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Floating Drug Delivery System A Novel Approach: An Overview

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ABSTRACT

Controlled release (CR) dosage forms have been extensively used to improve therapy with several important drugs. Oral controlled release and site specific drug delivery system has been of great interest in pharmaceutical field to achieve improved therapeutic advantage. Gastro retentive drug delivery system is one of such novel approaches to prolong gastric residence time, thereby targeting site specific drug release in the stomach for local or systemic effects. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the gastric emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Floating drug delivery systems are low-density systems that float over the gastric content and remain buoyant in the stomach for a prolonged period of time. They enhance drug bioavailability, reduce drug wastage and provide controlled drug delivery and better patient compliance. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single -unit and multiple unit floating systems, and their classification and formulation aspects are covered in detail.

Keywords: Controlled release (CR), Gastro retentive, Floating drug delivery.

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INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve promptly and then maintain a desired drug concentration.[1]Pharmaceutical companies worked with different pharmaceutical product types include products of different administration route (e.g., oral to parenteral), new specific functionality/delivery systems (e.g., immediate release tablet to modified release tablet) and different dosage forms of the same administration route (e.g., capsule to tablet, solution to suspension). [2] The oral ingestion is the predominant and most preferable route for drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drug. [3] Conventional oral controlled dosage forms suffer from mainly two adversities. The short gastric retention time (GRT) and unpredictable gastric emptying time (GET). A relatively brief GI transit time of most drug products impedes the formulation of single daily dosage forms. These problems can be overwhelmed by altering the gastric emptying. Therefore it is desirable, to formulate a controlled release dosage form that gives an extended GI residence time.[4] ime controlled oral drug delivery systems offer several advantages over immediate-release dosage forms, including the minimization of fluctuations in drug concentrations in the plasma and at the site of action over prolonged periods of time, resulting in optimized therapeutic concentrations and reduced side effects; a reduction of the total dose administered (while providing similar therapeutic effects) and a reduction of the administration frequency leading to improved patient compliance.[3]

Davis, in 1968 firstly described the concept of floating drug delivery systems (FDDS) after experiencing gagging or chocking by some persons, while swallowing medicinal pills. The researchers suggested that such difficulty could be overcome by providing pills having a density less than 1.0 gm/ ml, so that pill will float on water surface.[5]

Definition of FDDS

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. [6]

Gastrointestinal retention:

Gastro retentive 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. To successfully modulate the gastrointestinal transit time of a drug delivery system through floating drug delivery system (FDDS) For maximal gastrointestinal absorption of drugs and site specific delivery, one needs to have a good fundamental understanding of the anatomic and physiological characteristics of the human GIT.[7]

Basic GIT Physiology: [8]

Anatomically the stomach is divided in to three regions-Fundus, Body and Antrum (pylorus) (Fig.1).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. 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 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 (Figure 2).

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 (Figure 2). [8]

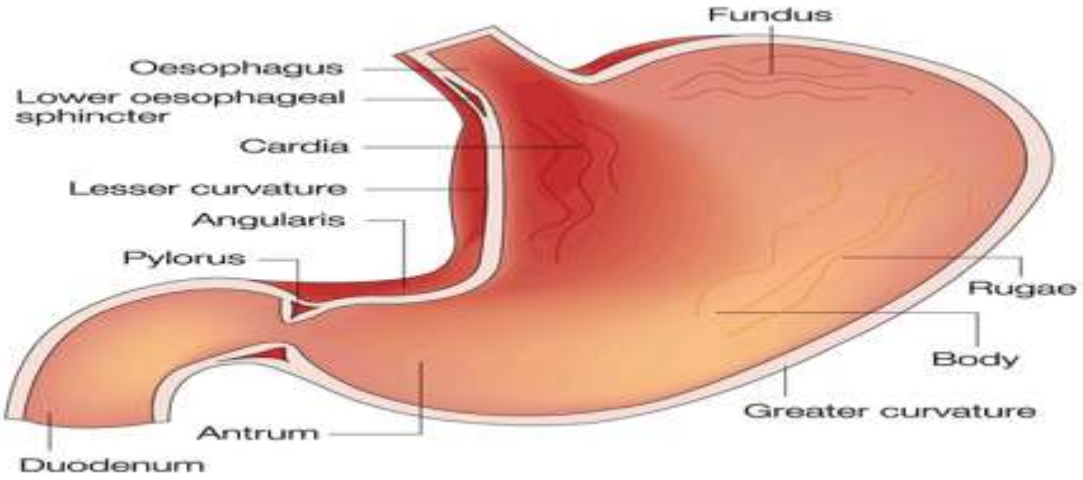

Figure 1: Structure of stomach [8]

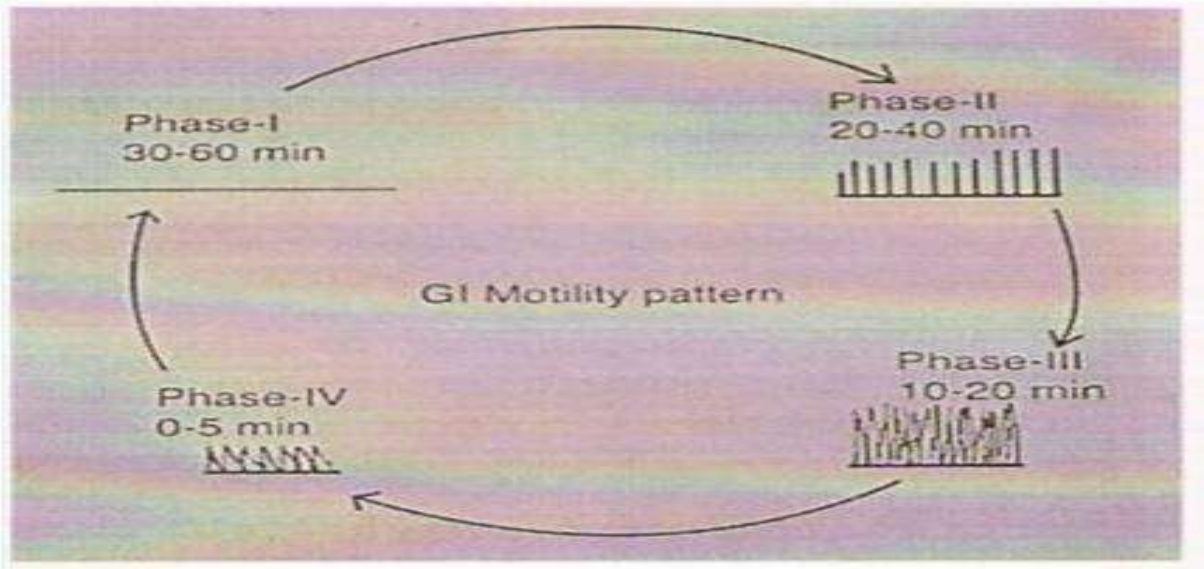

Figure 2: Gastrointestinal motility pattern [8]

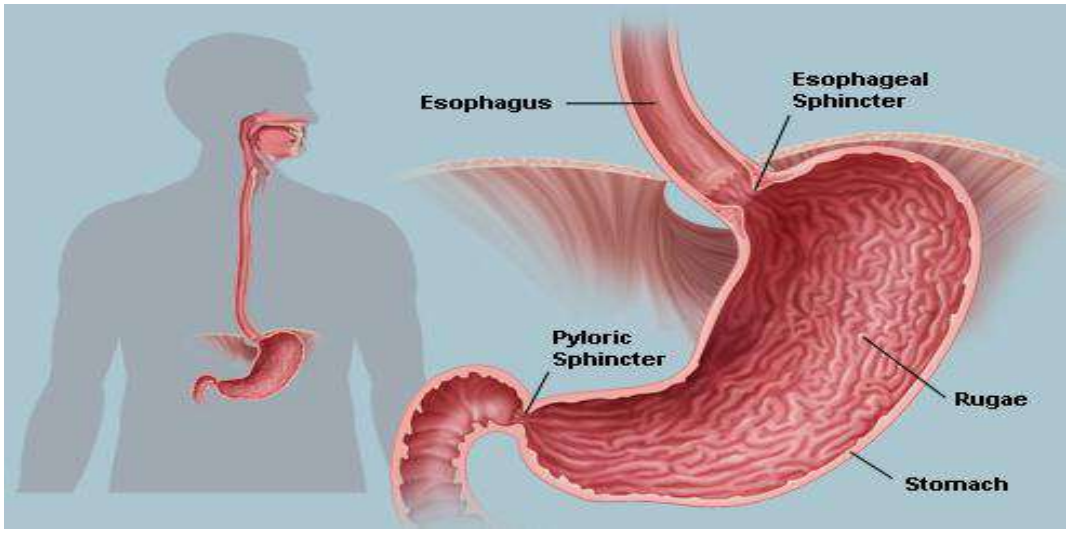

Figure 3: Gastro intestinal tract [8]

In fed conditions, only one phase (Phase IV) is present and continues as long as there is food in the stomach. It consists of regular and frequent contractions. These contractions are not severe as those in the third phase of fasted motility pattern. During fed state onset of IMMC is delayed resulting in slow down of gastric emptying [9,10]which is called postprandial motility.

FACTORS AFFECTING GASTRIC RESIDENCE TIME OF FDDS: [11]

FORMULATION FACTORS:

Size of tablets:

Retention of floating dosage forms in stomach depends on the size of tablets. Small tablets are emptied from the stomach during the digestive phase, but large ones are expelled during the house keeping waves. Floating and non-floating capsules of 3 different sizes having a diameter of 4.8 mm (small units), 7.5 mm (medium units), and 9.9 mm (large units), were formulated and analyzed for their different properties. It was found that floating dosage units remained buoyant regardless of their sizes on the gastric contents throughout their residence in the gastrointestinal tract, while the non-floating dosage units sank and remained in the lower part of the stomach. Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during digestive phase while the non-floating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase.

Density of tablets:

Density is the main factor affecting the gastric residence time of dosage form. A buoyant dosage form having a density less than that of the gastric fluids floats, since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. A density of less than 1.0g/ml i.e. less than that of gastric contents has been reported. However, the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy capabilities.

Shape of tablets:

The shape of dosage form is one of the factors that affect its gastric residence time. Six shapes (ring tetrahedron, cloverleaf, string, pellet, and disk) were screened *in vivo* for their gastric retention potential. The tetrahedron (each leg 2cm long) rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 hr.

Viscosity grade of polymer:

Drug release and floating properties of FDDS are greatly affected by viscosity of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 LV) were found to be more

beneficial than high viscosity polymers (e.g., HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity.

IDIOSYNCRATIC FACTORS:

Gender:

Women have slower gastric emptying time than do men. Mean ambulatory GRT in meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

Age:

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

Posture:

Upright position:

An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size. Floating dosage forms show prolonged and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus by antral peristaltic movements.

Supine position:

This position offers no reliable protection against early and erratic emptying. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally, these units may be swept away by the peristaltic movements that propel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects.

Concomitant intake of drugs:

Drugs such as prokinetic agents (e.g., metoclopramide and cisapride), anti Cholinergics (e.g., atropine or propantheline), opiates (e.g., codeine) may affect the performance of FDDS. The coadministration of GI-motility decreasing drugs can increase gastric emptying time16.

Feeding regimen:

Gastric residence time increases in the presence of food, leading to increased drug dissolution of the dosage form at the most favorable site of absorption. A GRT of 4-10 h has been reported after a meal of fats and proteins.

Suitable Drug Candidates For Gastro Retention: [12]

In general, appropriate candidates for CRGRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

Narrow absorption window in GI tract, e.g., riboflavin and levodopa.

Primarily absorbed from stomach and upper part of GI tract, e.g., calcium supplements, chlordiazepoxide and cinnarazine.

Drugs that act locally in the stomach, e.g., antacids and misoprostol.

Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole.

Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.

Drugs Those are Unsuitable for Gastro Retentive Drug Delivery Systems: [12]

Drugs that have very limited acid solubility e.g., phenytoin etc.

Drugs that suffer instability in the gastric environment e.g., erythromycin etc.

Drugs intended for selective release in the colon e.g., 5-amino salicylic acid and corticosteroids.

MECHANISM OF FLOATING SYSTEM: [13]

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 (Figure 4 (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 4(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 intragastric buoyancy Capability variations

F = F buoyancy - F gravity = (Df - Ds) g * v

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

g = acceleration due to gravity.

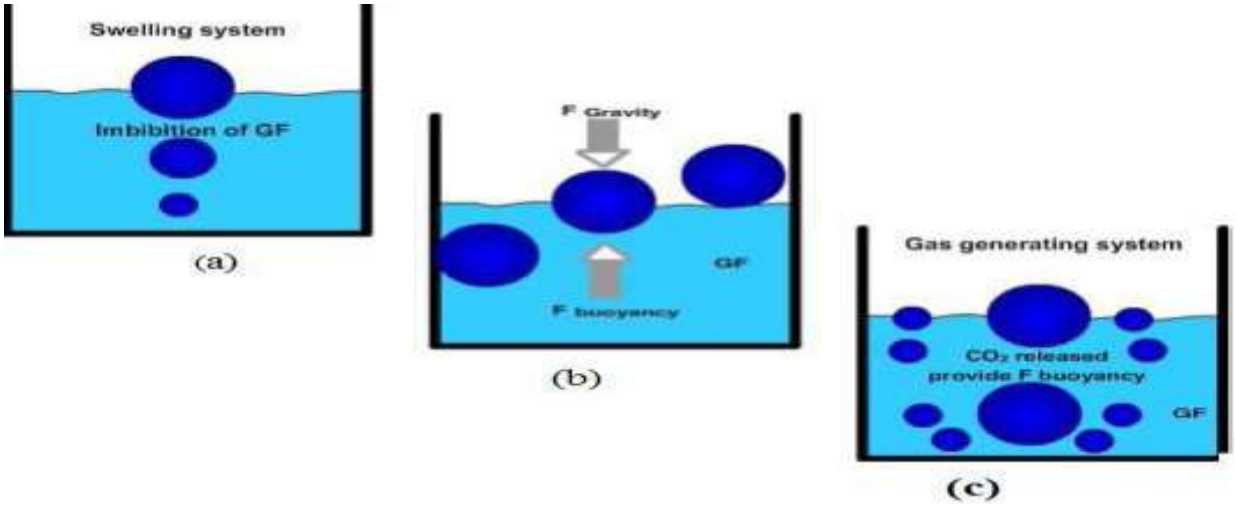

Figure 4: Mechanism of floating systems, GF= Gastric fluid [13]

FORMULATION EXCIPIENTS USED IN FDDS: [14]

Polymers:

The following polymers used in preparations of FDDS -HPMC K4 M, Calcium alginate, Eudragit S100, Eudragit RL, Propylene foam, Eudragit RS, ethyl cellulose, poly methyl methacrylate, Methocel K4M, Polyethylene oxide, β Cyclodextrin, HPMC 4000, HPMC 100, CMC, Polyethylene glycol, polycarbonate, PVA, 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 M and Carbopol.

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.

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

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

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

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

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

APPROACHES TO INCREASE GASTRIC RETENTION: [15]

Various new approaches have been worked out to improve the retention of oral dosage form in the stomach.

Swelling and expanding systems:

In this the dosage form can be retained in the stomach for a longer time by increasing the size so that it cannot be passed through the pylorus into the intestine. The dosage form should attain this large size once it is in the stomach and should also be strong enough to be able to withstand the powerful waves in the stomach. The swelling systems utilize swellable hydrocolloids as a means to achieve buoyancy. These hydrocolloids swell unrestrained via imbibitions of gastric fluid to an extent that it prevents the exit from the stomach. These systems are called as "plug-type systems" since they have a tendency to remain lodged near the pyloric sphincter. Expanding systems work on the principle that by the use of super porous hydrogels that expand dramatically when immersed in water, swell rapidly in the stomach, causing medication to move more slowly from stomach to intestine.

Bio/Mucoadhesive Systems:

The term bio/mucoadhesion implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion. Bioadhesive drug delivery systems (BDDS) are used to localize a delivery device in the lumen to enhance the drug absorption in a site specific manner. This approach helps to increase gastric residence time of the dosage forms binding them to gastric mucosa or epithelial cell surfaces. Thus it shows that the anionic polymers have better binding capacity than neutral or cationic polymers. The mechanism of bioadhesion is thought to be the formation of electrocution and hydrogen bonding at the mucus-polymer boundary. The adhesion is favored by rapid hydration. These bio-adhesive systems do not seem to be a very feasible solution as this bond formation is prevented by the acidic environment and thick mucus present in the stomach. Some of the excipients that are used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc. Some investigators have tried out a synergistic approach between floating and bioadhesion systems.

Modified shaped systems:

These dosage forms are larger than the pyloric opening and so they are retained in the stomach. There are some drawbacks associated with this approach which include permanent retention of rigid, large sized single unit forms can cause bowel obstruction, intestinal adhesion and gastroplasty.

Co-administration of gastric emptying delaying drugs:

This involves co- administration of a drug to delay gastric emptying together with a therapeutic drug. This has not received the favor of clinicians and regulatory agencies because of the questionable benefit-to-risk ratio associated with these devices.

Altered density dosage forms:

The density of the dosage forms influence GI transit time to a large extent compared to their diameter. GRT can be improved by altering the density i.e., low density floating systems and high density non-floating systems.

a) Low-density or floating drug delivery system:

This approach is based on the principle that the dosage form or substance, which has a density less than the gastric fluid (≈1.004g/cm^3) floats on the gastric contents. They also float due to the gaseous phase formed inside the system after they come in contact with the gastric environment. Floating systems release the drugs locally in the stomach and these are useful for poorly soluble or unstable drugs in intestinal pH. Various attempts have been made to develop floating systems, which will float in the gastric contents for a long time. These dosage forms are prepared by incorporating a high level of one or more gel forming hydrocolloids eg: hydroxy ethyl cellulose, hydroxy propyl cellulose, hydroxy propyl methyl cellulose and Sodium carboxy methyl cellulose into the formulation and then compressing these granules into a tablet or encapsulating into capsules. For the formulation of this device it must comply with the following criteria:

- It should have a proper structure to form a cohesive gel barrier.
- It must maintain lower specific gravity than that of the gastric contents.
- It should dissolve slowly enough to serve as a drug reservoir.

On contact with gastric fluid the hydrocolloid in this intragastric floating device start to become hydrated and forms a colloid gel barrier around its surface with thickness growing with time. This gel barrier controls the rate penetration of solvent into the device. It maintains a bulk density of less than 1 and thus remains buoyant in the gastric fluid inside the stomach for up to 6 hour.

Intragastric Floating Drug Delivery System (IGFDDS):

An IGFFDS can be made to float in the stomach by incorporating a floatation chamber, which may be a vacuum, filled with air or a harmless gas. This can be achieved by-

i) Inflatable Gastrointestinal Delivery System:

The residence time of the drug delivery device in the stomach can also be sustained by incorporation of an inflatable chamber, which contains liquid (e.g., ether) that gasifies at body temp which results the chamber to inflate in the stomach.

ii) Intragastric Osmotically Controlled Drug Delivery System:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device.

b) High Density or Non-floating Drug Delivery Systems:

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae near the pyloric region, which is the part of the stomach 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. Thus with pellets, the GI transit time can be extended from an average of 5.8–25 hours which depends more on density than the diameter of the pellets. This is achieved by formulating of dosage forms with the density that must exceed density of normal stomach content (≈1.004g/cm).Depending on the mechanism of buoyancy, two different methods like non-effervescent and effervescent systems have been used in the development of floating drug delivery systems (FDDS).

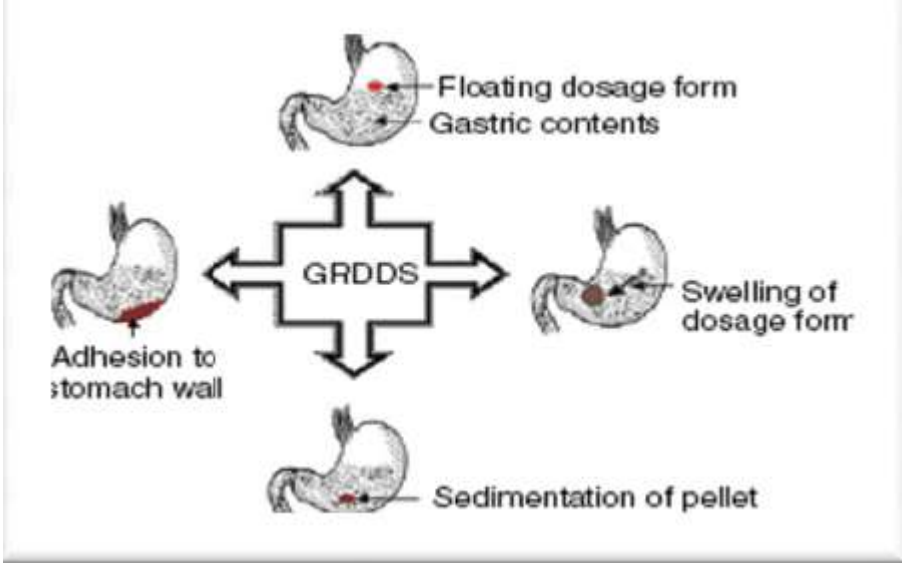

Figure 5: Techniques of GRDDS [16]

FLOATING DRUG DELIVERY SYSTEMS: [17]

These are oral dosage forms (capsule or tablet) that are designed to prolong the residence time of the dosage form within the GI tract . It is formulation of a drug and gel forming hydrocolloids meant to remain buoyant in stomach. This not only prolongs GI residence time but also does so in an area of the GI tract that would maximize drug reaching its absorption site in solution and hence, ready for absorption. The recent scientific and patent literature shows increased interest in academics and industrial research group regarding the

novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time.

TYPES OF FLOATING DRUG DELIVERY SYSTEMS: [18]

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

- Effervescent System
- Non-Effervescent System

Effervescent System:

Effervescent systems include use of gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.

These effervescent systems further classified into two types.

- Gas generating systems
- Volatile liquid/vacuum systems

Gas generating systems:

Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS):

These are formulated by intimately mixing the CO2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuation in plasma drug concentration.

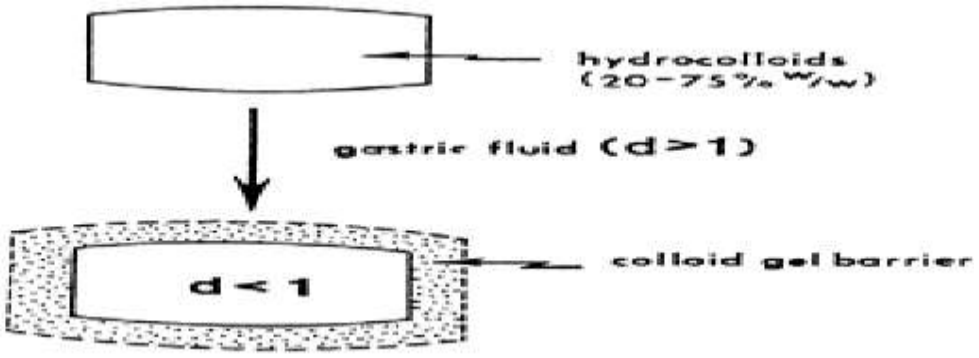

Figure 6: Intragastric floating tablet [18]

12.1.1.2 Intra Gastric Bilayed Floating Tablets:

These are also compressed tablet as shown in Fig and containing two layer i.e.(1)Immediate release layer (2) Sustained release layer.

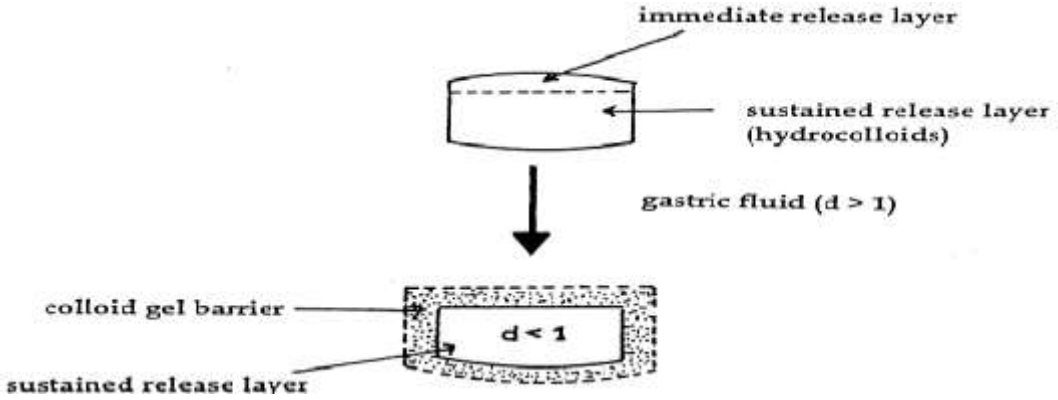

Figure 7: Intragastric floating bilayer tablet [18]

Multiple Unit Type Floating Pills:

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the systems.

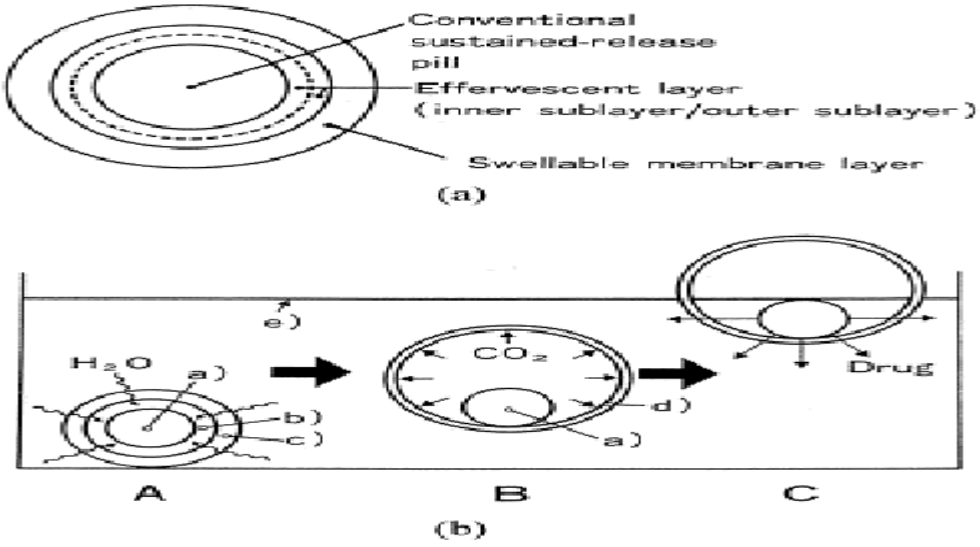

Figure 8: (a) Multiple-unit oral floating dosage system. (b)Stages of floating mechanism [18]

Volatile liquid / vacuum containing systems:

Intragastric Floating Gastrointestinal Drug Delivery System:

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment.

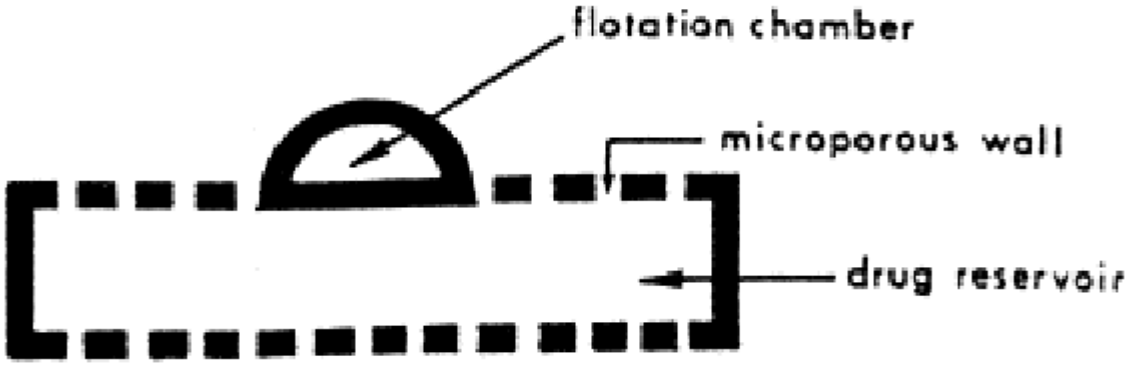

Figure 9: Intragastric floating drug delivery device [18]

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 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.

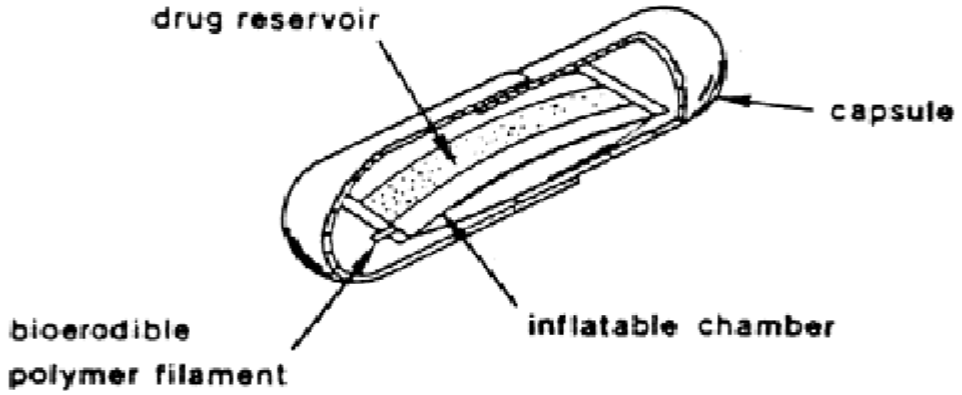

Figure 10: Gastro-inflatable drug delivery device [18]

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 semi-permeable membrane into osmotically active compartment to dissolve the osmotically salt. An osmotic pressure is then created which acts on the collapsible bag and in turn forces the bag 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 deflat the support. The deflated drug delivery system is then emptied from the stomach.

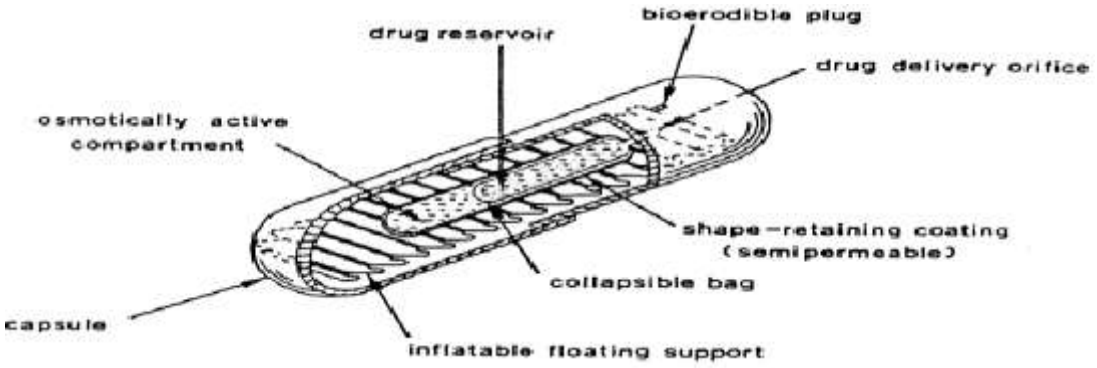

Figure 11: Intragastric osmotic controlled drug delivery system [18]

Non Effervescent Systems:

The non effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bio-adhesive polymer such as chitosan and carbopol. The various type of this systems are as follows:

Single layer floating tablets:

They are formulated by intimate mixing of drug with gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

Bilayer floating tablets:

A bilayer tablet contain two layer immediate release layer which release initial dose from

system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

Alginate beads:

Multi unit floating dosage forms are developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence, time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.

Hollow microspheres:

Hollow microspheres (microballons), loaded with drug in their outer polymer shells were prepared by a novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of drug and enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours in vitro.

Advantages of Gastroretentive Drug Delivery Systems: [19]

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.

Enhanced first-pass biotransformation:

In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

Sustained drug delivery/reduced frequency of dosing:

For drugs with relatively short biological half-life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

Targeted therapy for local ailments in the upper GIT:

The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while systemic concentrations, following drug absorption and distribution, are minimal.

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.

Improved selectivity in receptor activation:

Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

Reduced counter-activity of the body:

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

Extended time over critical (effective) concentration:

For certain drugs that have non-concentration dependent pharmacodynamics, such as etalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

Minimized adverse activity at the colon:

Retention of the drug in the GRDF 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 beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganisms resistance.

Site specific drug delivery:

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper 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.

Table 1: Marketed Products of GRDDS [20]

Brand Name	Drug	Company, Country	Remarks
Cifran OD®	Ciprofloxacin(1 gm)	Ranbaxy,India	Gas generating fioating tablets
Madopar®	Levodopa(100mg)	Roche products, USA	Floating controlled release capsule
Valrelease®	Diazepam(15 mg)	Hoffmann LaRoche,USA	Floating capsule
Topalkan®	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid alginate preparation
Oflin OD®	Ofloxacin(400 mg)	Ranbaxy,India	Gas generating floating tablets

METHODS OF MANUFACTURING: [21]

High-speed rotary tablet presses are mostly used. Different granulation technologies are available, ranging from dry granulation and wet granulation methods which include two-step granulation (granulating acid and alkali phase separately) to one-step granulation using water or organic solvents.

Wet Granulation:

The acid and carbonate parts of the effervescent formulation can be granulated either separately or as a mixture with water (crystal water of citric acid, liquid water, or water vapor), ethanol (possibly diluted with water), isopropanol, or other solvents.

When granulating either with solvents containing water or pure water, the effervescent reaction will start. Care must be taken to maintain adequate control of the process. Vacuum processing is often beneficial due to the ability to control the effervescent reaction and the drying process. Citric acid is moistened and added to the NaHCO3. Partial wet fusion occurs, and granules are formed by kneading in a suitable mixer. The granules are tableted while still damp, with the moist citric acid acting as a lubricant. The compressed tablets are transferred immediately and continuously to ovens where they are dried at 70–75^{0}C. Drying also hardens them. As soon as they leave the dryer, the tablets are packed in aluminum foil lined with polyethylene.

Dry Granulation:

Slugging of the material is done by using heavy-duty tableting equipment or with roller compaction.

Direct Compression:

Direct compression normally requires careful selection of raw materials to achieve a free-flowing, non-segregating, compressible mixture.

Tableting:

By using single punch and rotary machines tablets are prepared.

EVALUATION OF FDDS:

Various parameters that need to be evaluated in gastro-retentive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, and mechanical properties are also performed. [22]

Pre-formulation study:

FTIR Analysis: [23,24]

FTIR is a technique mostly used to identify organic, polymeric, and some inorganic materials as well as for functional group determination. It is important tool to analyze the purity of the drug. FTIR spectrum shows the fundamental peaks corresponding to the chemical nature of the drug and excipients. There is always a possibility of drug-polymer interaction in any formulation due to their intimate contact. FTIR studies are carried out in order to determine such type of interaction among drug and other excipients in developed formulation. Pressed pellet technique is commonly used for FTIR study. In this technique finely ground dried solid sample is intimately mixed with about 100 times its weight of powdered potassium bromide in a small agate pestle morter. This mixture is pressed under a high pressure (25000 psi/g) in a IR tablet press to form a small pellet which is transparent to Infra red radiations. spectra was recorded over the wave number 400-4000 cm^{-1}.

DSC Studies: [25]

DSC is used to characterize water of hydration of pharmaceuticals. DSC helps to detect crystallization, degradation, phase transformation in solid sample. As the temperature increases, an amorphous solid will become less viscous. At some point, the molecules may obtain enough freedom of motion to spontaneously arrange themselves into a crystalline form. This is known as the crystallization temperature . This transition from amorphous solid to crystalline solid is an exothermic process, and results in a peak in the DSC signal. As the temperature increases the

sample eventually reaches its melting temperature. The melting process results in an endothermic peak in the DSC curve. The ability to determine transition temperatures and enthalpies makes DSC a valuable tool in producing phase diagrams for various chemical systems. Thermograms of formulated preparations are obtained using DSC instrument equipped with an intracooler. The sample preparations are hermitically sealed in an aluminium pan and heated at a constant rate of 10ºC/min; over a temperature range of 25º C - 65º C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50ml/ min.

Powder X-ray Diffraction: [26,27]

XRD is the predominant tool for the study of polycrystalline materials and is eminently suited for the routine characterization of pharmaceutical solids. Powder x-ray diffraction studies have been widely used to understand crystallinity of solid. This uses Bragg's equation to study the crystal structure of solids by following equation.

$$n\lambda = 2\ d \sin\theta \qquad \ldots (2)$$

Where, n is order of diffraction, θ = angle of diffraction, λ is wave length of x-rays, and d is spacing distance between two planes of crystals. By knowing the angle of diffraction (θ), spacing (d) can be calculated. If spacing 'd' get changed significantly then it is considered that polymorphic changes have taken place or crystal habit have changed. But with same 2θ, peak intensity gets reduced then it interpreted as reduction of crystallinity of solid.

Pre-compression evaluation:

Angle of Repose: [28]

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height (h).

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

Where, θ = angle of repose,

h = height of the heap,

r = radius of the heap.

The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

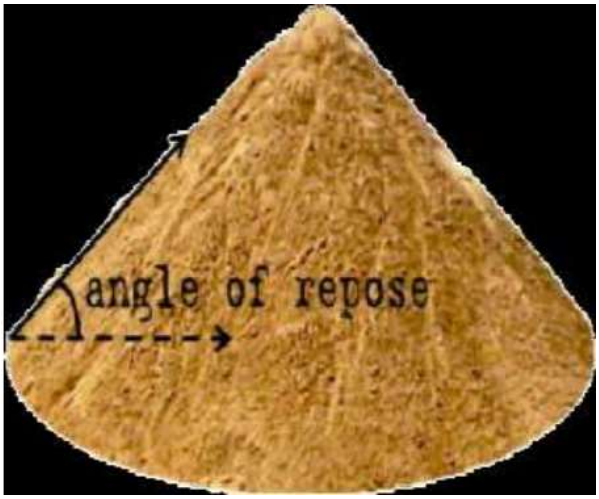

Figure. 12: Angle of repose [28]

Table2: The relationship between Angle of repose and powder flow

Angle of Repose	Powder Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very Poor

Compressibility Index: [28]

The flow ability of powder can be evaluated by comparing the bulk density (ρ^o) and tapped density (ρ^t) of powder and the rate at which it packed down.

Compressibility index was calculated by –

$$\textbf{Compressibility Index (\%)} = (\rho^t - \rho^o)*100 / \rho^t$$

Where ρ^o = Bulk density g/ml, ρ^t = Tapped density g/ml.

Bulk Density: [29]

Bulk density denotes the total density of the material. It includes the true volume of inter-particle spaces and intra-particle pores. The packing of particle is mainly responsible for bulk. Bulk density is defined as:

Bulk Density= Weight of the powder/Bulk volume of the powder

Percentage Porosity: [29]

Whether the powder is porous or nonporous, the total porosity expression for the calculation remains the same. Porosity provides information about hardness, disintegration, total porosity etc.

% Porosity = Void volume * 100/ Bulk volume

Hausner's ratio (HR): [5]

This was calculated as the ratio of tapped density to bulk density of the sample.

HR = Tapped Density/Bulk Density

Post-compression Evaluation:

Tablet Thickness and Size: [30]

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using vernier caliper.

Tablet Hardness: [30]

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in kg/cm^2.

Weight variation test: [5]

To study weight variation twenty tablets of the formulation were weighed using a citizen electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

$$\textbf{Percentage Deviation (PD)} = (W_{avg}-W_{initial})*100/W_{avg}$$

Where,

W_{avg} = average weight and

$W_{initial}$ = initial weight.

Table .3: Standards for uniformity of weight as per I.P [5]

Average weight of Tablet	% Deviation
80 mg or < 80 mg	10
>80 mg to < 250 mg	7.5
>250 mg or more	5

Friability: [30]

Friability is the measure of tablet strength. Electro lab EF- 2 friabilator (USP) was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined. The % loss should not be more than 2% as per USP.

% loss = (Initial wt. of tablets – Final wt. of tablets)/ Initial wt. of tablets ×100

Uniformity of Drug content: [5]

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in 0.1N HCl, the drug content was determined

measuring the absorbance at lambda max after suitable dilution using a Simadzu UV- Visible double beam spectrophotometer 1800.

Determination of in-vitro dissolution study: [5]

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. Samples are withdrawn periodically from the dissolution medium, 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.

In-vitro buoyancy studies: [5]

The in vitro buoyancy was determined by floating lag time method described by Dave B.S. The tablets were placed in 100ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of dosage form and its buoyancy in 0.1 N HCl and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

Weight gain and water uptake (WU): [5]

Weight gain or water uptake can be studied by considering the swelling behavior of Floating dosage form. The study is done by immersing the dosage form in simulated gastric fluid at 37^oC and determining the dimensional changes like tablet diameter and/ or thickness at regular 1-h time intervals until 24 h, the tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then reweighed and WU is measured in the terms of percent weight gain, as given by equation -

$$\mathbf{WU = (W_t - W_O) \; X \; 100 \; / \; W_O}$$

In which W_t and W_o are the weights of the dosage form at time t and initially, respectively.

Stability study: [5]

Stability is the essential factor for quality, efficacy and safety of drug product. The drug product with insufficient stability can result in change of their physical (hardness, dissolution rate, phase

separation) as well as chemical characteristics (formation of high risk decomposition substances).

Ultrasonography: [5]

Ultrasonic waves reflected substantially different acoustic impedances across interface enable the imaging of some abdominal organs. Most dosage forms do not sharp acoustic mismatches across their interface with the physiological solution. Therefore, ultra sonography is not routinely used for the evaluation of FDDS. The characterization included assessment of intragastric location of the hydro gels, solvent penetration into the gel and interactions between gastric wall and FDDS during peristalsis.

Drug release kinetics of floating tablets: [5]

To analyze the mechanism of drug release and release rate kinetics from the dosage form, the data obtained were fitted into zero order, first order, Higuchi release and Korsmeyer and Peppas release model using Graph Pad Prism 5.0 software, which is specially meant for curve fitting and statistical data analysis.

Zero-Order release kinetics:

To studies the zero-order releases kinetics the release rate data are fitted to the fallowing equation.

$$F=k.t \quad \text{(1)}$$

Where, **F** is the fraction of drug release, **k** is the release rate constant and **t** is the release time.

First – order release kinetics:

To study the first-order release kinetics the release rate data are fitted to the fallowing equation.

$$F= 100\times (1-e^{-kt}) \quad \text{(2)}$$

Where, **F** is the fraction of drug release, **K** is the release rate constant, **e** is exponent coefficient and **t** is the release time.

Higuchi release model:

To study the Higuchi release model the release rate data are fitted to the fallowing equation.

$$F= K.t^{1/2} \quad \text{(3)}$$

Where, **F** is the fraction of drug release and **K** is the release rate constant.

Korsmeyer and Peppas release model:

To study the Korsmeyer and Peppas release model the release rate data are fitted to the fallowing equation.

$$M_t/M_\infty = K.t^n \quad \text{(4)}$$

Where, $\mathbf{M_t/M}$ is the fraction of drug release, **n** is the diffusion exponent for the drug release that is dependent on the shape of the matrix dosage form.

Gastro retention: [5]

The inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. The use of X-rays involves exposing a patient to an X-ray beam, thus permitting the visualization of the GI transit of the dosage form.

X-Ray/Gamma Scintigraphy: [31]

X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form now a day. 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 radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a emitting radionuclide in a formulation allows indirect external observation using a camera or scintiscanner. In case of scintigraphy, the rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GI tract.

CONCLUSION

Drug delivery using various gastro retentive technological approaches have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drug candidates. Based on the literature surveyed, it may be concluded that gastro retentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The currently available polymer mediated non-effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles appear to be a very much effective approach to the modulation of controlled oral drug delivery. Gastro retentive drug delivery system gives maximum benefit to patient so that maximum patience compliance associated with it.

FUTURE POTENTIAL

FDDS approach may be used for various potential active agents with narrow absorption window, e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, amino glycosides and tetracyclines) which are absorbed from very specific

regions of GI tract and whose development has been halted due to the lack of appropriate pharmaceutical technologies. In addition, by continual supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoietin, vasopressin, insulin, low molecular weight heparin, and LHRH. Some of the unresolved critical issues related to the rational development of FDDS include, the quantitative efficiency of floating delivery systems in the fasted and fed states and the correlation between prolonged GRT and SR/PK characteristics. However, we are as close as we have ever been to see a greater transition of gastric retention devices from developmental level to the manufacturing and commercial level.

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