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# BUOYANCY BASED GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS- A REVIEW

**S.R. Naigaonkar[1]*,**U.M.Joshi[1], K.R. Biyani[1]

[1]Department of Pharmaceutics, Anuradha College Of Pharmacy, Chikhli. Dist. Buldana.(Maharashtra) pin code-443201

***ABSTRACT***

*The purpose of the review was to compile recent literature with special focus on recent advancement like floating pellets, tablets, capsules ,bioadhesives, gel system, microparticles. Attempt have been made in the research and development of rate-controlled oral drug delivery systems to overcome physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. In this review, current & recent developments of Stomach Specific FDDS are discussed. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. Although tremendous advances have been seen in oral controlled drug delivery system in the last two decades, this system has been of limited success in the case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract).This review also summerised various sophisticated and modern in-vitro technique of formulation, advantages and application of FDDS. Also covered various patented work on FDDS.*

**Correspondence to Author**

**S.R. NAIGAONKAR**

Department of Pharmaceutics, Anuradha College Of Pharmacy, Chikhli. Dist. Buldana.(Maharashtra) pin code-443201

**Email:**

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## INTRODUCTION

The oral route is the most promising route of drug delivery. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate and provide the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for

extended time period; enhancement of duration of activity for short half-life drugs; elimination of side effects; reducing frequency of dosing and wastage of drugs; optimized therapy and better patient compliances.

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.[1]

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.[2]

**DEFINITION:-** Floating systems or dynamically controlled systems are low-density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hallow Microspheres.[3]

**NEEDS FOR GASTRIC RETENTION:-**

·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. [4]

**IDEAL DRUG CHARACTERISTICS FOR GRDDS :-**

Ideal drug charecteristics for GRDDS are as follows,

1. Drugs acting locally in the stomach, e.g. Antacids and drugs for H. Pylori viz., Misoprostol
2. Drugs that are primarily absorbed in the stomach and upper part of GI, e.g. Amoxicillin, Calcium Supplements, Chlordiazepoxide and Cinnarazine
3. Drugs that is poorly soluble at alkaline pH, e.g. Furosemide, Diazepam, Verapamil HCL, Chlordiazepoxide etc.
4. Drugs with a narrow window of absorption in GIT, e.g. Riboflavin, Para Amino benzoic Acid, Cyclosporine, Methotrexate, Levodopa etc.
5. Drugs which are absorbed rapidly from the GI tract. e.g. Metonidazole, tetracycline.
6. Drugs that degrade or unstable in the colon. e.g. Captopril, Ranitidine HCL, Metronidazol, Metformin HCl.
7. Drugs that disturb normal colonic microbes, e.g. Amoxicillin Trihydrate, antibiotics against Helicobacter pylori. [5]

**DRUGS UNSUITABLE FOR GRDDS:-**

Drugs which are unsuitable for GRDDS are as follows,

1. Drugs that have very limited acid solubility. e.g. phenytoin etc.
2. Drugs that suffer instability in the gastric environment. e.g. erythromycin etc.
3. Drugs intended for selective release in the colon. e.g. 5- amino salicylic acid and corticosteroids etc.[6]

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). 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.[7]

**Stomach Physiology**:

The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube, with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions. In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds called rugae.[8]

There are four major types of secretary epithelial cells that cover the surface of the stomach and extend down into gastric pits and glands:

Mucous cells, Parietal cells, Chief cells, G cells.

The contraction of gastric smooth muscle serves two basic functions

- Ingested food is crushed, ground, mixed and liquefying to form Chyme.
- Chyme is forced through the pyloric canal into the small intestine, a process called gastric emptying.[9]

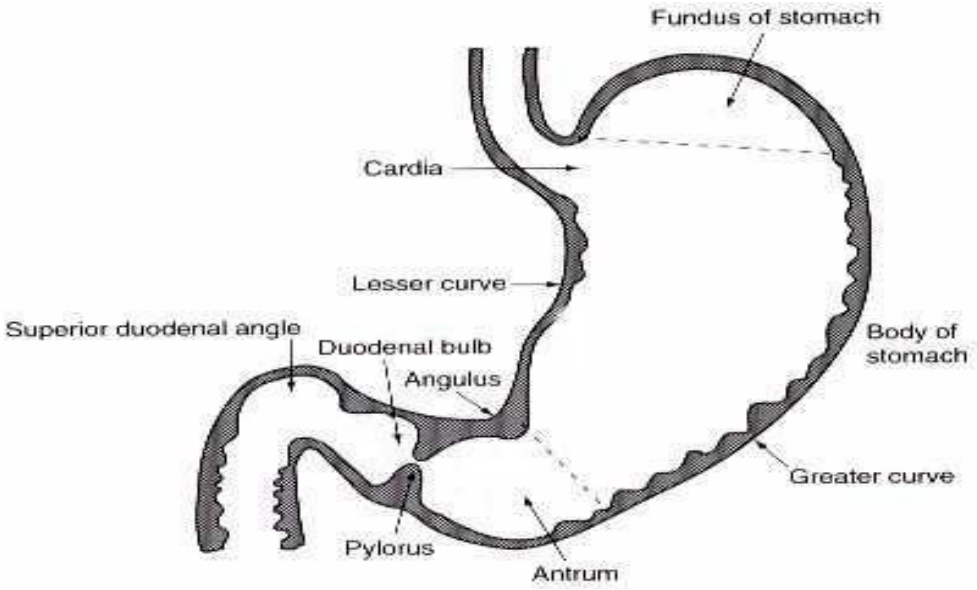


Fig.1. Anatomy of stomach.

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 inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the inter digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into 4 phases.[10,11,12.]

**APPROACHES FOR THE GASTRIC RETENTION:-**

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include –

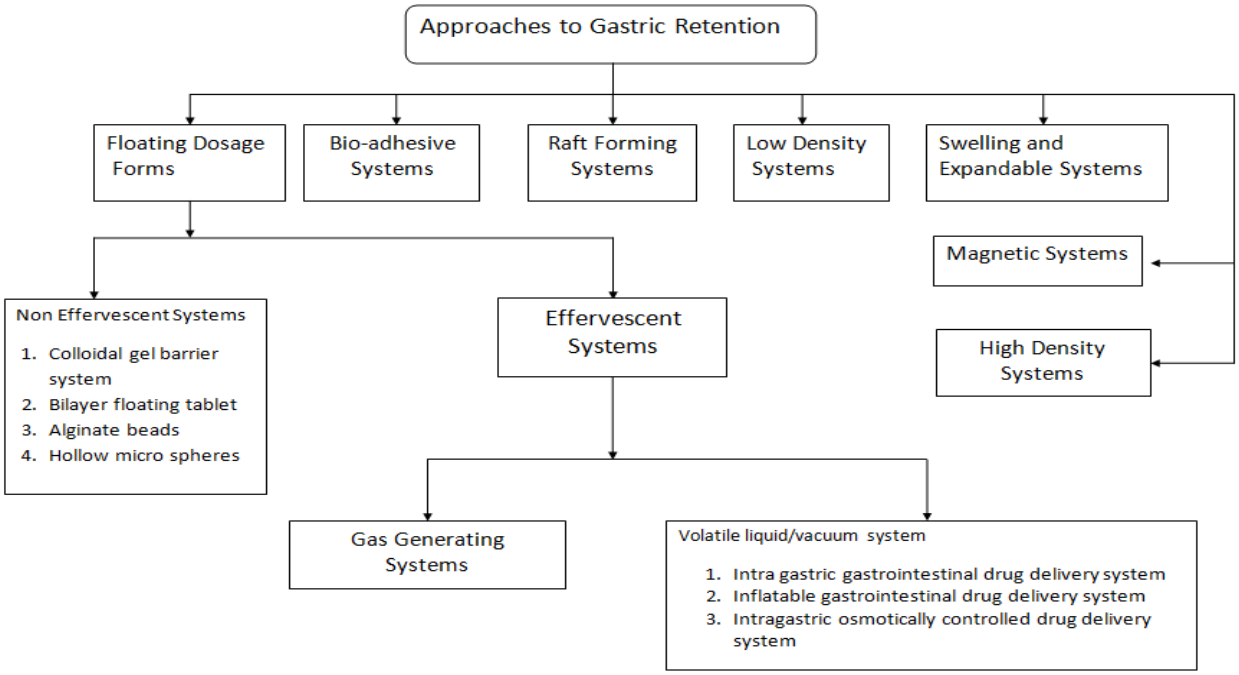


Fig .2. Approaches to gastric retention

**a) Floating Systems:**

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, non - effervescent and effervescent systems.[13]

**b) Bio/Muco-adhesive Systems:**

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane.

The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.

The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism. These mechanisms are:

1) The wetting theory.
2) The diffusion theory.
3) The absorption theory.
4) The electron theory.

**Binding of polymers to the mucin/epithelial surface can be divided into three categories:**

a. Hydration – mediated adhesion-
b. Bonding –mediated adhesion-
c. Receptor – mediated adhesion- [14,15.]

**c) Swelling and Expanding Systems:**

These are the dosage forms, which 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 of time. These systems may be named as “plug type system”, since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state.[16]

A balance between the extent and duration of swelling is maintained by the degree of cross linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.[17]

**d) High Density Systems:-**

These systems with a density of about 3 g/cm3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm3 acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.[18,19,20]

**e) Incorporation of Passage Delaying Food Agents:-**

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C10-C14.[21]

**f) 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. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.[22,23.]

**g) Osmotic Regulated Systems:**

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bio erodible capsule. In the stomach the capsule quickly disintegrates to release the intra gastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.[24]

**CLASSIFICATION OF FDDS BASED ON MECHANISM OF BUOYANCY**

Following are the buoyancy based classification of FDDS,

**A) Single unit**

Single unit dosage forms are easiest to develop but suffers from the risk of losing their effects too early due to their all-or-none emptying from the stomach and, thus they may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastro intestinal tract.

**Non effervescent systems:-**

One or more gel forming, highly swellable, cellulosic hydrocolloids (e.g. hydroxyl ethyl cellulose, hydroxyl propyl cellulose, hydroxypropyl methyl cellulose [HPMC] and sodium carboxy methyl cellulose), polysaccharides, or matrix forming polymers(e.g. polycarbophil, polyacrylates, and polystyrene) are incorporated in high level (20-75% w/w) to tablets or capsules.[25,26.]

**Effervescent systems or gas generating systems**

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid, and citric acid. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.[27]

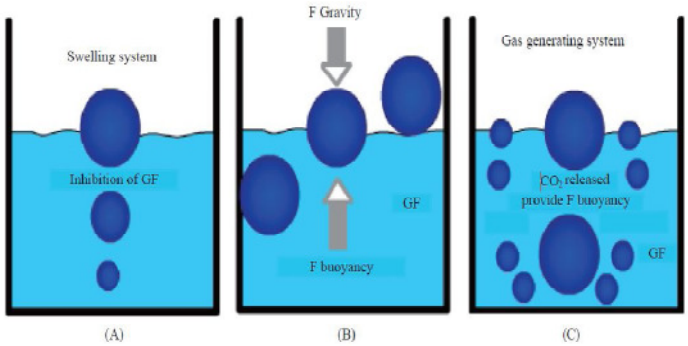


Fig.3. The mechanism of floating systems

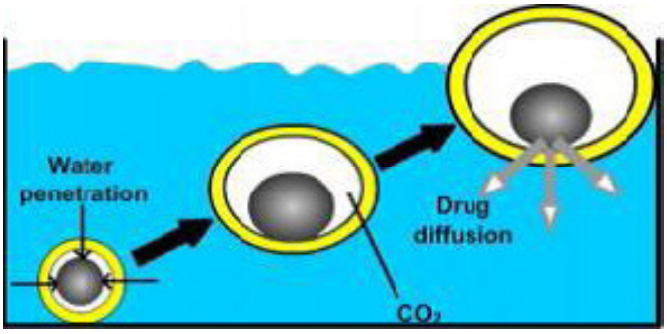


Fig. 4. Effervascent system

·**Volatile liquid containing system:**

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 inflatation of the chamber in the stomach.[28]

**B) Multiple unit**

Single unit formulations are associated with problems such as sticking together or being obstructed in gastrointestinal tract, which may have a potential danger of producing irritation. Multiple unit systems avoid the 'all-or-none' gastric emptying nature of single unit systems. It reduces the inter subject variability in absorption and the probability for dose dumping is lower.

**A) Non-effervescent systems**

A little or no much report was found in the literature on non-effervescent multiple unit systems, as compared to the effervescent systems.

**Colloidal gel barrier systems:**

Hydrodymamically balance system (HBSTM) was first design by Sheth and Tossounian in 1975. Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporates a high level of one or more gel forming highly swellable cellulose type hydrocolloids.e.g. HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms.[28]

**Microporous Compartment System:**

This technology is based on the encapsulation of drug reservoir inside a Microporous compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the un-dissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolve drug for continuous transport across the intestine for absorption.[29,30]

**Alginate beads:**

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40°C for 24 hours, leading to the formation of porous system, which can maintain a floating source over 12 hours.[29,31]

**B) Effervescent systems**

A multiple unit system comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment was prepared. Freeze-drying technique is also reported for the preparation of floating calcium alginate beads.

**C) Raft forming systems**

The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in

contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The raft floats because of the buoyancy created by the formation of CO2 and act as a barrier to prevent the reflux of gastric Contents like HCl and enzymes into the esophagus. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of to make the system less dense and float on the gastric fluids. Reckitt and Colman Products Ltd. have come out with such formulation in the treatment of H. pylori infection of GIT.[32,33,34.]

**D. Magnetic System:-**

This approach to enhance the GRT is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.[35,36] The technological approach in rabbits with bioadhesive granules containing ultra-fine ferrite. They guided them to oesophagus with an external magnet for the initial 2 minutes and almost all the granules were retained in the region after 2hours.[37]

**ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM:-**

Floating drug delivery systems have numerous advantages listed below:

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.

6) When there is vigorous intestinal movement and a short transit time, 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) 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 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.[38,39]

**DISADVATAGES OF FLOATING DRUG DELIVERY SYSTEM**

Following are the disadvantages of FDDS includes,

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.[40]

**FACTORS AFFECTING FLOATING DRUG DELIVERY SYSTEM:-**

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include use of floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified

shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system:

• **Density** – gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density;

• **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;

• **Shape of dosage form** – tetrahedron and ring shaped devices with a flexural modulus of 48 and22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retentionat 24 hours compared with other shapes.[41]

• **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;

**Fed or unfed state** – under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. 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;[42]

• **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;[43]

• **Caloric content** – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats;

• **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;[44]

• **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)

• **Age** – elderly people, especially those over 70, have a significantly longer GRT;[45]

• **Posture** – GRT can vary between supine and upright ambulatory states of the patients.[45]

• **Concomitant drug administration** – anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride; can affect floating time.

• **Biological factors** – diabetes and Crohn's disease, etc.[46]

**METHODOLOGY:-**

Various manufacturing techniques used in FDDS formulation are as follows,

**Direct compression technique**

It involves compressing tablets directly from powder material without modifying the physical nature of material itself. Direct compression vehicles and carriers must have good flow and compressible characters, this properties are imparted by pre disposing these vehicle to slugging, spray drying or crystallization. Most commonly used carriers are dicalcium phosphate trihydrate, tri calcium phosphate etc.[47,48,49.]

**Melt Granulation technique**

It is a process by which the pharmaceutical powders are agglomerated by using a melt able binder and no water or organic solvents are required for granulation. Because there is no drying step, the process is time consuming and uses less energy. Granules were prepared in a lab scale high shear mixer, using a jacket temperature of 60 ºC and an impeller speed of 20000 rpm.[47,48,49.]

**Melt solidification technique:**

This process involves emulsification of the molten mass in the aqueous phase followed by its

solidification by chilling. The carriers used for this technique are lipids, waxes, polyethylene glycol. Drug is incorporated into these carriers to achieve controlled release.[47,48,50]

**Effervescent technique**

The floating chamber of the drug delivery system can be filled with inert gas ($co_2$)by the effervescent reaction between organic acid (citric acid) and bicarbonate salts.[47,48]

**Spray drying technique**

It involves dispersing the core material in a liquefied coating material and spraying the core-coating mixture in to the environment to effect solidification of coating. Solidification is accomplished by rapid evaporation of the solvent in which coating material is solubilised.[49]

**Solvent Evaporation**

In this method, the capacity of the continuous phase is insufficient to dissolves the entire volume of disperse phase solvent. Thus, solvent evaporates from the surface of the dispersion to obtain hardened microsphere.[50]

**Wet granulation technique**

Wet granulation process involves the wet massing of powders, wet sizing or milling and drying. Wet granulation forms the granules by binding the powders together with an adhesive instead of compaction. The wet granulation technique employs a solution suspension or slurry containing a binder which is usually added to the powder mixture however the binder may be incorporated into the dry powder mix and the liquid may be added by itself.[48]

**Ionotropic gelation technique:-** where gelation of anionic polysaccharide sodium alginate, the primary polymer of natural origin, was achieved with oppositely charged calcium ions (counter ion)10 to form instantaneous microparticles.[50]

**APPLICATION OF FLOATING DRUG DELIEVERY SYSTEM:**

Following are important application of Floating Drug Delivery System,

**1. Enhanced Bioavailability:**

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.[50]

**2. Sustained drug delivery:**

Oral CR formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the HBS systems which can remain in the stomach for long periods and have a bulk density <1 as a result of which they can float on the gastric contents. These systems are relatively larger in size and passing from the pyloric opening is prohibited.[51]

**3. Site specific drug delivery systems:**

These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine .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. Eg: Furosemide and Riboflavin.[52]

**4. Absorption enhancement:**

Drugs which are having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption.[53]

**5. Minimized adverse activity at the colon:**

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented.[54]

**6. Reduced fluctuations of drug concentration:**

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects 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.[55]

**MECHANISM OF FLOATING SYSTEM**

While the system is floating on the gastric the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach 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. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to main submerged object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

F = F buoyancy - F gravity = (Df - Ds) gv

Where, F= total vertical force, Df = fluid density, Ds = object density, v = volume and g = acceleration due to gravity.[56]

**CHARECTERIZATION PARAMETERS:-**

Various characterization parameters where discuss with example,

**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 was determined using Sieve analysis, Air elutriation analysis, Photo analysis, Optical microscope, Electro résistance counting methods (Coulter counter), Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy, Air Pollution Emissions Measurements,[57]

**2. Floating properties:**

Effect of formulation variables on the floating properties of gastric floating drug delivery system was determined by using continuous floating monitoring system and statistical experimental design.[58]

**3. Surface topography**:

The surface topography and structures were determined 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.[59]

**4. Determination of moisture content:**

The moisture content of the prepared formulations was determined by Karl fisher titration, vacuum drying, Thermo gravimetric methods, Air oven method, Moisture Meters, Freeze drying as well as by physical methods.[60]

**5. Swelling studies:**

Swelling studies were performed to calculate molecular parameters of swollen polymers. Swelling studies was determined by using Dissolution apparatus, optical microscopy and other sophisticated techniques which include H1NMRimaging, Confocal laser scanning microscopy (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) used. [61]

**Swelling ratio = Weight of wet formulation / Weight of formulations**

**6. 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 was 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.[62]

**7. Percentage entrapment efficiency:**

Percentage entrapment efficiency was reliable for quantifying the phase distribution of drug in the prepared formulations. Entrapment efficiency was determined by using three methods such as Micro dialysis method, Ultra centrifugation, and pressure Ultra filtration.[63]

**8. In-vitro release studies:**

In vitro release studies (USP dissolution apparatus (usp-24) lab India disso 2000) were 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. [64]

**9. Powder X-ray diffraction:**

X-ray powder diffraction (Philips analytical, model-pw1710) is the predominant tool for the study of polycrystalline materials and is eminently suited for the routine characterization of pharmaceutical solids. Samples were irradiated with α radiation and analyzed between 2 ºC and 60 ºC .The voltage and current used were 30KV and 30mA respectively.[65]

**10. Fourier transform infrared analysis:**

Fourier transform infrared spectroscopy (FTIR, Shi-madzu, 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 FTIR. 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.[65]

**11. Differential Scanning Colorimetry (DSC) :**

DSC are used to characterize water of hydration of pharmaceuticals .Thermo grams of formulated preparations were 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.[65]

**Polymers and other ingredients used in preparations of floating drugs:[55,56,57.]**

**1. Polymers:**

The following polymers used in preparations of floating drugs -

HPMC K4 M, Calcium alginate, Eudragit S100, Eudragit RL, Propylene foam, Eudragit RS, ethyl cellulose, poly methyl methacrylate, Methocel K4M, Polyethylene oxide, β Cyclodextrin, HPMC 4000, HPMC 100, CMC, Polyethylene glycol, polycarbonate, PVA, Polycarbonate, Sodium alginate, HPC-L, CP 934P, HPC, Eudragit S, HPMC, Metolose S.M. 100, PVP, HPC-H,

HPC-M, HPMC K15, Polyox, HPMC K4, Acrylic polymer, E4 M and Carbopol.

**2.Inert fatty materials (5%-75%) :** Edible, inert fatty material having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. E.g. Beeswax, fatty acids, long chain fatty alcohols, Gelucires 39/01 and 43/01.

**3. Effervescent agents :** Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine).

**4. Release rate accelerants (5%-60%):** eg. lactose, mannitol.

**5. Release rate retardants (5%-60%):** eg. Dicalcium phosphate, talc, magnesium stearate.

**6. Buoyancy increasing agents (upto80%):** eg. Ethyl cellulose.

**7. Low density material:** Polypropylene foam powder (Accurel MP 1000).

**Marketed product of Floating drug delivery System:-[66,67,68.]**

| Sr no | Brand name | Drug | Remark | Company |
|---|---|---|---|---|
| 1 | Cifran OD® | Ciprofloxacin | Gas generating floating tablet | Ranbaxy |
| 2 | Valrelease® | Diazepam | Floating Capsule | Hoffman-LaRoche USA |
| 3 | Oflin OD® | Ofloxacin | Gas generating floating tablet | Ranbaxy |
| 4 | Cytotec® | Misoprostol | Bilayer Floating Capsule | Pharmacia USA |

| | | | | |
|---|---|---|---|---|
| 5 | Conviron | Ferrous Sulphate | Colloidal gel forming FDDS | Ranbaxy, India |
| 6 | Topalkan | Al- Mg antacid | Floating liquid Alginate preparation | Pierre Fabre Drug, France |

**Table no.1**.Marketed Product

**RECENT ADVANCES IN FLOATING DOSAGE FORMS:**

Recent advancement in Floating dosage forms includes Tablets, Capsules, Pellets, gel system, microsphere are discussed below,

**Tablets:-**

Strübing et al investigated the mechanism of floating and drug release behaviour of poly(vinyl acetate)- based floating tablets with membrane controlled drug delivery. Tablets containing propranolol HCl with Kollidon® SR as an excipient for direct compression and different Kollicoat® SR 30 D/Kollicoat® IR coats, varying from 10 to 20 mg polymer/cm2, were investigated with regard to drug release in 0.1 mol/l HCl. Furthermore, the onset of floating, the floating duration and the floating strength of the device were determined.

In addition, benchtop MRI studies of selected samples were performed. Coated tablets with a 10 mg polymer/cm2 SR/IR, and an 8.5: 1.5 coating exhibited the shortest lag-times prior to drug release and the onset of floating, and also the fastest increase in and the highest maximum values of the floating strength.[69]

Jang et al prepared a gastro-retentive drug delivery system of DA-6034, a new synthetic flavonoid derivative, for the treatment of gastritis using an effervescent floating matrix system (EFMS). The therapeutic limitations of DA-6034 caused by its low solubility in acidic conditions were overcome by using the EFMS, which was designed to allow the tablets to float in gastric fluid and release the drug continuously. The release of DA-6034 from the tablets in acidic media was significantly improved by using EFMS, and this was attributed to the effect of the solubilizers and the alkalizing agent such as, sodium bicarbonate, used as gas generating agent. DA-6034 EFMS tablets showed enhanced gastro-protective effects in gastric ulcer-induced beagle dogs, indicating the therapeutic potential of EFMS tablets for the treatment of gastritis.[70]

**Floating and Pulsatile Drug delivery System:-**

Sher et al have proposed a specific technology, based on combining floating and pulsatile principles, to develop a drug delivery system, intended for chronotherapy of arthritis. This was achieved by using low density microporous polypropylene, Accurel MP 1000®, as a multiparticulate carrier along with the drug of choice, ibuprofen. The amount of carrier amount and solvent volume were kept constant in designing this simple system by adsorbing the drug via melting or solvent evaporation using different carrier: drug ratios. For solvent evaporation, methanol (M) and dichloromethane (DCM) were used. The drug-loaded multiparticulate system was subjected to a series of characterization and evaluation processes showing the effect adsorption.[71]

**Capsule:-**

Burns et al. developed a dissolution method for a floating dosage form using Halo-propranolol capsules containing propranolol base dissolved in oleic acid. They observed that the standard paddle method was unable to provide either sufficient mixing or sufficient mechanical erosion of the sustained release component of the formulation. Finally they reported that the modified paddle method resulted in reproducible biphasic release dissolution profiles when paddle speeds were increased from 70 rpm to 100 rpm and dissolution medium pH changed from 6 to 8.[72]

**Microparticles:-**

Sato et al., performed in vitro evaluation of floating and drug releasing behaviors of hollow microspheres (micro balloons) prepared by emulsion solvent evaporation method. They performed the study using 5 different drugs, out of which riboflavin and indomethacin did not follow Higuchi equation. Finally, they reported that by incorporating a polymer like HPMC within shell of micro balloons, the release rates of Riboflavin from micro balloons could be controlled.[73]

Lee et al., developed oral drug delivery system using floating microspheres. They prepared floating acrylic resin microspheres with an internal hollow structure by solvent diffusion and evaporation method. The microspheres yield depended upon diffusion rate of ethanol/isopropanol in organic phase. They got the best results for the volume ratio of

ethanol:isopropanol:dichloromethane as 8:2:5 with optimum rotation speed and temperature to be 250 rpm and 25 degree Celsius, respectively.[74]

Varshosaz et al., developed and characterized floating micro balloons for oral delivery of cinnarizine. The objective of this study was to produce floating micro balloons of cinnarizine by diffusion solvent method to increase drug solubility and hence increased bioavailability. They evaluated the effect of stirring rate, stirring time after addition of oily phase into aqueous and

type of polymer. They reported that highest floating percent was found to be 77.5% in formulation with eudragit S100 at 200 rpm for 1 hr.[75]

**Bioadhesives:-**

Uma et al. prepared floating microspheres containing the antiurease drug acetohydroxamic acid (AHA) by novel quasi emulsion solvent diffusion method. The microspheres were coated with 2 %w/v solution of polycarbophyll using air suspension coating. The result suggested that AHA loaded floating microspheres were superior as potent urease inhibitors while urease plays an important role in colonization of H.pylori.[76]

**Floating Gel System**

Rajnikanth et al, developed a new intragastric floating in situ gelling system for control release of amoxicillin. They prepared gellan based amoxicillin floating in vivo gelling systems (AFIG). They compared the clinical efficacy of prepared gelling system with amoxicillin suspension against H. pylori and found that the required amount of H. pylori, eradication was 10 times in comparison to the corresponding amoxicillin suspension.[77]

**Floating Pellets**

Sungthogjeen et al. prepared a multiple-unit floating drug delivery system based on gas formation technique. They designed a system, coated with double layer of sodium bi carbonate and an outer gas entrapped polymeric membrane of aqueous colloidal NF30D. They reported that only the system using polymeric membrane could float.[78]

**U.S.PATENTS FOR FLOATING DRUG DELIVERY SYSTEM**

Some of the patents issued for floating drug delivery system are summerised below,

| S No. | U.S. Patent | Year of Grant | Formulations | References |
|---|---|---|---|---|
| 1. | 3507952 | 1972 | S.R formulation | 79 |
| 2. | 3786813 | 1974 | Hollow floating device | 80 |
| 3. | 4844905 | 1987 | Granules | 81 |
| 4. | 4814179 | 1989 | S.R tablet | 82 |
| 5. | 5169638 | 1992 | Floating powder | 83 |
| 6. | 5232704 | 1993 | S.R, floating dosage form | 84 |
| 7. | 5288506 | 1993 | Antacid powder formulation | 85 |
| 8. | 4434153 | 1994 | Hydrogel | 86 |
| 9. | 5651985 | 1997 | Polymer complex | 87 |
| 10. | 5783212 | 1998 | C.R.Tablet | 88 |
| 11. | 6290989 | 2001 | C.R.capsule | 89 |
| 12. | 6207197 | 2001 | C.R.Microspheres | 90 |
| 13 | 9702918 | 2001 | Floating system | 88 |
| 14 | 7838028 | 2010 | Multi pulse floating tablet | 91 |
| 15 | 7682629 | 2010 | Floating p'ceutical composition | 91 |
| 16 | 6776999 | 2004 | Expandable GRT | 91 |
| 17 | 6685962 | 2004 | GRT CRDD Forms | 91 |

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