

Review: An Overview on Floating Drug Delivery System

Hemant Maheta,* MR Patel, KR Patel, MS Patel

Department of Pharmaceutics,

Shri B.M.Shah College of Pharmaceutical Education and Research,
Modasa, Gujarat, India.

*hsmehta19@gmail.com



ABSTRACT

The purpose of writing this review on floating drug delivery systems was special focus on the principle mechanism of floatation to achieve gastric retention. Conventional oral dosage forms has short residence times & unpredictable gastric emptying time. The idea of gastric retention comes from the need to localize drugs at a specific region of gastrointestinal tract (GIT) such as stomach in the body. Many drugs get absorbed only in the upper intestinal tract, designing such molecules as once-daily formulations are exclusive for these molecules. Thus GI retention platforms had emerged. Gastroretentive drug delivery systems are designed to be retained in the stomach for a prolonged time. Gastroretentive drug delivery systems have potential for use as controlled release drug delivery system. The use of floating drug delivery system is one method to achieve prolonged gastric residence times, providing opportunity for both local & systemic drug action. Thus, gastroretention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients. This article aims at reviewing the floating drug delivery system including types, approaches for designing the floating dosage form, advantages & disadvantages of FDSS.

Keywords: Gastric residence time, Gastroretention, Gastrointestinal tract, narrow absorption window, floating drug delivery systems.

INTRODUCTION

The focus of pharmaceutical research is steadily shifted from the development of new chemical entities to the development of novel drug delivery system of existing drug molecule to maximize their effectiveness in terms of therapeutic action, reducing frequency of dosing and wastage of drugs, patient compliance and reduced adverse effects.^[1] To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. Oral drug delivery is the most desirable and preferred

method of drug delivery for achieving both systemic and local therapeutic effects. For many drugs, conventional oral formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient. The real challenge in the development of a controlled drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form in the stomach or the upper small intestine until all the drug is completely released in the desired period of time.^[2, 3] The gastro intestinal tract (GIT) is the major route of drug delivery to the systemic circulation. Oral controlled release dosage forms are not

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suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the GIT. This is due to the relatively less transit time of the dosage form in these anatomical segments. Thus after only a short period of less than 6 h, the controlled release formulation has already left the upper GIT and the drug is released in short, non absorbing distal segment of the GIT. This results in a short absorption phase, which is then accompanied by lesser bioavailability. These types of problem can be overcome by floating drug delivery system. [4-7]

Definition of floating drug delivery systems: [8]

Floating drug delivery systems (FDDS) are those systems which have a bulk density less than gastric fluids and because of this, these systems remain buoyant (3-4 hours) for a prolonged period of time in the stomach without affecting the gastric emptying rate. The drug is released slowly at the desired rate from the system and after release of the drug; the residual system is emptied from the stomach. As a result GRT is increased and fluctuations in plasma drug concentration can be better controlled.

Mechanism of Floating Systems: [9]

While the system is floating on the gastric content the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force 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 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 objects. The apparatus helps in optimizing FDDS with respect to stability to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

$$F = F_{\text{buoyancy}} - F_{\text{gravity}} \\ = (D_f - D_s) g v$$

Where, F = Total vertical force, D_f = fluid density, D_s = object density, v = volume

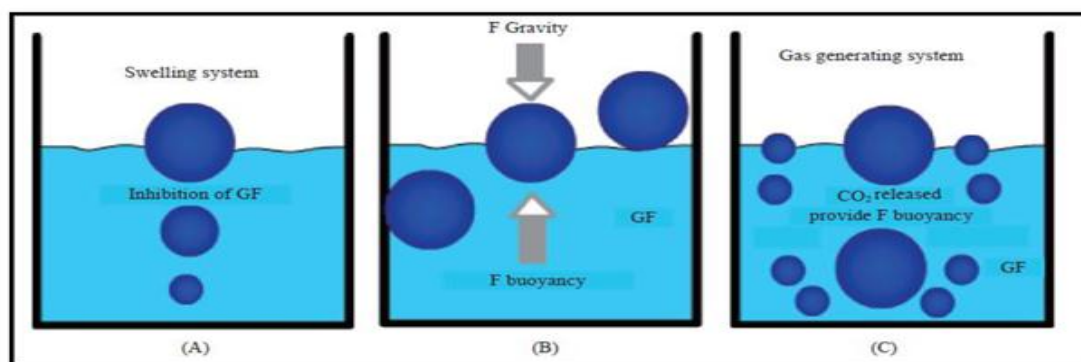


Fig: 1 Mechanism of Floating Systems

APPROACHES TO DESIGN THE VARIOUS FLOATING DOSAGE FORM: [10-15]

Two types of floating Dosage systems Single- and multiple-unit floating dosage systems have been designed by using the following approaches.

SINGLE-UNIT DOSAGE FORMS

Low-density approach

In this approach, the globular shells with density lower than that of gastric fluid can be used as carrier for drug for making single-unit floating dosage form. Popcorn, polystyrol and

poprice have been used as drug carriers in coated shells. For the undercoating of these shells sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been exploited. These shells are then further coated with a mixture of drug polymer. Depending on the type of release desired, either of the polymer ethyl cellulose or hydroxypropyl cellulose can be used. The product floats on the gastric fluid and gradually releases the drug for a long period of time.

Fluid- filled floating chamber

In this type of dosage forms, a gas-filled floatation chamber is incorporated into a microporous component that covers the drug reservoir. Along the top and bottom walls there is provision for opening through which the GIT fluid enters into the device to dissolve the drug. The side walls in contact with the fluid are sealed to ensure undissolved drug remains in the device. The fluid present in the system for floatation could be air or any other suitable gas, liquid, or solid that has an appropriate specific gravity and should be inert. This device should be of swellable size. Device remains floats within the stomach for a long period of time and slowly releases the drug. After the complete release of the drug, the shell disintegrates, goes to the intestine, and finally eliminated from the body.

Hydrodynamically balanced systems (HBS)

These systems enhance the absorption because they are designed such that they stay in GIT for prolong time. Drugs which have a better solubility in acidic environment and site-specific absorption in the upper part of GIT are suitable candidates for such systems. These dosage forms must have a bulk density of less than 1. It should maintain its structural integrity and should constantly release the drug .The solubility of chlordiazepoxide hydrochloride²⁹ is 150 mg/mL at pH 3 to 6 and is ~0.1 mg/mL at neutral pH. So, HBS capsule of this drug is a

better than conventional one to solve the solubility problem.

Bilayer and matrix tablets

Floatable characteristics also shown by some types of bilayer and matrix tablets. The polymers which have been exploited are sodium carboxymethylcellulose (CMC), hydroxypropyl cellulose, Hydroxypropyl methylcellulose, ethyl cellulose and Crosspovidone.

3-layer principle

By the development of an asymmetric configuration drug delivery system, 3-layer principle has been improved.3-layer principle helps in modulating the release extent and for achieving zero-order release kinetics. The design of the system is such that it floats on the stomach content and prolong gastric residence time which further results in longer total transit time which maximize the absorptive capacity and hence better bioavailability is achieved. These benefits can be applicable to drugs with pH-dependent solubility, drugs which are absorbed by active transport mechanism from the small intestine or the drugs with narrow absorption window.

Problems with single-unit formulations

Single-unit formulations can stick together or being obstructed in the GIT, which can cause irritation.

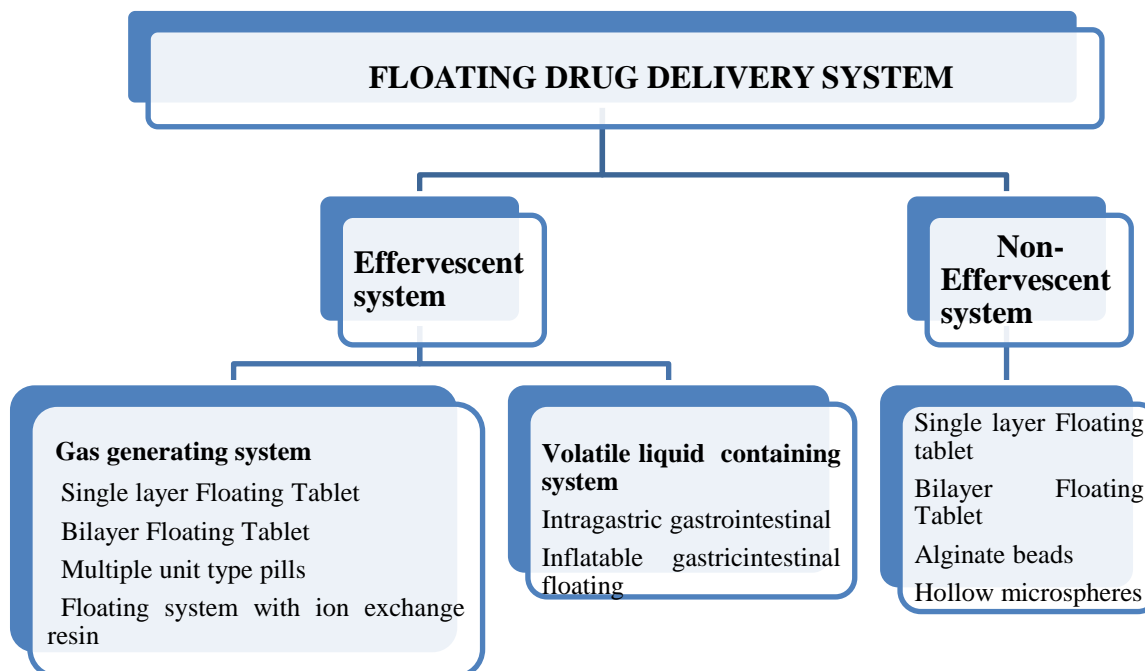
MULTIPLE-UNIT DOSAGE FORMS

Multiple-unit dosage form is designed to develop a reliable formulation that provide all the benefits of a single-unit form and also overcome the disadvantages of single-unit formulations. Microspheres have been used because of their high loading capacity. The polymers such a albumin, starch, gelatin, polyacrylamine, polymethacrylate and polyalkylcyanoacrylate have been used for the preparation of microspheres. Microspheres

show an excellent in vitro floatability because of its characteristic internal hollow structure. Several devices of carbon dioxide multiple-unit oral formulations have been described in the

recent patent literature with features that unfold, extend or are inflated by carbon dioxide generated in the devices after administration.

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM: [16-25]



A) Effervescent system:-

These are matrix types of systems prepared with the help of swellable polymers (methylcellulose and chitosan) and various effervescent compounds (sodium bicarbonate, tartaric acid, and citric acid). They are formulated in such a way that when come in contact with acidic gastric contents, CO_2 liberate and gas entrapped in swollen hydrocolloids which provides buoyancy to the dosage form.

a) Volatile liquid containing systems:

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid (such as ether, cyclopentane), that gasifies at body temperature to cause the inflammation of the chamber in the stomach. The device may also

consist of a bio-erodible plug made up of PVA, Polyethylene, etc. that gradually dissolves and causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

Intra-gastric floating gastrointestinal drug delivery system

This system can be made to float in the stomach, because of floating chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro porous compartment.

Inflatable gastrointestinal delivery system

In these systems an inflatable chamber is incorporated, which contains liquid ether that

gasifies at body temperature to cause the chamber to inflatable in the stomach. These systems are fabricated by loading the chamber with the drug reservoir, which can be a drug impregnated polymeric matrix, than encapsulated in a gelatin capsule. After oral administration the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir into the gastric fluid.

b) Gas generating systems:

In these system effervescent reactions occurs between carbonates/bicarbonates salts and citric/tartaric acid to liberate CO₂, which gets entrapped in the gelling matrix of the systems. Thus decreasing its specific gravity and making it to float over the gastric fluid.

I) Floating pills:

These systems consist of two layers, inner effervescent layer containing sodium bicarbonate and tartaric acid, the outer swellable polymeric membrane. The inner layer is further divided into two sub layers to avoid physical contact between sodium bicarbonate and tartaric acid. When this pill is immersed in buffer solution at 37°C, it settles down at the bottom and buffer solution enters into the effervescent layer through the outer swellable membrane. Swollen pills or balloons are formed due the generation of carbon dioxide as a result of reaction between sodium bicarbonates and tartaric acid. The carbon dioxide generated is entrapped within the delivery system making the device to float. These systems were found to float completely within 10 minutes and have good floating ability independent of pH, viscosity of the medium and the drug is released in a controlled manner.

II) Floating capsules:

Floating capsules are prepared by filling a mixture of sodium alginate and sodium

bicarbonate, these float due to the generation of carbon dioxide which gets trapped in the hydrating gel network on exposure to an acidic environment.

III) Floating systems with ion exchange resins:

These systems are formulated by using ion exchange resin that is loaded with bicarbonate by mixing the beads with sodium bicarbonate solution. These loaded beads were then surrounded by a semi permeable membrane to avoid the sudden loss of carbon dioxide. Upon coming in contact with gastric contents there is an exchange of chloride and bicarbonate ions resulting in generation of carbon dioxide thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads, which releases the drug at a predetermined.

IV) Tablet

a) Intragastric single layer floating tablets or Hydrodynamically Balanced system

These formulations have bulk density lower than gastric fluids and thus float in the stomach that increases the gastric emptying rate for a prolonged period. These are formulated by intimately mixing the gas (CO₂) generating agents and the drug within the matrix tablet. The drug is released slowly at a desired rate from the floating system & the residual system is emptied from the stomach after the complete release of the drug. This leads to and increases in the gastric residence time & a better control over fluctuations in plasma drug concentration.

b) Bi-layer tablet

Bilayer tablet can also prepared by gas generating matrix in one layer and second layer with drug for its sustained release effect.

c) Triple layer tablet

Triple layer tablet also having first swellable floating layer, second sustained release layer of two drugs and third rapid dissolving layer

B) Non-effervescent systems:

This type of system after swallowing swells unrestrained via. Imbibition of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the “plug type system” since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact after oral administration and maintains a relative integrity of shape and a bulk density of less than 1. This is based on the mechanism of swelling of polymer or bio adhesion to mucosal layer in GIT. The most commonly used excipients are gel forming materials such as polycarbonate, poly acrylate, polystyrene etc. this 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. The various types of this system are as follows:

Single layer floating tablets

This can be formulated by intimate mixing of drug with gel forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than 1. The air entrapped by the swollen polymer confers buoyancy to these dosage forms.

Bilayer floating tablets

A bilayer tablet contains two layers, one is immediate release layer which releases the initial dose from system while the other is sustained release layer which absorbs the gastric fluid and maintains a bulk density of less than 1 and thereby it remains buoyant in the stomach (Fassihi and Yang developed a zero-order controlled release). Multilayer tablet composed of at least 2 barrier layers and one drug layer. All the layers are made of swellable, erodible polymers and the tablet was found to swell on contact with aqueous medium. As the tablet dissolved, the barrier layers eroded away

to expose more of the drug. Gas evolving agent is added in either of the barrier layers, this caused the tablet to float and increased the retention of tablet in a patient’s stomach.

Colloidal gel barrier systems

It 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. On coming in contact with gastric fluid, the hydrocolloids in the system hydrate and form 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.

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 dissolved drug for continuous transport across the intestine for absorption.

Alginate beads

To develop Multi-unit floating dosage forms the freeze-dried calcium alginate has been used. Spherical beads of approximately 2.5 mm in diameter can be prepared by the precipitation of calcium alginate via dropping sodium alginate solution into aqueous solution of calcium chloride. 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 force over 12 hours. On the other hand,

multiple-unit dosage forms appear to be better suited since they claimed to reduce the inter subject variability in absorption and lower the probability of dose-dumping

Hollow microspheres

A novel emulsion solvent diffusion method was used to prepare hollow microspheres loaded with drug in their outer polymer shell. The ethanol: dichloromethane solution of the drug and enteric acrylic polymers is poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hours. The drug released was high in pH 7.2 than in pH 6.8. Hollow microspheres (micro balloons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method.

Ideal drug candidates for floating drug delivery:

- Drugs those are locally active in the stomach. Eg. Misoprostol, antacids etc.
- Drugs which have narrow absorption window in the GIT. Eg. Furosemide, L-dopa, Para-amino benzoic acid, riboflavin.etc.
- Drugs that exhibit low solubility at high pH values. Eg. Diazepam, Chlordiazepoxide, Verapamil hydrochloride.
- Drugs those are unstable in the intestinal or colonic environment. E.g. Captopril, ranitidine HCl, Metronidazole.
- Drugs that disturb normal colonic microbes. E.g. antibiotics against Helicobacter pylori.
- Drugs having a specific site of absorption in the upper part of small intestine.

- Drugs having a bulk density of less than 1 to remain in the stomach for a prolonged period of time.

FACTORS AFFECTING GASTRIC RETENTION: [26]

A) PHYSIOLOGICAL FACTORS:-

a) Density:

Gastric retention time is a function of dosage form buoyancy that is dependent on the density. A buoyant dosage form having a density less than that of the gastric fluids floats, since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. A density of less than 1.004g/ml i.e. less than that of gastric contents has been reported.

b) 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.

c) 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.

B) BIOLOGICAL FACTORS:

a) 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. However, in the fed state, MMC delayed and GRT is considerably longer.

b) 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.

c) Caloric content:

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

d) 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.

e) 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.

f) Age:

Low gastric emptying time is observed in elderly than do in younger subjects. Intrasubject and intersubject variations also are observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have a significantly longer GRT.

g) Posture:

GRT can vary between supine and upright ambulatory states of the patient. An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size. In supine subjects large dosage forms experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally, these units may be swept away by the peristaltic movements that propel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects.

h) Concomitant drug administration:

Anticholinergic like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide and cisapride, affect the gastric emptying and hence gastric residence time of an oral dosage form.

Methods for Preparing Floating Dosage Form^[26]

Direct compression technique

Involves compressing tablets directly from powdered material without modifying the physical nature of the material itself. Direct compression vehicles or carriers must have good flow and compressible characters these properties are imparted by predisposing these vehicles to slugging, spray drying or crystallization. Most commonly used carriers are di calcium phosphate trihydrate, tri calcium phosphate etc.

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 less time consuming and uses less energy. Granules were prepared in a lab scale high shear mixer, using a jacket temperature of 60 °c and an impeller speed of 20000 rpm.

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 glycols. Drug is incorporated into these carriers to achieve controlled release.

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. The method of introducing the binder depends on its solubility and on the components of the mixture since, in general, the mass should merely be moist rather than wet or pasty, and there is a limit to the amount of solvent that may be employed. Once the granulating liquid has been added mixing continues until a uniform dispersion is attained and all the binder has been activated. Then the wet mass is made to undergo wet screening by passing through a hammer mill or multi mill equipped with screens having large perforations. The milled wet mass is dried by either using tray drier or fluidized bed drier, after complete the drying lubrication materials is blended with dried granules. This lubricated granules is made to undergo compression.

Effervescent technique:

The floating chamber of the drug delivery system can be filled with inert gas [CO₂] by the effervescent reaction between organic acid [citric acid] and bicarbonate salts.

Spray drying techniques:

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.

Advantages of FDDS: ^[27]

- FDDS is highly advantageous in the treatment of the disorders related to the stomach. As the prime objective of such systems is to produce a gastro retentive product or a product which has an enhanced retention time in the stomach.

- Drugs with considerably short half life can be administered in this manner to get an appreciable therapeutic activity.
- Enhancement of the bioavailability for drugs which can be metabolized in the upper GIT.
- They also have an advantage over the conventional system as it can be used to overcome the adversities of gastric retention time as well as the gastric emptying time.
- The duration of treatment through a single dose, which releases the an active ingredient over an extended period of time
- The active entity is delivered specifically to the site of action, thus minimizing or eliminating the side effects

Disadvantages of FDDS: ^[27]

- The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach.
- Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
- High variability in gastric emptying time due to its all (or) non-emptying process.
- Patients should not be dosed with floating forms just before going to bed.
- Floating system is not feasible for those drugs that have solubility (or) stability problem in gastric fluids.
 - The dosage form should be administered with a minimum of glass full of water (200-250 ml).
 - The drugs, which are absorbed throughout GIT, which under go first-pass metabolism (Nifedipine, Propranolol etc.) are not desirable candidate.

MARKETED PRODUCTS OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Brand name	Delivery System	DRUG (dose)	Company Name
Valrelease®	Floating capsule	Diazepam (15 mg)	Hoffmann-LaRoche
Madorap® HBS (Prolopa® HBS)	Floating, CR cap	Benserazide (25 mg) and L-Dopa (100 mg)	Roche Products,USP
Liquid Gaviscon®	Effervescent Floating liquid alginate preparations	Al hydroxide (95 mg), Mg Carbonate (358 mg)	GlaxoSmithkline, India
Topalkam®	Floating liquid alginate preparation	Al-Mg antacid	Pierre Fabre Drug, France
Almagate Flot Coat®	Floating dosage form	Al-Mg antacid	Pierre Fabre Drug, France
Conviron®	Colloidal gel forming FDDS Bilyer floating capsule	Ferrous Sulphate	Ranbaxy, India
Cytotech®	Bilayer Floating Capsule	Misoprostol (100µg/200µg)	Pharmacia, USA
Cifran OD®	Gas-generating floating form	Ciprofloxacin (1 gm)	Ranbaxy, India

CONCLUSION

Developing an efficient FDDS is a real challenge and the drug delivery system must remain for a sufficient time in the stomach. Various techniques and approaches have been employed to develop FDDS has emerged as one of the most promising gastro-retentive drug delivery system. The FDDS has an additional advantage for drugs that are absorbed primarily in the upper part of the GIT, *i.e.*, the stomach, duodenum, and jejunum. Recently many drugs have been formulated as floating drug delivery systems with an objective of sustained release and restricting the region of drug release to stomach. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The most important criteria which has to be looked into for the productions of a floating drug delivery system is that the density of the dosage form should be less than that of gastric fluid. And hence, it can be concluded that these dosage forms serve the best in the treatment of diseases related to the GIT and for extracting a prolonged action from a drug with a short half life.

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