World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

FLOATING DRUG DELIVERY: AN OVERVIEW

Juno S.*, Subash Chandran M. P., Prasobh G. R., Anu A. L., Subodh S. Satheesh and Pooja Nair K. R.

Department of Pharmaceutics, SreeKrishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India. 695502.

***Corresponding Author: Juno S.**
Department of Pharmaceutics, SreeKrishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India. 695502.

Article Received on 30/10/2019 **Article Revised on 20/11/2019** **Article Accepted on 10/12/2019**

ABSTRACT

Oral controlled release delivery systems are programmed to deliver the drug in predictable time frame that will increase the efficacy and minimize the adverse effects and increase the bioavailability of drugs. It is most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Recent technological and scientific research has been devoted to the development of rate controlled drug delivery systems to overcome physiological adversities such as short gastric residence times and unpredictable gastric emptying times. Differences in gastric physiology such as gastric pH and motility exhibit both intra and inter subject variability demonstrating significant impact on gastric residence time and drug delivery behavior. This triggered an increased interest towards formulation of novel delivery systems which retained in the stomach for prolonged and predictable period of time. Several approaches such as floating drug delivery systems (FDDS), swelling and expanding systems, bioadhesive systems, modified shape systems, high density systems or other delayed gastric emptying devices have been discovered till now. FDDS are of particular interest for drugs that are locally active and have narrow absorption window in stomach or upper small intestine, unstable in the intestinal or colonic environment, and exhibit low solubility at high pH values. This review article is in pursuit of giving detailed information on the pharmaceutical basis of their design, classification, advantages, *in vitro* and *in vivo* evaluation parameters, and the future potential of FDDS.

KEYWORDS: Floating drug delivery, Gastric pH, Swelling, Bioadhesive, Dosage form.

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. 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.[1] 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. The gastro intestinal tract (GIT) is the major route of drug delivery to the systemic circulation. Oral controlled release dosage forms are not 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.[2]

Floating drug delivery systems (FDDS) are those systems which have a bulk density less than gastric fluids and because of this, these systems remains 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.[3]

Basic GIT Physiology

Anatomically the stomach is divided in to three regions Fundus, Body and Antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested materials, where as the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions.3 Gastric emptying occurs in both the fasting and fed states. During the fasting state an interdigestive series of electrical events take place which cycle both through stomach and intestine every 2-3 hrs, which is called as interdigestive myloelectric cycle or migrating myloelectric cycle (MMC) which is further divided in to four phases.[4]

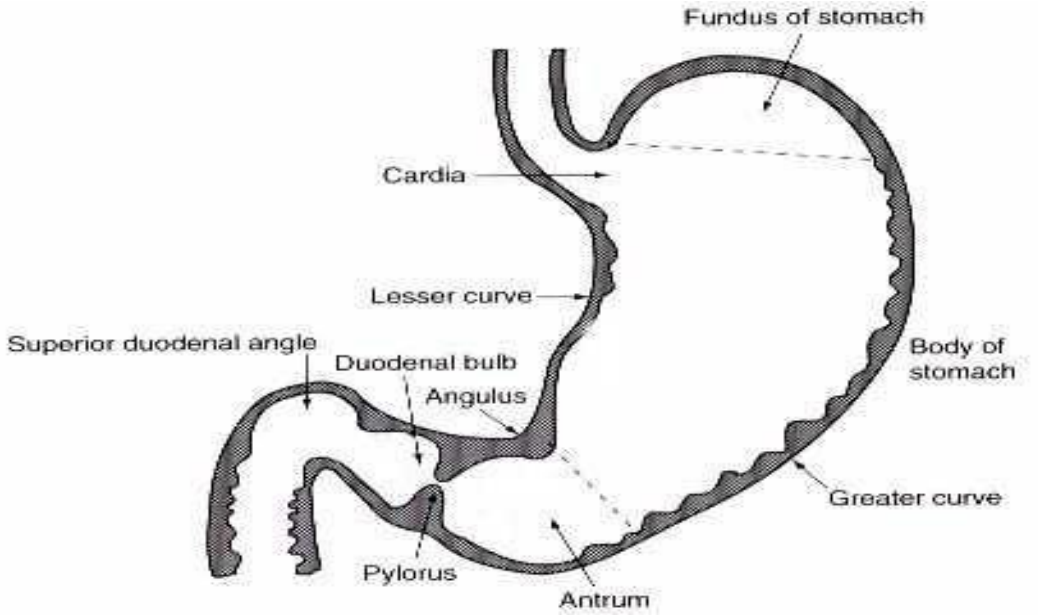

Figure 1: Anatomy of stomach.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state which is also termed as digestive motility pattern.

- Phase 1-(Basic phase)-last from 30-60 minutes with rare contractions.
- Phase 2-(Preburst phase)-last for 20-40 minutes with intermittent action potential and contractions.
- Phase 3-(Burst phase) - last for 10-20 minutes which includes intense and regular contractions for short period.
- Phase 4-last for 0-5 minutes and occurs between phase 2 and 1 of 2 consecutive cycles.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state which is also termed as digestive motility pattern.[5]

Mechanism of Floating Systems

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.[6] 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 intra gastric buoyancy capability variations.

F= F buoyancy - F gravity
(D f - D s) g v

Where, F = Total vertical force,
Df = fluid density,
Ds = object density,
v = volume

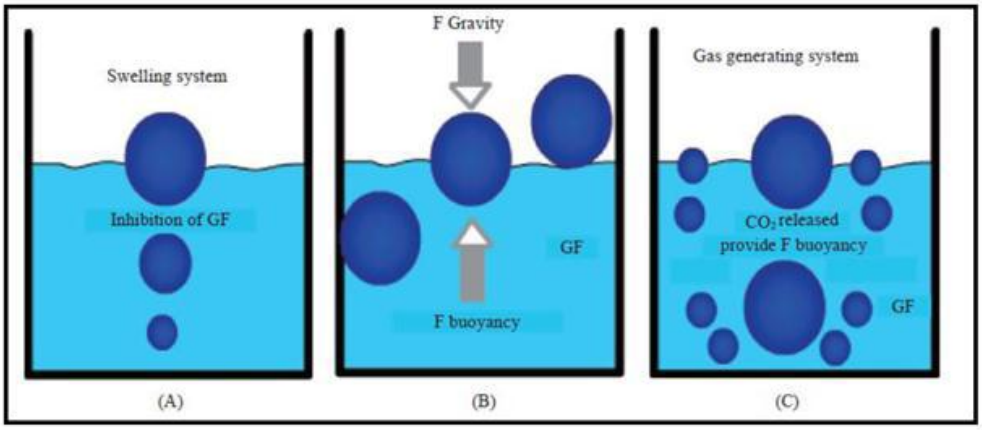

Fig: 2 Mechanism of Floating Systems.

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.[7]

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.[8]

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.[9] It should maintain its structural integrity and should constantly release the drug .The solubility of chlordiazepoxide hydrochloride 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.[10] 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.[11]**ASS**

Classification of Floating Drug Delivery System.[12,13,14]

A) Effervescent System

These are matrix types of systems prepared with the help of swellable polymers (methylcelluose 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.

Intragastric floating gastrointestinal drug delivery system

This system can be made to float in the stomach, because of floating chamber, which may be a vacuum of 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.[15] 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.[16]

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 isan 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.[17]

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.[18] 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.[19]

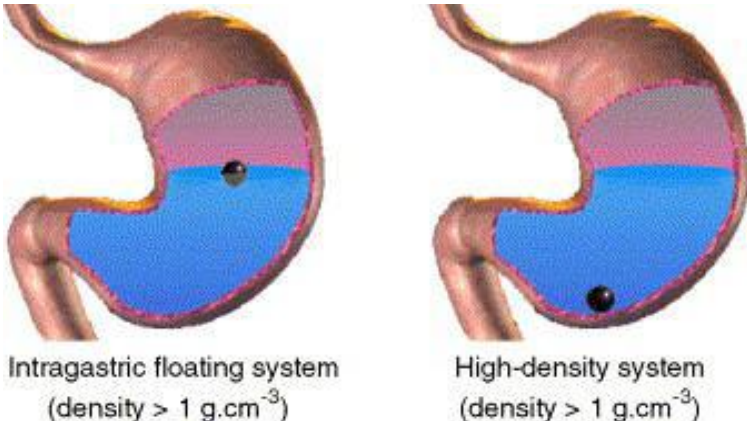

Fig. 3: Diagram of Gastroretentive drug delivery system (low density and high density systems).

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 barrier layers and one drug layer.[20] 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.[21] 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 shelf. 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[22]

- 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 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.

Advantages of Fdds[23]

- Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.
- FDDS are advantageous for drugs meant for local action in the stomach eg: Antacids
- FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhoea to keep the drug in floating condition in stomach to get a relatively better response.
- Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.
- The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts, Antacids.
- 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 metabolized in the upper GIT.

Disadvantages of Fdds[23]

- Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
- Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.
- One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently.
- These systems also require the presence of food to delay their gastric emptying.
- 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.

Factors Affecting Gastric Residence Time of Fdds

There are several factors that can affect gastric emptying of an oral dosage form which include density, size and shape of dosage form, feeding state, biological factors such as age, gender, posture, body mass index, disease state etc.

Effect of Dosage Form Size & Shape

Small size tablets are emptied from the stomach during the digestive phase while large size units are expelled during the house keeping waves found that floating unit with a diameter equal or less than 7.5 mm had larger gastric residence time (GRT) compared to non-floating units but the GRT was similar for floating and non-floating units having a large diameter of 9.9 mm.[24] They found that GRT of non-floating units were much more variable and highly dependent on their size which are in the order of small < medium < large units. Moreover, in supine subjects, size influences GRT of floating and non-floating form. Tetrahedron and ring shaped devices have a better GRT as compared with other shapes.

Gender, Posture & Age

Mean ambulatory GRT in males (3.4±0.6 hour) is less compared with their age and race-matched female counterparts (4.6±1.2 hour) regardless of their weight, height and body surface. Women emptied their stomach at a lower rate than men even when hormonal changes due to menstrual cycle were minimized. The mean GRT in the supine state (3.4±0.8 hour) was not stastically significant from that in the upright, ambulatory state (3.5±0.7 hour). In case of elderly, the GRT was prolonged especially in subject more than 70 years old (mean GRT – 5.8 hour).

Effect of Food & Specific Gravity

To float FDDS in the stomach, the density of dosage form should be less than gastric content i.e.1.0 g/cm3. Since, the bulk density of a dosage form is not a sole measure to describe its buoyant capabilities because the magnitude of floating strength may vary as a function of time and gradually decrease after immersing dosage form into fluid as a result of development of its hydrodynamic equilibrium. Various studies have shown the intake of food as main determinant of gastric emptying rather than food. Presence of food is the most important factor effecting GRT than buoyancy.[25] GRT is significantly increased under fed condition since onset of MMC is delayed. Studies show that GRT for both floating and non-floating single unit are shorter in fasted subjects (less than 2 hour), but significantly prolonged after a meal (around 4 hour).

Nature of Meal & Frequency of Food

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to fed state, to increase gastric emptying rate and prolonging the drug release. Diet rich in protein and fat can increase GRT by 4-10 hours.

Type of Formulation

Multiple unit formulation show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profile or containing incompatible substances and permit a large margin of safety against dosage form failure compared with single unit dosage form.

Table 1: Drugs used in the formulations of stomach specific floating dosage forms

Si. No.	Dosage Forms	Drugs
1.	Floating microspheres	Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen30, Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol , Tranilast.31,32
2.	Floating granules	Diclofenac sodium, Indomethacin and Prednisolone.
3.	Films	Cinnarizine33, Albendazole.
4.	Floating tablets and Pills	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin trihydrate, Atenolol, Fluorouracil, Isosorbide mononitrate34, Para- aminobenzoic acid, Piretanide35, Theophylline, Verapamil hydrochloride, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol36, pentoxyfilline and Diltiazem HCl.
5.	Floating Capsules	Chlordiazepoxide hydrogen chloride, Diazepam37, Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid38 and Pepstatin, and Propranolol.

Methods For Preparing Floating Dosage Form[25,26]

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.

Applications of Floating Drug Delivery Systems[27]
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.

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.

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.

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.

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. This Pharmacodynamic aspect provides the rationale for GRDF formulation for betalactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

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.

Future Potential
- Floating dosage form offers various future potential as evident from several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying.
- Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability.
- Buoyant delivery system considered as a beneficial strategy for the treatment of gastric and duodenal cancers.
- The floating concept can also be utilized in the development of various anti-reflux formulations.
- Developing a controlled release system for the drugs, which are potential to treat the Parkinson's disease.

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extend the time for drug absorption. FDDS promises to be a potential approach for gastric retention. Number of commercial products and patents issued in this field are the evidence of it. The aim is to improve the bioavailability of the drug with narrow absorption window in gastrointestinal tract region. By prolonging the drug resident time in GI region improves the solubility of drug that is less soluble in high PH and reduces drug waste, reduction in plasma level fluctuation. 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.

REFERENCES

1. Jain NK. Progress in Controlled and Novel Drug Delivery Systems. First Ed. CBSS. Gopalakrishnan. Journal of Pharmaceutical Science and Technology. Publishers and Distributors, New Delhi, Bangalore, 2004; 3(2): 84-85.
2. Goyal M, Prajapati R, Purohit KK and Mehta SC. Floating drug delivery system, Journal of current pharmaceutical research, 2011; 5(1): 7-18.

3. Klausner EA, Sara E, Lavy E, Friedman M and Hoffman A. Novel levodopa gastro-retentive dosage form: in-vivo evaluation in dogs. J. Control. Release, 2003; 117-126.
4. Kale RD and Tayade PT. A multiple unit floating drug delivery system of Piroxicam using Eudragit polymer. Indian J PharmScie, 2007; 69(1): 120- 123.
5. Sangekar S. Evaluation of effect of food and specific gravity of the tablets on gastric retention time Int J Pharm, 1987; 35(3): 34-53.
6. Moursy NM, Afifi NH, Ghorab DM and El-Saharty Y. Formulation and evaluation of sustained release floating capsules of Nicardipine hydrochloride. Pharmazie, 2003; 58: 38-43.
7. Kamalakkannan V, Pyratchikody A, Viswanadhan VP, "Enhancement of Drugs bioavailability by Floating Drug Delivery System-A Review.'' Int. J. Drug Delivery, 2011; 3(4): 558-570.
8. Geetha A, Rajendrakumar J. A Review on floating drug delivery system. Int. J. Pharmaceutical Research & Biomedical Analysis, 2012; 1(1): 1-13.
9. Devereux, JE; Newton, JM and Short, MB "The influence of density on the gastrointestinal transit of pellets", J Pharm Pharmacol, 1990; 42(7): 500-501.
10. Bolton, S and Desai, S. US 4,814,179, 1989.
11. Gupta, P; Virmani, K and Garg, S. "Hydrogels: From controlled release to pH responsive drug delivery", *Drug Discovery Today*, 2002; 7(10): 569-579.
12. Groning, R and Heun, G, "Dosage forms with controlled gastrointestinal transit", Drug Dev Ind Pharm, 1984; 10: 527-539.
13. R. Talukder and R. Fassihi, Gastroretentive Delivery Systems: A mini Review. Drug Development and Industrial Pharmacy, 2004; 30(10): 1019-1028.
14. R. Hejazi and N. Amiji, Stomach specific anti *H.Pylori* therapy. I: Preparation and characterization of tetracycline of a floating multiple unit capsule, a high density loaded chitosan microspheres. Int. J.Pharm, 2002; 235: 87-94.
15. M P Cooerman, P Krausgrill, K J Hengels, Local gastric and serum amoxicillin concentration after different oral application forms. Antimicrob Agents Chemother, 1993; 37: 1506150g.
16. B S Dave, A F Amin, M Patel, Gastroretentive dru delivery system of Ranitidine HCl formulation and in vitro evaluation. AAPS PharmSciTech, 2004; 5; 1- 10.
17. T T Fell, Targeting of drugs and delivery systems to specific sites in the gastrointestinal tract. J Anat, 1996; 189: 517-519.
18. S K Sarna, Cyclic motor activity: migrating motor complex. Gastroenterology, 1985; 89: 894-913.
19. M Schemann and J H Ehlein, Mechanical characteristics of phaseII and phase II of the interdigestive migrating motor complex in dogs. Gastroenterology.1986; 91: 117-123.
20. I R Wilding, A J Coupe, S S Davis. The role of ϒ scintigraphy in oral drug delivery. Adv Drug Deliv Rev, 1991; 7: 87-117.
21. L Shargel, A Yu, Applied Biopharmaceutics and pharmacokinetics, 4th ed.; Appleton and Lange; Philadelphia, 1999.
22. A H El-Kamel, M S Sokar, S S Al Gamal, V F Naggar, Preparation and evaluation of ketoprofen floating oral delivery system. Int J Pharm, 2001; 220: 13-21.
23. S Garg, S Sharma, Gastroretentive drug delivery systems. Business briefing: Pharm Tech, 2003; 160-166.
24. R Khosla, L C Feely, S S Davis, Gastrointestinal transit of non-disintegrating tablets in fed subjects. Int J Pharm; 1989; 53: 107-17.
25. C H Kutchai, The gastrointestinal system. In principal of physiology; 2nd Ed.; MR Berna, M N Levy; Eds.; Mosby Year book;St. Louis MO, 1996; 652-686.
26. S M Reddy, V R Sinha, D S Reddy, Novel and colonspecific drug delivery system for pharmacotherapy of peptide and non-peptide drugs. Drugs Today, 1999; 35(7): 537-580.
27. P Mojaverian, P H Vlasses, P E Kellner, M L Rocci. Effect of gender, posture and age on gastric residence time of an indigestible solid: Pharmaceutical considerations. Pharm Res, 1998; 5(10): 639-643.