Available online on www.jadd.in

Journal of Advanced Drug Delivery 2014; 1(2); 96-113

ISSN: 2348-3792

Review Article

A Review On: Floating Drug Delivery System

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Available online: April, 2014

Abstract

Floating Drug delivery system are designed to prolong the gastric residence time after oral administration at particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. Conventional pharmaceutical dosage forms with narrow absorption window in the gastrointestinal tract have poor absorption. Therefore, gastroretentive drug delivery systems (GRDDS) have been developed, which offer the advantages in prolonging the gastric emptying time. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste and improves the drug solubility that are less soluble in a high pH environment. Several techniques such as floating drug delivery system, low density systems, raft systems, mucoadhesive systems, high density systems, superporous hydrogels and magnetic systems have been employed. Review focused on formulation aspect of effervescent floating drug delivery system with their evaluation techniques. The purpose of this comprehensive review is to compile the work going on this delivery system. Which provide the valuable information related to formulation aspect to achieve gastric retention and discussed the various factors affect and to overcome it

Keywords: Gastroretentive drug delivery systems, Floating tablet, effervescent, non effervescent.

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subjectto many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small

intestinal mucosa.[1] Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Gastroretensive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[2] These systems are also advantageous in improving GIT absorption of drug having narrow absorption windows and site-specific absorption limitations. These systems are useful in case of those drugs which are best absorbed in stomach for e.g. Albuterol. Hence, this review article focuses on the concurrent technological developments andadvancements in gastro retentive drug delivery system with special emphasis on theapproaches and the advantages of GRDDS. The uniform distribution of the floatingmicrospheres along the GIT could result in more reproducible drug absorption and reducedrisk of local irritation. This gave birth to oral controlled drug delivery and led to development of gastro retentive floating microspheres. [3]

Basic Gastrointestinal Tract Physiology[4,5]

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. 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 interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington.

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. 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.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

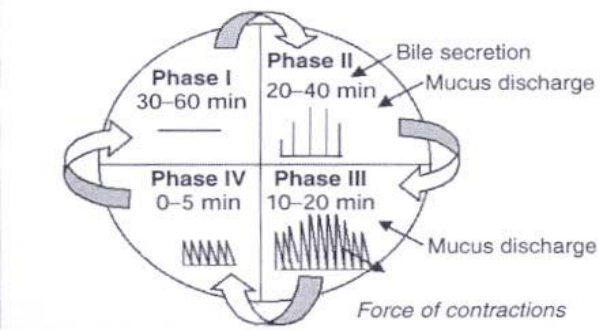

Fig. I : Motility pattern in GIT

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. 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.

FACTORS AFFECTING GASTRICRETENTION [6]

The gastric retention time (GRT) of dosage form is controlled by several factors that affect their efficacy as a gastroretentive system.

Density – GRT is a function of dosage form buoyancy that is dependent on the density.

Size – Dosage form units with a diameter of more than 9.5mm are reported to have an increased GRT.

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.

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

Fed or unfed state – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material fromthe stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

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.

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

Frequency of feed – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender – Mean ambulatory GRT in males (3.4hours) is less compared with their age and race-matched female counterparts (4.6 hours), regardless of the weight, height and body surface.

Age – Elderly people, especially those over 70, have a significantly longer GRT.

Posture – GRT can vary between supine and upright ambulatory states of the patient**.**15

Concomitant drug administration– Anticholinergics like Atropine and Propantheline, Opiates like Codeine andProkinetic agents like Metoclopramide and Cisapride.

- **Biological factors** – Diabetes and Crohn's disease.

Advantages of FDDS :-[7,8,9]

1. The Floating systems are advantageous for drugs meant for local action in the stomach. E.g. antacids.

3. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.

4. The Floating systems are advantageous for drugs absorbed through the stomach. . E.g. Ferrous salts, antacids.

5. 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.

6. 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.

Disadvantages of FDDS:-[7,8 ,9]

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.

2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.

3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

Classification of floating drug delivery system: - [9,10,11]

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, 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.

Floating drug delivery systems are classified depending on the use of two formulations

Variables: effervescent and non-effervescent systems.

FDDS can be divided into non effervescent and gas-generating system:

A) Non-effervescent systems:-

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the

mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxyl propyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

This system can be further divided into four sub-types:

1. Colloidal gel barrier system:-

Sheath and Tossounian first designated this 'hydro dynamically balanced system' **[13].** Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on theStomach content. This prolongs GRT and maximizes the amount of drug that reaches itsAbsorption sites in the solution form for ready absorption. This system incorporates a highLevel of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxylPropyl cellulose, hydroxyl ethyl cellulose, hydroxyl propyl methyl cellulose (HPMC), polysaccharides and matrix forming polymer such as poly carbophil, polyacrylate and Polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydratesAnd forms a colloid gel barrier around its surface.

2. Micro porous compartment system

This technology is based on the encapsulation of a drug reservoir inside a micro porous Compartment with pores along its top and bottom walls**.**[12]The peripheral walls of the drug

Reservoir compartment are 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 delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

3. Alginate beads

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate**.** [13]

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 ofCalcium alginate. The beads are then separated, snap-frozen in liquid nitrogen and freezedried at -40 º C for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.

4. Hollow microspheres / micro balloons

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel Emulsion solvent diffusion method. [14]

The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is

generated in the dispersed polymer Droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The micro balloon floated continuously over the surface of an Acidic dissolution media containing surfactant for more than 12 hours.

B) Effervescent systems:-

1. Gas generating systems:-

These buoyant systems utilize matrices prepared with swellable polymers such as methocel,

Polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citricAcid or tartaric acid).[15] The system is so prepared that upon arrival in the stomach; carbon dioxide is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate,Multiple unit floating pills that generate carbon dioxide when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and poly vinyl pyrrolidone coated with hydroxyl propyl methyl cellulose (HPMC) and floating systems based on ion exchange resinTechnology, etc.

(A) Intra gastric single layer floating tablets or Hydrodynamically Balanced System (HBS):-

"Hydro dynamically balanced systems" (HBS) are designed to prolong the stay of the dosageForm in the gastro intestinal tract and aid in enhancing the absorption. Such systems are bestSuited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. (Fig.II).

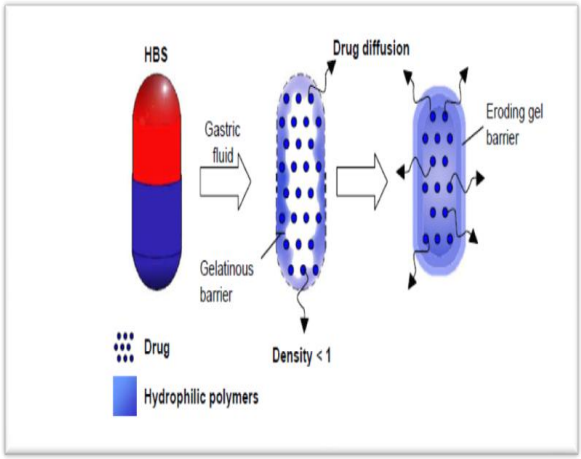

Fig.II :- Hydrodynamically balanced system

(B) Intra gastric bilayered floating tablets:

These are also compressed tablet as shown in figure 2 and contain two layer i.e.

1) Immediate release layer and

2) Sustained release layer.

2. Volatile liquid / Vacuum containing systems:-

(a) Intragastric floating gastrointestinal drug delivery system[16]

"Fluid- Filled Floating Chamber" type of dosage forms includes incorporation of a gas filled Floatation chamber into a micro porous component that houses a drug reservoir. Apertures or Openings are present along the top and bottom walls through

which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid or solid having an appropriate specific gravity and an inert behavior. The device is of swallowable size, remains a float within the stomach for a prolonged time and after the complete release the shell disintegrates, passes off to the intestine and is eliminated. (Fig.III)

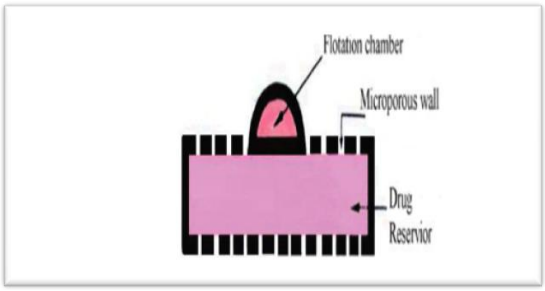

Fig III :- Intragastric floating gastrointestinal drug delivery system

(b) Inflatable gastrointestinal delivery systems:-

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oraladministration, the capsule dissolves to release the drug reservoir together with the inflatablechamber. The inflatable chamber automatically inflates and retains the drug reservoircompartment in the stomach. The drug continuously released from the reservoir into the gastric fluid. (fig.IV)

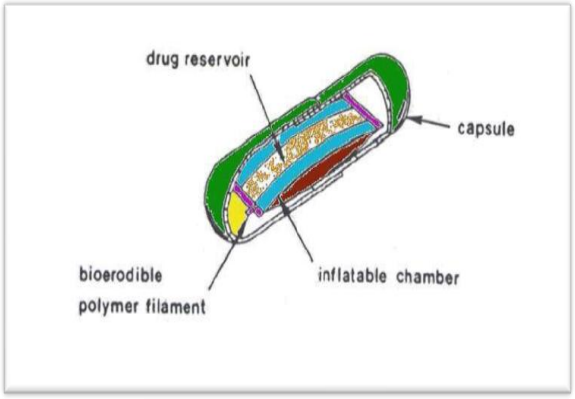

Fig IV :- Inflatable gastrointestinal delivery systems

(c) Intragastric osmotically controlled drug delivery system:-

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the

semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. The floating support is also made to contain a bio-erodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery System is then emptied from the stomach.

d) Intra gastric low density system:-[17]

In "Low-density Approach" the globular shells apparently having lower density than that of Gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage Form can also be obtained by using a fluid-filled system that floats in the stomach.

(e) Intragastric coated shell system:-[18]

In "Coated Shells" popcorn, poprice, and polystyrol have been exploited as drug carriers. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture. The polymer of choice can be either ethyl cellulose or hydroxyl propyl cellulose depending On the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration.

(f) Self correcting floatable drug delivery system:-[19]

"Self-correcting floatable asymmetric configuration drug delivery system" employs a disproportionate 3-layer matrix technology to control drug release. The 3-layer principle has been improved by development of an asymmetric configuration drug delivery system in order

To modulate the release extent and achieve zero-order release kinetics by initially maintaining

A constant area at the diffusing front with subsequent dissolution/erosion toward the completion of the release process. The system was designed in such a manner that it floated To prolong gastric residence time *in vivo*, resulting in longer total transit time within the Gastrointestinal tract environment with maximum absorptive capacity and consequently greater bioavailability. This particular characteristic would be applicable to drugs that have pH dependent solubility, a narrow window of absorption, and are absorbed by active transport from either the proximal or distal portion of the small intestine.

C. Expandable systems[20]

Expandable gastro retentive dosage forms (GRDFs) have been designed over the past 3 decades. They were originally created for possible veterinary use but later the design was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their GRT. After drug release, their dimensions are minimized with subsequent evacuation from the stomach.

Gastroretentivity is enhanced by the combination of substantial dimensions with high rigidity of the dosage form to withstand

the peristalsis and mechanical contractility of the stomach. Positive results were obtained in preclinical and clinical studies evaluating the GRT of expandable GRDFs. Narrow absorption window drugs compounded in such systems have improved *in vivo* absorption properties.

D. Bio/Muco-adhesive systems

Bio adhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site specific manner. This approach involves the use of bio adhesive polymers, which can adhere to the epithelial surface in the stomach . Gastric muco adhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of muco adhesion as a gastro retentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin, etc.

E. High-density systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm-3) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets 27. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–2.4g/cm3.

Mechanism of Floating Systems[20]

When microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy . Hollow microspheres of acrylic resins, Eudragit, polyethylene oxide, and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent developments. 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 are the mostly 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 prolonged period

of time. While the system is floating on the gastric contents (given in the Fig.), the drug is released slowly at the desired rate from the system. After release of drug, the residual system is eliminated 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 effect, a minimal level of floating force (F) is also required to maintain the buoyancy of the dosage form 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 a submerged object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and sustainability of floating forces produced in order to prevent any unforeseeable variations in intragastric buoyancy[19].(Fig:V)

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.

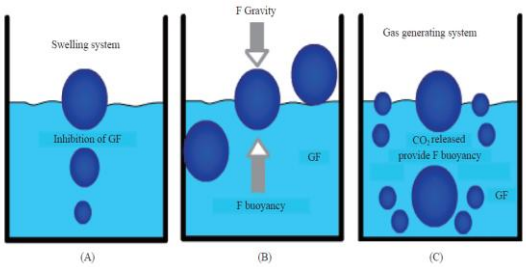

Figure V . Mechanism of floating systems, GF= Gastric fluid

SPECIFIC EVALUATION TESTS FOR FDDS: [21]

A) **GRANULES**

Floating drug delivery systems like floating tablets can be tested for various parameters. In case of tablets, pre-compressed tests and post-compressed tests exist.

Pre-compression tests:

The pre-compressed tests under tablets are similar to that of floating granules.

Angle of repose:"It is the maximum angle possible between the surface of a pile of powder and horizontal plain." It is a pre-compression parameter used for the determination of flow property ofpowders/ granules, represented by 'θ'. It can be determined by funnel method [22]. It can be determined by taking the accurately weighed powder blend and allowing it to flow freely through the funnel, fixed to a stand at definite height. The height (*h*) and diameter (*d*) of the powder cone are measured and the angle of repose can be calculated by the formula,

$$\tan \theta = h/r \text{ (or) } \theta = \tan^{-1} h/r$$

Tapped density & Bulk density:[22]Tapped and bulk densities are the pre-compression parameters used in assessing the compactness of the tablet. Loose bulk density (Db) is the ratio of weight of the untapped powder sample to its initial volume. Tapped bulk density (Dt) is the ratio of weight of the powder sample to its tapped volume

Bulk density (Db) = W/Vb.

Tapped Bulk density (Dt) = W/Vt.

Carr's Compressibility index and Hausnerratio: These are the pre-compression parameters that are measures of the relative importance of inter-particulate interactions. The Carr's compressibility index (also called as Carr's Consolidation index or Carr's Index) and Hausner's ratio can be calculated from the measured values of tapped density (Dt) and bulk density (Db), as follows, [23]

Carr's Compressibility index = (Dt – Db)/Dt x 100.

Hausner's ratio = Dt/Db.

Size &shape: Size and shape can be determined commonly, by using microscope. The particle size and shape plays a major role in determining solubility rate of the drugs and thus potentially its bioavailability. The dimensions of the formulation can be determined by using the suitable method like Vernier calipers, Screw gauge, Sieve analysis, Optical microscope, Air elutriation analysis, photoanalysis, electroresistance counting methods (Coulter counter), Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy, Air pollution emissions measurements etc.

EVALUATION OF FLOATING TABLETS[24]

Floating/buoyancy lag time

It is the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

Floating time

The test for floating time is usually performed in simulated gastric fluid maintained at 370 C, by using USP dissolution apparatus containing 900 ml of 0.1 N HCl as the dissolution medium. The time for which the dosage form floats is termed as the floating or flotation time.

Determination of In – Vitro Dissolution Study

Dissolution study is carried out in USP –II type dissolution apparatus (paddle type) .Dissolution study was performed at 50 rpm in 900ml 0.1(N) HCL. 5ml of sample was withdrawn at a predetermined interval and the volume of dissolution medium was maintained by adding same volume of dissolution medium. The absorption of withdrawn sample was measured spectro-photometrically with suitable dilution and the corresponding concentration was determined from the respective calibration curve.

Determination of drug content in tablets [25]

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of solvent, followed by stirring for 30 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectro photometrically in UV.

Determination of hardness of tablet

Randomly sampled twenty tablets in each batch of formulations should be used for the determination of hardness with the help of Monsanto type hardness tester.

Determination of weight variation

Twenty tablets selected at the random are weighed accurately and the average weight of the tablet is calculated. Then the deviation of individual weight from the average weight is calculated.

Determination of thickness of the tablet

The individual crown to crown thickness of ten tablets is determined using slide calipers for each batch.

X-Ray/Gamma Scintigraphy

It helps to locate dosage form in the GIT and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radiopaque material into a solid dosage form enables it to be visualized by X rays. Similarly, the inclusion of a γ- emitting radionucleide in a formulation allows indirect externalobservation using a γ-camera or scintiscanner.

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS:-[26, 27]

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

Sustained Drug Delivery:-

HBS systems can remain in the stomach for long periods and hence can release the drug over aprolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of G1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. Recently sustained release floating capsules of Nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared With conventional MICARD capsules (8 hours). Similarly a comparative study, between the Madopar HBS and Madopar standard formulation was done and it was shown that the drug was released up to 8 hours in vitro in the former case and the release was essentially complete in less than 30 minutes in the latter case. 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:-

These systems are particularly advantageous for drugs that are specifically absorbed from Stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide.Furosemide is primarily absorbed from the stomach followed by the duodenum. It has beenReported that a monolithic floating dosage form with prolonged gastric residence time was Developed and the bioavailability was increased. AUC obtained with the floating tablets wasApproximately 1.8 times those of conventional furosemide tablets. A bilayer-floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E1 used as a protectant of gastric ulcers caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, desired therapeutic levels could be achieved and drug waste could be reduced.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. E.g.: Furosemide and Riboflavin.

Absorption Enhancement:-

Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant increase in the bioavailability ofFloating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%).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.

Enhanced Bioavailability[(28)]

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

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.

Marketed Products of FDDS:-[7,29,30.](Table-I)

Sr.No.	Brand Name	Drug (Dose)	Company, Country	Remarks
1.	Modapar®	Levodopa (100 mg), Benserazide (25 mg)	Roche Products, USA	Floating CR capsule
2.	Valrelease®	Diazepam (15 mg)	Hoffmann LaRoche, USA	Floating capsule
3.	Liquid Gavison®	Al hydroxide (95 mg), Mg carbonate (358 mg)	Glaxo Smith Kline, India	Effervescent floating liquid alginate preparation
4.	Topalkan®	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid alginate preparation
5.	Conviron	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
6.	Cifran OD®	Ciprofloxacin (1 gm)	Ranbaxy, India	Gas-generating floating tablet
7.	Cytotec®	Misoprostal (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule
8.	Oflin OD®	Ofloxacin (400mg)	Ranbaxy, India	Gas generating floating tablet

9.	Glumetza	Metformin Hydrochloride	Depomed	Gas-generating floating tablet

Drugs Used In FDDS [7,29,30,31]

List of drugs explored for various floatable drug delivery systems**: (Table II)**

Sr.No.	Dosage Form	Drugs
1.	Microspheres	Aspirin, Grisiofulvin, p-nitroanilline, Ibuprofen, Terfinadine, Tranilast, Verapamil, Ketoprofen.
2.	Granules	Diclofenac sodium, Indomethacin, Predmisolone,*Cinnarizine, Diltiazem, Fluorouracil, Isosorbidemononitrate, Isosorbidedinitrate.*
3.	Films	Drug delivery Device.Cinnarizine,*Piretanide, Prednisolone, Quinidine gluconate*
4.	Powders	Several basic drugs.
5.	Capsules	ChlordiazepoxideHCl, Diazepam, Furosemide, L- Dopa, and benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic acid, Nicardipine, *Verapamil HCl.*
6.	Tablets/pills	Acetaminophen, Acetylsalicylic acid, Amoxicillin trihydrate, Ampicillin, Atenolol, Chlorpheniramine maleate, Cinnazirine, Diltiazem, Fluorouracil, Isosorbidemononitrate, Isosorbidedinitrate, p-aminobenzoic acid, Piretanide, Prednisolone, Quinidine gluconate, Riboflavin-5'-phosphate, Sotalol, Theophylline, Verapamil HCl. Furosemide, Ciprofloxacin, Pentoxyfillin, Captopril, Nimodipine, *Aspirin, griseofulvin, Ibuprofen, p-nitroaniline, Terfenadine, Tranilast.*

CONCLUSION:-

Dosage forms with a prolonged GRT will bring about new and important therapeutic options.They will significantly extend the period of time over which drugs may be released and thus prolong dosing intervals and increase patient compliance beyond the compliance level of existing CRDFs. Many of the "Once-a-day" formulations will be replaced by products with release and absorption phases of approximately 24 hrs. Also, GRDFs will greatly improve the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at gastric mucosa which are sustained over a large period. Finally, GRDFs will be used as carriers of drugs with the "absorption window. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing towards commercializing this technique.

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