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Review article

A comprehnsive review ongastro-retentive drug delivery system

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Abstract

The purpose of writing this review on Gastro-retentive drug delivery systems (GRDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The Physiological problems like short gastric residence time and unpredictable gastric emptying time were overcome with the use of floating dosage forms which provide opportunity for both local and systemic effect. Floating drug delivery system enable prolonged and continuous input of the drug to the upper part of the gastro retention tract and improve the bioavailability of medication that is characterized by a narrow absorption window. GRDDS have bulk density less than gastric fluids that have sufficient buoyancy to float over the gastric contents and remain in the stomach for longer duration of time without affecting gastric emptying rate. Various attempts have been made to develop gastro retentive delivery systems such as high density system, swelling, floating system. In floating multiple unit and single unit system are design and their classification and formulation aspect is cover in detail. Floating dosage forms can be prepared as tablets, capsule by adding suitable ingredients with excipients like hydrocolloids, inert fatty materials and buoyancy increasing agents. Various categories of drugs like antacids, antidiabetic, antifungal and anticancer drugs are formulated into FDDS. FDDS have bulk density less than gastric fluids that have sufficient buoyancy to float over the gastric contents and remain in the stomach for longer duration of time. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form and the future potential of FDDS.

Keywords: Gastro-retentive drug delivery systems, Effervescent, Non-effervescent, swelling index.

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1. Introduction

Floating drug delivery systems (FDDS) are aimed to retain the drug in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids.[1] The principle is very simple i.e., to make the dosage form less dense than the gastric fluids so that it can float on them. Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient 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. After release of drug, the residual system is emptied from the stomach. This result an increased gastric residence time and a better control of the fluctuations in plasma drug concentration. 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 [2].

Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substance. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract and drugs that are less soluble in or are degraded by the alkaline pH may benefit from prolonged gastric retention. In addition, for local and sustained drug delivery to the stomach and proximal small intestine to treat certain conditions, prolonged gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability and therapeutic efficacy, and possible reduction of dose size [3].

Basic Gastrointestinal Tract Anatomy and Physiology

Basically stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus

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and body acts as a reservoir for undigested material, the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions [4].

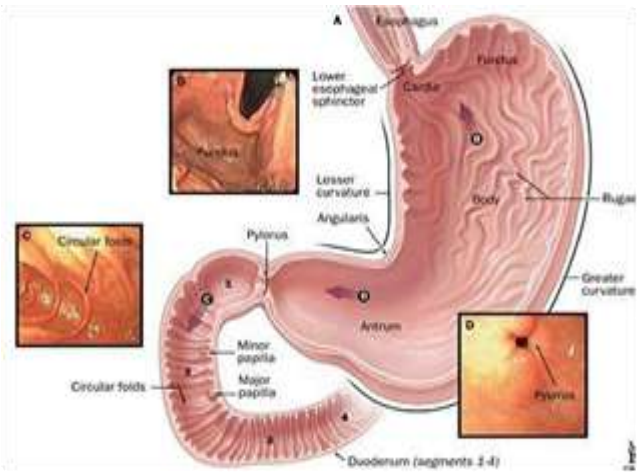


Fig no 1: Anatomy of stomach.

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 [5]. This is called the inter-digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases [6].

Phase I (basal phase)-Lasts from 40 to 60 minutes with rare contractions.

Phase II (pre-burst phase)-Lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

Phase III (burst phase) -Lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

Phase IV-Lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate [7]. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

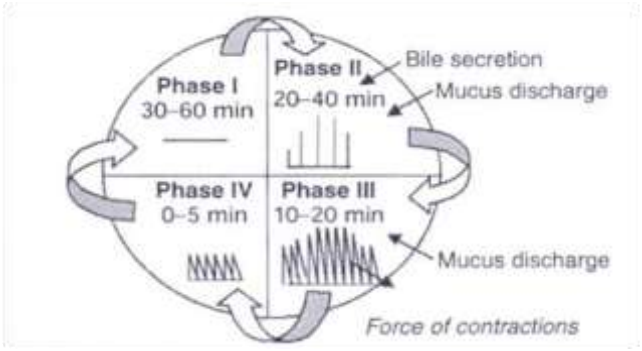


Fig no 2: Motility pattern in GIT.

Advantages of Floating Drug Delivery System.

Floating dosage systems are important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery [8&9]. These advantages include:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
6. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
7. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
8. Treatment of gastrointestinal disorders such as gastro esophageal reflux.
9. Simple and conventional equipment for manufacture.
10. Ease of administration and better patient compliance.
11. Site-specific drug delivery.

Disadvantages of floating drug delivery system

1. 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 [10].

2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
3. The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
4. Some drugs present in the floating system causes irritation to gastric mucosa.
5. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed.

Limitations of GRDDS

1. The residence time in the stomach depends upon the digestive state. Hence, FDDS should be administered after the meal.
2. The ability to float relies in the hydration state of the dosage form. In order to keep these tablets floating In vivo, intermittent administration of water (a tumbler full, every 2 hrs.) is beneficial.
3. The ability of drug to remain in the stomach depends upon the subject being positioned upright.
4. FDDS are not suitable for the drugs that have solubility or stability problems in the gastric fluid.
5. Drug like Nifedipine is well absorbed along the entire GIT and undergoes significant first pass metabolism, but it is not a desirable candidate for FDDS since the slow gastric emptying may lead to the reduced systemic bio-availability.

Criteria selection of drug candidate for GRDDS.

- Absorption from upper GIT e.g. Ciprofloxacin.
- Drugs having low pKa, which remains unionized in stomach for better absorption.
- Drugs having reduced solubility at higher pH, e.g. Rosiglitazone maleate, captopril and chordiazepoxide.
- Local action as it seen in the treatment of *Helicobacter pylori* by Amoxicillin.
- The bioavailability of drugs that get degraded in alkaline pH can be increased by formulating gastro-retentive dosage forms, e.g. Doxifluridine, which degrades in small intestine.
- To minimize gastric irritation this may be sudden increase of drug concentration in the stomach, e.g. NSAID.

Drug candidates suitable for gastro retentive drug delivery system.

- Drugs which act primarily in the stomach. Ex. Antacids. [11]
- Drugs that are primarily absorbed from the stomach. Ex.Amoxicillin, [12]
- Drugs those are poorly soluble at alkaline pH.Ex.Verapamil, Diazepam, etc.
- Drugs with a narrow window of absorption. Ex. levodopa, Cyclosporine,etc.
- Drugs which are rapidly absorbed from the GIT. Ex. tetracycline
- Drugs that degrade in the colon. Ex. ranitidine, metformin, etc.
- Drugs that disturb normal colonic microbes. Ex. Antibiotics against Helicobacter pylori.

Polymers and other ingredients used in preparations of floating drugs:-

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 methylmethacrylate, Methocel K4M, Polyethylene oxide, β Cyclodextrin, HPMC 4000, HPMC 100, CMC, Polyethylene glycol, polycarbonate, PVA, Polycarbo-nate, 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 MandCarbopol.

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), calcium carbonate. [13]

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).

Effect of formulation variables on the floating properties of the gastric floating drug delivery system:-

Shoufeng Li *et.al* [14] continuously monitored the floating kinetics of floating drug delivery system using a continuous floating monitoring system which consisted of an electric balance interfacing with a computer. They studied the effect of several formulation variables, such as different types of HPMC, HPMC/Carbopol ratio, and addition of magnesium stearate. Addition of magnesium stearate significantlyimproved the floating capacity of GFDDS. HPMC of higher viscosity grades exhibited a greater floating capacity. For the polymer with same viscosity, i.e. K4M and E4M, the degree of substitution of functional group has not shown any significant contribution. A better floating behavior was observed at higher HPMC/Carbopol ratio. Carbopol appeared to have a negative effect on the

floating behavior of the GFDDS.

Patel *et.al*,[15] studied the effect of varying ratio of HPMC K4M to HPMC K100LV and SLS content on t50%, Q12, release rate constant and diffusion exponent. The release rate was higher at 1% SLS concentration compared to 2% SLS concentration and without SLS condition. This finding maybe owing to the solubilization effect of SLS at 1% level, which is not observed at 2%, drug may have beenentrapped in the micelle formation causing a decrease in rate of drug release.

Patel.*et.al*, [16] prepared floating tablets of carbamazepine by applying effervescent approach. Floating tablet of carbamazepine are prepared using polymers HPMC and ethyl cellulose. It was observed that as the amount of ethyl cellulose was increased in the formulation from 0% to 25%, the Flag decreased, whereas as the amount of HPMC K4M increased from 20% to 45%, the Flag increased, indicating that a high amount of HPMC K4M is undesirable to achieve low Flag.

Streubel *et.al*, [17] studied the effect of type of polymer (PMMA, EC, and Eudragit) on the floating properties of microsphere. The release rate was maximum with eudragit RS, than ethyl cellulose and minimal with PMMA, which could be due to the different permeability of the drug within these polymers. Eudragit RS and ethyl cellulose containing micro particle showed biphasic drug release; an initial burst effect followed by slower drug release phase. In contrast PMMA containing microparticles showed more sustained drug releases, which were not biphasic.

Narendra.*et.al*. [18] prepared bilayer floating tablets of Metoprololtartarate. Effect of formulation variables on drug release and floating time was studied. When the total polymer content-to-drug ratio increased, the drug release rate at 8 hours decreased, whereas floating time increased. Floating time also increased by increasing HPMC: SCMC (sodium carboxy methyl cellulose) ratio. The polymer grade was found to have no effect on floating time.

Tang *et.al*, [19] prepared floating alginate beads with calcium alginate, sunflower oil and drug. The alginate beads with oil addition were able to float over the medium for 24 hours under constant agitation, while non-oily beads could not. The buoyancy decreased for the beads with less oil inclusion or more drug incorporation. Thick coatings of eudragit also decreased buoyancy.

Sharma *et al*, [20] was prepared a multiparticulate floating drug delivery system, using porous calcium silicate (fluorite RE) and sodium alginate. Meloxicam was adsorbed on the fluorite RE was used to prepare calcium alginate beads. An increase in FLR quantity in beads resulted in an increasing in floating lagtime and decrease in sinking rate, probably because of the number of air trapped pores in beads increased with increase in FLR quantity.

Li*et.al*, [21] was developed a gastric system for oral controlled delivery of calcium. Three formulation variables, HPMC loading, citric acid loading and magnesium stearate loading were studied to know their effect on drug release and floating properties. All three-formulation variables significantly affected the drug release profile, whereas floating characteristic was affected by only HPMC loading.

Mechanism of Floating Systems

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing 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. Among these, the floating dosage forms have been most commonly used. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents (given in the Figure (a)), the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side (Figure b). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intra gastric buoyancy capability variations [22].

F = F buoyancy - F gravity

= (Df - Ds) gv

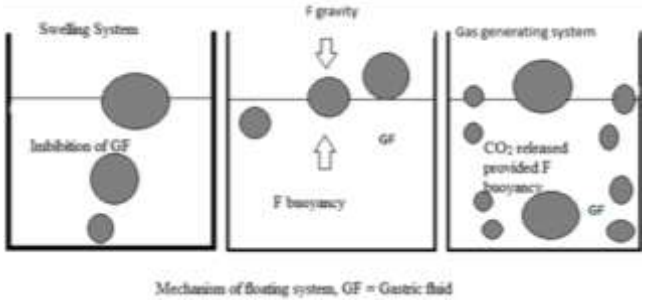
Where, F= total vertical force,

Df = fluid density,

Ds = object density,

v = volume and

g = acceleration due to gravity.



Mechanism of floating system, GF = Gastric fluid

Fig No 3: Mechanism of floating Tablet.

Classification of floating drug delivery systems (GRDDS):

(A) Effervescent FDDS
(I) Gas generating system
(II) Volatile liquid containing system
(B) Non- Effervescent FDDS
(I) Colloidal gel barrier system
(II) Microporous compartment system
(III) Floating microsphere
(IV) Alginate floating beads.
(C) Raft forming system.
(A) Effervescent System FDDS

These are matrix type of system. Prepared with the help of swellable polymer such as methylcellulose and Chitosan and various effervescent compounds. Ex: sodium bicarbonate, tartaric acid, citric acid.
These are formulated in such a way that when they come in contact with gastric content, $CO_2$is liberated and gets entrapped in swollen hydrocolloid which provides buoyancy to dosage form. The design of delivery system was based on swellable asymmetric triple layer tablet approach [23&24].

(I) Gas Generating Systems –

These are low density FDDS is based on the formation of CO_2 within the device following contact with body fluids. The materials are fabricated so that upon arrival in stomach, co2is librated by acidity of the gastric content and is entrapped in the gellified hydrocolloid this produce upward motion of the dosage form and maintain its buoyancy. Decrease in specific gravity cause dosage form to float on the chime. The co2 generating components may be intimately mixed within the tablet matrix in which case a single layer or bilayered is produced which contain the gas generating mechanism in one hydrocolloid containing layer and the drug in the other layer formulated for a sustained release effect [25, 26].

(II) Volatile liquid containing systems (Osmotically Controlled DDS) –

As an Osmotically controlled floating system, the device comprised of a hallow deformable unit that was convertible from a collapsed position after an extended period of time. A housing was attached to the deformable unit and it was internally divided into a first and second chamber with the chambers separated by an impermeable, pressure responsive movable bladder. The first chamber contain an active drug , while the second chamber contain a volatile liquid, such as cyclopentane or ether that vaporizes at physiological temperature to produce a gas, enabling the drug reservoir to float. To enable the unit to exit from the stomach, the device contained a bio-erodible plug that allowed the vapors to escape. [27]

B) Non-Effervescent FDDS:-

Non-Effervescent FDDS use a gel forming (or) swellable cellulose type of hydrocolloids, Polysaccharide, matrix forming polymer like polycarbonate, polymethacrylate and polystyrene. One of the formulation methods involves the mixing of the drug with gel forming hydrocolloids which swell in contact with gastric fluid after oral administration and maintains integrity of shape and a bulk density barrier, the air trapped by swollen polymer confer buoyancy to the dosage forms [28&29].

(I) Colloidal Gel Barrier Systems (Hydrodynamic Balanced Systems) –

Such system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption site in the solution form for ready absorption, this system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid e.g.(HPMC),polysaccharides and matrix forming polymer such as polycarbophil, polystyrene and polyacrylate. On coming in the contact with GI fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface [30].

(II) Microporous compartment systems-

This technology is based on the encapsulation of a drug reservoir inside a Microporous compartment with pores along its top and bottom walls. The peripheral wall of the drug reservoir compartment is completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the gastric fluid to an extent that it prevents their exist from the drug and carrier the dissolved drug for continuous transport across the intestine for absorption [31].

(III) Floating microspheres / micro balloons –

Hallow microspheres are considers as most promising buoyant system as they are more advantageous because of central hallow space inside the microsphere. Hallow microsphere is loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent Diffusion method [32].

(IV) Alginate beads / floating beads –

Multi-unit floating dosage forms have been developed from freeze calcium alginate [33]. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of

calcium chloride. Causing the precipitation of calcium alginate. The beads are than separated, snap-frozen in liquid nitrogen and freeze-dried at 400C for 24 h, leading to the formation of a porous system, this can maintain a floating force for over 12 h. these floating beads gave a prolonged residence time of more than 5.5 h.

(C) Raft forming systems:

Raft forming system have received much attention for the delivery of antacid and drug Delivery for gastro infection and disorders on contact with gastric fluid a gel forming Solution swells and forms a viscous cohesive gel containing entrapped co2 bubbles. Which Forms raft layer on top of gastric fluid which releases drug slowly in stomach. (Often used for gastro esophageal reflux treatment [34].

Factors Controlling Gastric Retention Of Dosage Forms:

Density of dosage forms

The density of a dosage form affects the gastric emptying rate and determines the location of the system in the stomach. A density of < 1.0 gm/cm3 is required to exhibit floating property. [35]Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach.

Shape of dosage form

Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. Mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units. The larger dosage form the greater will be the gastric retention time (GRT) due to larger size of the dosage form.

Size of dosage form.

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. [36]

Single or multiple unit formulation

Multiple unit formulations show a more predictable 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.

Food intake and its nature

Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form. The increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms [37].

Caloric content

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

7) Effect of gender, posture and age

- **Gender:** Generally females have slower gastric emptying rates than male. Meanamblatory GRT in males (3.4 ± 0.6 h) is less compared with their age and race matched female counterparts (4.6 ± 1.2 h), regardless of the weight, height and body surface).
- **Posture:**-The effect of posture does not have much more difference in the mean gastric retention time (GRT).
- **Age**:-In case of elderly persons, especially those over 70, have a significantly longer GRT so gastric emptying is slowed down.

Evaluation of floating drug delivery system

1. In-vitro dissolution study:

The test for in vitro drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37^0 C. Dissolution tests are performed using the USP dissolution apparatus. The samples were withdrawn periodically from the dissolution medium and replaced with the same volume of fresh medium each time, and then analyzed for their drug contents after an appropriate dilution. Recent methodology as described in USP XXIII states that the dosage unit is allowed to sink to the bottom of the vessel before rotation of blade is started. A small, loose piece of non-reactive material such as not more than a few turns of wire helix may be attached to the dosage units that would otherwise float. However, standard dissolution methods based on the USP or British Pharmacopoeia (BP) have been shown to be poor predictors of in vitro performance for floating dosage forms.

2. Buoyancy / Floating Test:

The time between the introductions of the tablet into the medium and its rise to upper one third of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time. These tests are usually performed in simulated gastric fluid or 0.1 mole.lit^{-1}HCl maintained at 37o C, by using USP dissolution apparatus containing 900 ml of 0.1 molar HCl as the dissolution medium. [38&39]

3. Swelling Study

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake [40&41]. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain, as given by the equation.

WU = (W1 – W0)/ W0 x 100
Where, **Wt**= Weight of dosage form at time t.
W0=Initial weight of dosage form.

4. In-vivo study:

For *in vivo* studies, X-Ray/Gamma Scintigraphy is the main evaluation parameter for floating dosage form. In each experiment, the animals are allowed to fast overnight with free access to water, and a radiograph is made just before the administration of the floating tablet to ensure the absence of radio-opaque material. Visualization of dosage form by X-ray is due to the inclusion of a radio-opaque material. The formulation is administered by natural swallowing followed by 50 mL of water. The radiographic imaging is taken from each animal in a standing position, and the distance between the source of X-rays and the animal should kept constant for all imaging, so that the tablet movement could be easily noticed. Gastric radiography was done at 30-min time intervals for a period of 5 h using an X-ray machine. Gamma Scintigraphy is a technique whereby the transit of a dosage form through its intended site of delivery can be non-invasively Imaged *in vivo* via the judicious introduction of an appropriate short lived gamma emitting radioisotope. The inclusion of a γ-emitting radionuclide in a formulation allows indirect external observation using a γ-camera or scintiscanner. But the main drawback of γ-Scintigraphy are the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique and the complicated and expensive preparation of Radiopharmaceutical [42].

Application of floating drug delievery system:-

1) Sustained Drug Delivery: Oral CR formulations are encountered with problems such as gastric residence time in the GIT. The HBS systems can be used to overcome these problems with which can remain in the stomach for long periods and they can float on the gastric contents because they have a bulk density <1. Passing from the pyloric opening is prohibited due to the systems are relatively bigger in size [43].

2) Enhanced Bioavailability: The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non- GRDF CR polymeric formulations. Related to absorption and transit of the drug in the gastrointestinal tract there are different processes, which act concomitantly to influence the magnitude of drug absorption [44].

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 the systemic exposure to the drug is limited. Along with this the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency e.g. Riboflavin and Furosemide [45&46].

4) Absorption Enhancement: Drugs which are having poor bioavailability are potential candidates to be formulated as floating drug delivery systems because of site specific absorption from the upper part of the GIT, there by maximizing their absorption [47&48].

5) Reduced Fluctuations of Drug Concentration: CRGRDF administration produces blood drug concentrations within a narrower range followed by continuous input of the drug 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. [48].

Conclusion

Drug absorption in the stomach is a variable process depending upon various factors such as gastric emptying, physiological factors etc. Floating delivery system can provide sufficient gastric retention which may help to provide sustained release dosage form. As a result it enhances absorption and minimizes fluctuation. Different approaches for GRDD are studied each having their own merits and demerits. Due to unpredictability of human GIT development of efficient GRDFs is a real challenge to pharmaceutical technological sector as the drug delivery system must remain for a sufficient time in the stomach which is not compatible with normal physiology of our body. In spite of its various limitations serious efforts are being done to commercialize this delivery system. In the future it is can be easily assumed that GRDD systems will become more popular in terms of delivering drug to the systemic circulation with improving efficiency of various type of pharmacotherapy's.

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