due to gastric fluid ingestion to the point where it prevents them from exiting the stomach. The drug is mixed with a gel that swells when it comes into contact with gastric fluid and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier in the formulation methods of such type dosage forms. The air trapped by the swollen polymer gives these dosage forms buoyancy. Excipients such as hydroxypropyl methyl cellulose (HPMC), poly acrylate polymers, polyvinyl acetate, carbopol agar, sodium alginate, calcium chloride, polyethylene oxide, and polycarbonates are commonly used in these systems.[12] This system is further subdivided into four types:

1. Colloidal Gel Barrier System:

These systems contain drugs that have gel-forming hydrocolloids that allow them to float on the stomach content. This increases GRT and increases the amount of drug at its absorption sites in solution form for ready absorption. This system contains a high concentration of one or more gel-forming, highly soluble cellulose hydrocolloids such as hydroxypropyl cellulose and hydroxyethyl cellulose. When this hydrocolloid comes into contact with gastric fluid, it hydrates and forms a colloid gel barrier around its surface, which aids in the sustained release of the drug.

2. Microporous Compartment System:

A drug reservoir is encapsulated inside a micro porous compartment with pores along its top and bottom walls in this technology. The drug reservoir compartment's peripheral walls are completely sealed. This seal prevents the gastric surface from coming into direct contact with the undissolved drug. In the stomach, the flotation chamber containing the delivery system allows it to float over the gastric content entrapped air. Gastric fluid enters through an aperture, dissolves the drug, and transports the dissolved drug across the intestine for continuous absorption. [13]

3. Alginate Beads:

Freeze dried calcium alginate was used to create multi-unit floating dosage forms. Calcium alginate can be precipitated into spherical beads of approximately 2.5 mm diameter by dropping sodium alginate solution into aqueous calcium chloride solution. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at 40oC for 24 hours to form a porous system capable of maintaining a floating force for more than 12 hours. These floating beads extended the residence time to over 5.5 hours (fig. 5).

4. **Hollow Microspheres / Microballons**:

An 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 40oC to prepare hollow microspheres loaded with drug in their outer polymer shelf. The gas phase is formed in the dispersed polymer droplet by the evaporation of dichloromethane formed in the internal cavity of the polymer and drug microspheres.[14] For more than 12 hours, the micro balloon floated continuously over the surface of an acidic dissolution media containing surfactant.

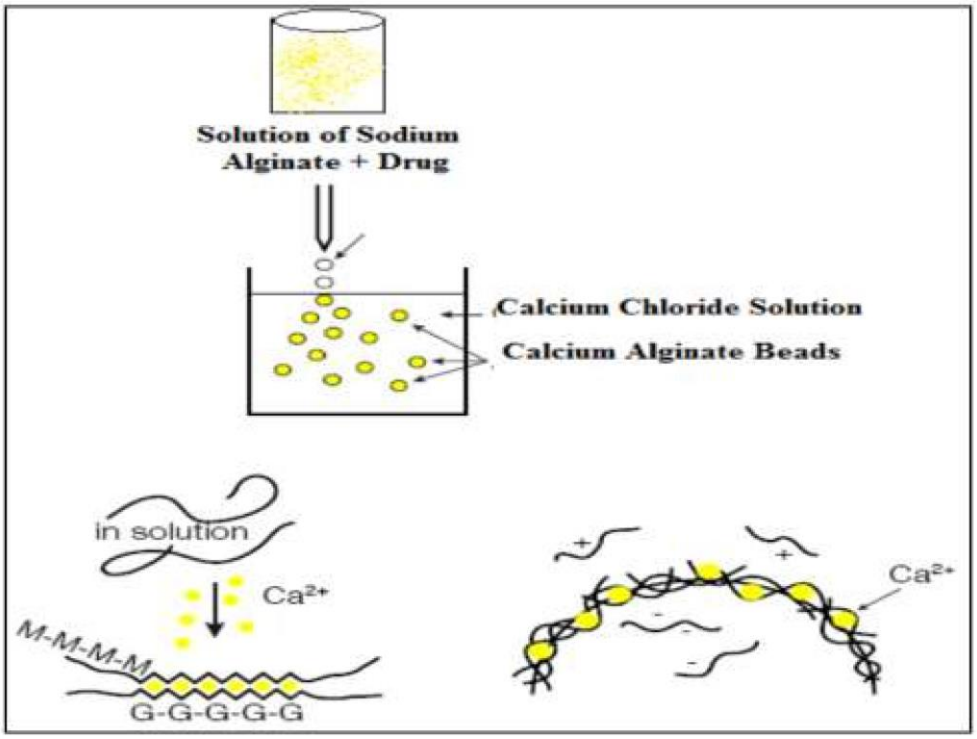


Fig. 5: Mechanism Of Gel Formation Through The Interaction Between Calcium Ions And Sodium Alginate

Effervescent Systems

These buoyant systems utilize matrices prepared with swell able polymers such as methocel polysaccharides (e.g., chitosan) and effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid. The system is so prepared that when it arrives in the stomach carbon dioxide is released, causing the formulation to float in the stomach.[15]

Volatile Liquid Containing Systems

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of PVA, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the **6**).

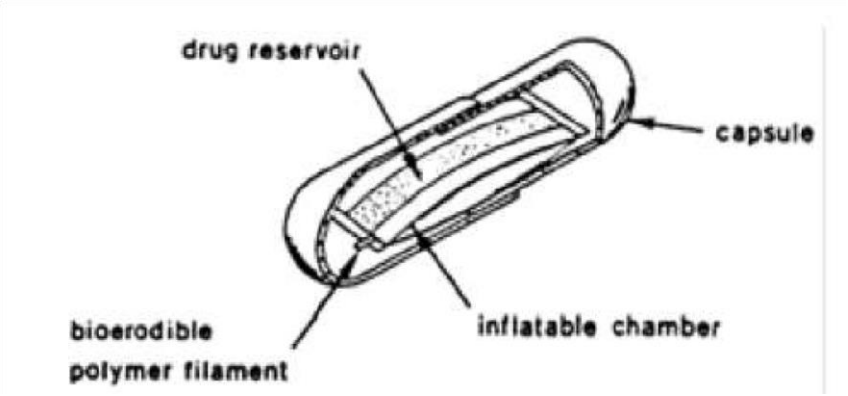


Fig. 6: Volatile Liquid Containing System

Gas-Generating Systems:

The effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2 occurred in this delivery system, which gets entrapped in the gelled hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chime. These systems contain matrices prepared with swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. [16]

The common approach used for the preparation of these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus carbon dioxide is released, causing the beads to float in the stomach[17] .Other reported approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating mini-capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology etc. (**fig. 7**).

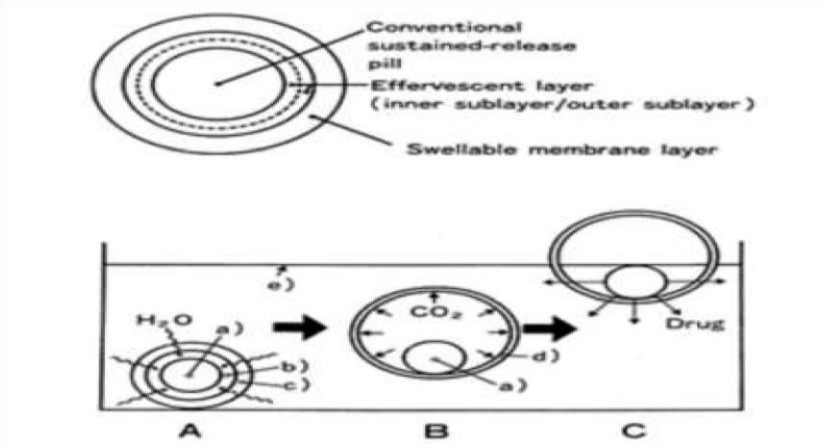


Fig. 7: effervescent (gas generating) system

Advantages of Floating Drug Delivery:

1. **Enhanced Bioavailability:**
2. The bioavailability of some drugs (e.g. riboflavin and levodopa) CR-GRDF is significantly enhanced in comparison to administration of non-GRDF CR polymeric formulations.
3. **Enhanced First-Pass Biotransformation:** When the drug is presented to the metabolic enzymes (cytochrome P-450, in particular CYP-3A4) in a sustained manner, the pre-systemic metabolism of the tested compound may be considerably increased rather than by a bolus input.
4. **Sustained Drug Delivery/Reduced Frequency Of Dosing:** The drugs having short biological half-life, a sustained and slow input from FDDS may result in a flip-flop pharmacokinetics and it reduces the dose frequency. This feature is associated with improved patient compliance and thus improves the therapy.
5. **Targeted Therapy For Local Ailments In The Upper GIT:** The prolonged and sustained administration of the drug from FDDS to the stomach may be useful for local therapy in the stomach.
6. **Reduced Fluctuations Of Drug Concentration:** The fluctuations in plasma drug concentration are minimized, and concentration-dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index. That makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.
7. **Reduced Counter-Activity Of The Body:** Slow release of the drug into the body minimizes the counter activity leading to higher drug efficiency.
8. **Extended Time Over Critical (Effective) Concentration:** The sustained mode of administration enables extension of the time.
9. **Improved Receptor Activation Selectivity:** FDDS reduces the drug concentration fluctuation over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.
10. **Minimized Adverse Activity At The Colon:** Retention of the drug in GRDF at stomach minimizes the amount of drugs that reaches the colon and hence prevents the degradation of drug that degraded in the colon
11. **Site Specific Drug Delivery:** A floating dosage form is a widely accepted approach especially for drugs which have limited absorption sites in upper small intestine.[18][19]

Limitations/Disadvantages

1. These systems require a high level of fluid in the stomach for drug delivery tom float and work efficiently-coat, water.
2. Not suitable for drugs that have solubility or stability problem in GIT.
3. Drugs such as Nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
4. Drugs which are irritant to gastric mucosa are also not desirable or suitable.
5. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
6. The dosage form should be administered with a full glass of water (200-250 ml).
7. These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract[20]

Mechanism of Floating Systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so 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 (given in **Figure 8 (a)**), the drug is released slowly at the desired rate from the system.

After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal.[21] To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature.

The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side (**Figure 8(b)**).

This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intra gastric buoyancy capability variations.

F = Fbuoyancy - Fgravity = (Df - Ds) gv

Where, F= total vertical force, Df = fluid density, Ds = Object density, v = Volume andg = acceleration due to gravity [4][22]

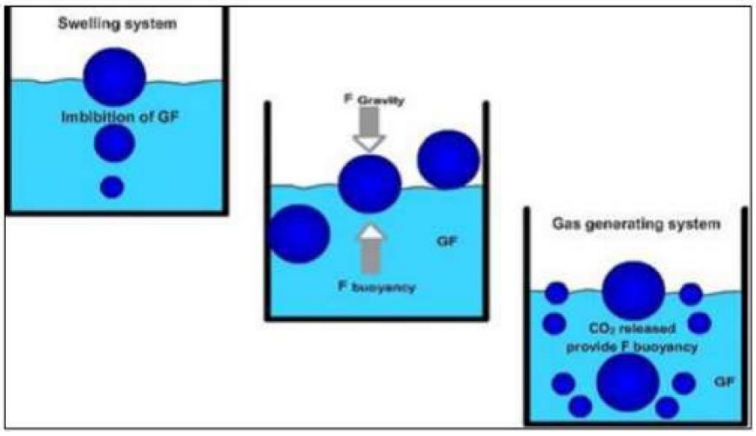


Fig. 8: Mechanism Of Floating System

Drug Candidates Suitable for FDDS:

1. Drugs that have narrow absorption window in GIT (e. g. L-DOPA, Para amino benzoic acid, furosemide, riboflavin).[5]
2. Drugs those are locally active in the stomach (e. g. misroprostol, antacids).
3. Drugs those are unstable in the intestinal or colonic environment (e. g. captopril, ranitidine HCl, metronidazole) [6].
4. Drugs that disturb normal colonic microbes (e. g. antibiotics used for the eradication of Helicobacter pylori, such as tetracycline, clarithromycin, amoxicillin).
5. Drugs that exhibit low solubility at high pH values (e. g. diazepam, chlordiazepoxide, verapamil) [7]. [23]

Factors Affecting Floating Drug Delivery System

1. Density:

Density of the dosage form should be less than the gastric contents (1.004gm/ml).

2. Size and Shape:

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kilopond per square inch (KSI) are reported to have better GIT for 90 to 100 % retention at 24 hours compared with other shapes.[8]

3. Fed or Unfed State:

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 2 hours.[24] 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 [9].

4. Nature of the meal:

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

5. Caloric Content: GRT can be increased between 4 to 10 hours with a meal that is high in proteins [10].

Characterization Parameters

1. 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 is determined using Sieve analysis, Air elutriation analysis, Photo analysis, Optical microscope (Olympus (India) Pvt. Ltd), Electro résistance counting methods (Coulter counter), Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy, Air Pollution Emissions Measurements etc. [11]. [25]

2. Floating Properties:

Effect of formulation variables on the floating properties of gastric floating drug delivery system is determined by using continuous floating monitoring system and statistical experimental design [12].

3. 3.Surface Topography:

The surface topography and structures are deter-mined using scanning electron microscope (SEM, JEOL JSM – 6701 F, Japan) operated with an acceleration voltage of 10k.v, Contact angle meter, Atomic force microscopy (AFM), Contact profiliometer.[26]

4. 4.Swelling Studies:

Swelling studies were performed to calculate molecular parameters of swollen polymers**.** Swelling studies is determined by using Dissolution apparatus, optical microscopy and other sophisticated techniques which include H1NMR imaging, Confocal laser scanning micro and fats scopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI) etc. The swelling studies by using Dissolution apparatus (USP dissolution apparatus (usp-24) Lab India Disso 2000) was calculated as per the following formula [13];Swelling ratio = Weight of wet formulation / Weight of formulations [27]

5. Determination of the Drug Content:

Percentage drug content provides how much amount of the drug that was present in the formulation. It should not exceed the limits acquired by the standard monographs. Drug content is determined by using HPLC, HPTLC methods, Near infrared spectroscopy (NIRS), Micro titrimetric methods, Inductively Coupled Plasma Atomic Emission Spectrometer (ICPAES) and also by using spectroscopy techniques

6. Percentage Entrapment Efficiency:

Percentage entrapment efficiency is reliable for quantifying the phase distribution of drug in the pre-pared formulations. Entrapment efficiency was deter-mined by using three methods such as Micro dialysis method, Ultra centrifugation, and pressure Ultra filtration.[28]

7. In-vitro Release Studies:

In vitro release studies (USP dissolution apparatus (usp-24) lab India disso 2000) are performed to provide the amount of the drug that is released at a definite time period. Release studies were performed by using Franz diffusion cell system and synthetic membrane as well as different types of dissolution apparatus [15].

8. Fourier Transforms Infrared Analysis:

Fourier transform infrared spectroscopy (FT-IR, Shimadzu, and Model-RT-IR-8300) is a technique mostly used to identify organic, polymeric, and some inorganic materials as well as for functional group determination. Fourier Transform Infrared Analysis (FT-IR) measurements of pure drug, polymer and drug-loaded polymer formulations were obtained on FT-IR. The pellets were prepared on KBr-press under hydraulic pressure of 150kg/cm2; the spectra were scanned over the wave number range of 3600 to 400 cm-1 at the ambient temperature [16]. [29]

9. Differential Scanning Calorimetry (DSC):

DSC (Shimadzu, Model-DSC-60/DSC-50/ MetlerToldeo) are used to characterize water of hydration of pharmaceuticals. Thermo grams formulated preparations are obtained using DSC instrument equipped with an intercooler. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample preparations were hermitically sealed in an aluminum pan and heated at a constant rate of 10°C/min; over a temperature range of 25°C – 65°C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50ml/min [17].

Application of Floating Drug Delivery Systems

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.[30] These are summarized as follows;

1. Sustained 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 of <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 e.g.: Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICAD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours) [18]. [31]

2. Site-Specific Drug Delivery:

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine (Riboflavin and Furosemide) e.g.: Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets [19] [32]

3. Absorption Enhancement:

Drugs that have poor bioavailability because of site 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 e.g. a sisignficantly increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%) [20].

CONCLUSIONS

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. FDDS promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique. Floating drug delivery systems (FDDS) are invented to retain the drug in the stomach and applicable for drugs with poor solubility and low stability in intestinal fluids. The basis behind FDDS is making the dosage form less dense than the gastric fluids to make it float on them.

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