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THE FLOATING DRUG DELIVERY SYSTEM AND IT`S IMPACT ON CALCIUM CHANNEL BLOCKER:A REVIEW ARTICLE

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ABSTRACT

The purpose of writing this review on floating drug delivery systems (FDDS) was to show that how this drug delivery system is best for calcium channel blocker and to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. 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. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems, and applications of these systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.

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HISTORY OF CALCIUM CHANNEL BLOCKERS

When people are diagnosed with heart disease, they may be treated in several different ways. Controlling risk factors that can be managed—cutting down on fat and cholesterol and quitting smoking—will be the first changes they will have to make. Exercise will become part of their lives, if possible. Drug therapy may be the next course of action. The variety and scope of cardiovascular drugs have increased tremendously in the past few decades, and new drugs are being approved annually. in the 1950s, effective oral diuretics became available. These drugs dramatically changed the treatment of heart failure and hypertension. In the mid-1960s a class of agents called beta blockers was discovered. This led to major changes in physicians' ability to treat patients with hypertension or angina pectoris. Calcium channel blockers and ACE inhibitors became widely used in the 1980s, and they, too, have allowed patients with hypertension, heart failure, and coronary artery disease to be treated more effectively. A considerable effort has been made in the last 15 years to evaluate the safety and efficacy of calcium channel blockers (CCBs) in the treatment of patients with chronic congestive heart

failure (CHF). Available studies have provided strong evidence for a potential detrimental effect of the first-generation calcium antagonists in patients with CHF, indicating the need for great caution when these drugs are used in patients with significant depression of left ventricular systolic function. A number of second-generation CCB have demonstrated a strong vasodilatory effect and favorable hemodynamic action but failed to show a similar improvement in exercise capacity, morbidity and mortality. Moreover, drugs such as Nicardipine and Nisoldipine have resulted in a detrimental effect in some patients and, therefore, cannot be considered safe when used in patients with moderate-to-severe heart failure [1].

The calcium channel blockers (CCB) are a heterogeneous group of drugs with widely variable effects on heart muscle, sinus node function, atrioventricular conduction, peripheral blood vessels, and coronary circulation. Ten of these drugs – nifedipine, nicardipine, nimodipine, felodipine, isradipine, amlodipine, verapamil, diltiazem, bepridil, and mibefradil – are approved in the United States for clinical use. Although these drugs are mainly used for the treatment of hypertension and stable angina pectoris, there has been a strong interest and increasing experience in the use of CCB in patients with congestive heart failure (CHF). When people are diagnosed with heart disease, they may be treated in several different ways. Controlling risk factors that can be managed—cutting down on fat and cholesterol and quitting smoking—will be the first changes they will have to make. Exercise will become part of their lives, if possible. Drug therapy may be the next course of action. The variety and scope of cardiovascular drugs have increased tremendously in the past few decades, and new drugs are being approved annually. In the 1950s, effective oral diuretics became available. These drugs dramatically changed the treatment of heart failure and hypertension. In the mid-1960s a class of agents called beta blockers was discovered. This led to major changes in physicians' ability to treat patients with hypertension or angina pectoris. Calcium channel blockers and ACE inhibitors became widely used in the 1980s, and they, too, have allowed patients with hypertension, heart failure, and coronary artery disease to be treated more effectively [2].

NEED TO FLATING CONTROL DRUG DELIVERY

Development of new drug molecule is expensive and time consuming. Improving safety efficacy ratio of "old" drugs has been attempted using different methods such as individualizing drug therapy and therapeutic drug monitoring. Delivering drug at controlled rate, slow delivery, and targeted delivery are other very attractive methods and have been pursued very vigorously [3].

For drugs with short half-lives and with a clear relationship between concentration and response, it will be necessary to dose at regular, frequent intervals in order to maintain the concentration within the therapeutic range. Higher doses at less frequent intervals will result in higher peak concentrations with the possibility of toxicity. For some drugs with wide margins of safety, this approach may be satisfactory. A trend in calcium channel blocker development has been to improve therapeutic efficacy and reduce the severity of side effects through altering dosage forms of calcium channel blocker by modifying release of the formulations to optimize drug delivery. These formulations are designed to increase patient compliance through a prolonged effect and reduce adverse effects through lowered peak plasma concentrations. Formulations can affect the safety of preparations by controlling the rate of release of the drug at sensitive sites, by delivering drug to specific sites to minimize systemic exposure, or delivering drug in such a way as to change the rate or extent of the formation of toxic metabolite [4].

INTRODUCTION TO FLOATING DRUG DELVERY SYSTEM

The aim of any drug delivery system is to afford a therapeutic amount of drug to the proper site in the body to attain promptly, and then maintain the desired drug concentration. In oral drug system not all drugs or therapeutic agents are

absorbed uniformly throughout the GIT. Some drugs are absorbed in a particular portion of GIT.

One of the novel approaches in the area of oral sustained release drug delivery is known as floating drug delivery system. Drugs those are having a narrow absorption window and having more solubility in gastric region are suitable candidates for FDDS[5].FDDS prolongs the retention time of dosage forms in the stomach or upper gastro intestinal tract, as to improve solubility, bioavailability and therapeutic efficacy of the drugs[6]. Several techniques have been proposed to increase the gastric residence time of dosage forms such as hydrodynamically balanced system [7], expanding or swelling system [8], hollow microsphere, powders, granules, and various other gastro retentive systems.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of muco adhesion, floatation, sedimentation, expansion modified shape system or by the simultaneous administration of pharmacological agent that delay gastric emptying. This review focuses on the principal mechanism of floatation to achieve gastric retention [9].

ABSORPTION WINDOW

Not all drug candidates get uniformly absorbed throughout the GI tract. Drugs exhibiting absorption from only a particular portion of GI tract or showing difference in absorption from various region of GI tract are said to have regional variability in intestinal absorption. Such drugs show "absorption window" which signifies the region of GI tract from where absorption primarily occurs. This absorption window is observed due to following factors [10]:

Physico-Chemical Factors:

pH-dependent solubility- a drug experiences a Ph range of 1-8 across the GI tract. A drug should be in the solubilized form to cross the biological membrane. Since most of the drugs are absorbed by passive diffusion of the unionized form, the extent of ionized and unionized forms at a certain pH can influence predominant absorption from a particular region of GI tract leading to the phenomenon of absorption window.

pH-dependent stability: Ph dependent degradation of drugs can cause variations in extent of absorption from regions in the GI tract.

Enzymatic degradation- Presence of certain enzymes in a particular region of GI tract can lead to regional variability in absorption of drugs which are substrates to that enzyme.

Physiological Factors:

Mechanism of absorption- Drugs absorbed by active and facilitated transport mechanisms show regional specificity due to the presence of these mechanisms only in a particular region of GI tract.

Microbial degradation- The human colon is inhabited by over 400 distinct species of bacteria and has up to 1010 bacteria per gram of content. Drugs that are degraded by microbes are likely to show regional variability in absorption from GI tract.

Biochemical Factors

Many drugs show poor bioavaibility due to biochemical processes like:

I.Intestinal metabolic enzymes (phase I drug metabolizing enzymes), cytochrome P450 (CYP3A)

ii.The multidrug efflux pump, p-glycoprotein present in the villus tip of enterocytes in the GIT.

Gastrointestinal Physiology of Stomach:

The complex anatomy and physiology, variations in acidity, bile salts, enzyme content and mucosal absorptive surface of GI tract, from mouth to the rectum significantly influence the drug release, dissolution and absorption from orally administered dosage form [11].

There are two distinct modes of GI motility and secretory patterns in humans and animals, in fasted and fed state. As a result, the BA of the orally administered drugs may be different depending on the state of feeding. Fasted state is associated with various cyclic events regulating the GI motility patterns, commonly called as migrating motor complex (MMC).the MMC is organized into alternating cycles of activity and quiescence and can be subdivided into basal,preburst and burst intervals also named as phase I,II,III,respectively[12].

PHASE I: the quiescent period lasts from 30-60 minutes and is characterized by lack of any

secretory and electrical activity and contractile motions.

PHASE II: exhibits intermittent action potential for 20-40 minutes with increasing contractile motions. Bile enters the duodenum during this phase while the gastric mucus discharge occurs during the later part of phase II and throughout phase III.

PHASE III: shows the prevalence of intense large and regular contraction that sweep off the undigested food. These are also called "housekeeper waves" and propagate for 10-20 minutes.

PHASE IV: is the transition period of 0-5 minutes between phase III and phase I. These interdigestive series of electrical events originate in the foregut and propagate to terminal ileum in the fasted state and repeat cyclically every 2-3 hours. Feeding results in the origination of a continuous pattern of spike potentials and contractions called the postprandial motility.

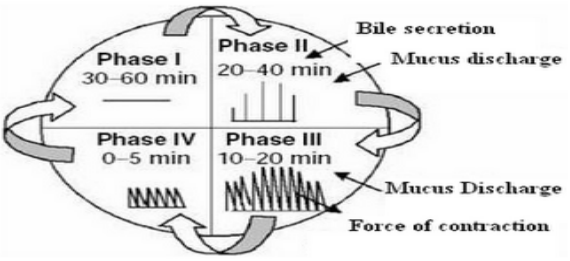


Figure 1: Schematic representation of interdigestive motility

When CRDDS is administered in the fasted state, MMC may be in any of its phase and this can influence the total gastric residence time and transit time in the GI tract. This assumes even more significance for drugs having absorption window, as this will affect the time the dosage form spends in the region preceding and around the window [13, 14].

DRUGS SUITABLE FOR FLOATING DRUG DELIVERY SYSTEM[15]:

Drugs those are locally active in the stomach e.g. misoprostol, antacids etc.

Drugs that have narrow absorption window in GIT e.g. L-DOPA, PABA, furosemide, riboflavin

Drugs those are unstable in the intestinal environment e.g. captopril, ranitidine, metronidazole

Drugs that disturbs the normal colonic microbes e.g. antibiotics against helicobacter pylori.

Drugs that exhibit low solubility at high ph values e.g. diazepam, verapamil HCL.

DRUGS UNSUITABLE FOR FDDS[15]:

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

Drugs that suffer instability in gastric acid environment e.g. erythromycin

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

REQUIREMENT FOR FLOATING SYSTEM[15]:

Physiological factors in the stomach, it must be noted that to achieve gastric retention, the dosage form satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, It must resist premature gastric emptying.Futhermore, once its purpose has been served, the device should be removed from the stomach with ease.

NEED FOR GASTRO RETENTION[16]:

Drugs that are absorbed from the proximal part of the GIT.

Drugs that are less soluble or are degrade by alkaline pH they encounters at lower part of GIT

Drugs that are absorbed due variable gastric emptying time.

Local or sustained delivery to the stomach to treat certain conditions

Particularly useful for the treatment of peptic ulcers caused by H.pylori infections.

FACTORS AFFECTING GASTRIC RETENTION[17]:

Density- GRT is a function of dosage form buoyancy that is dependent on density

Size- dosage form units with diameter of more than 7.5mm reported to have an increased GRT compared with those of 9.9mm diameter.

Shape of dosage form- tetrahedron and ring shaped devices with a flexi burl modulus of 48 and 22.5 kilo pounds per square inch are reported to have better.

Single and multiple unit formulation- multiple unit formulation show predictable release profile

compare to single unit dosage form as single unit formulation may have chance of performance failure.

Fed and unfed state- GI motility is characterized by periods of migrating motor complex (MMC) activity that occurs every 1.5-2 hours. The MMC sweeps the undigested material from the stomach and if the timing of administration of the formulation coincides with that of 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 or indigestible polymer can change motility patent of stomach to a fed state, thus a prolonging drug release and reducing gastric emptying rate.

Calorie content- high protein and fat diet can increase GRT up to 4 to 10 hours.

Frequency of feeding- successive meal increase GRT up to 400 times when successive meals are given compared with a single meal due to low frequency of MMC.

Gender- GRT in men is less compare with their age and race matched counterparts regardless of weight, height and body surface.

Age- elderly people those over 70, have longer GRT

Posture- GRT is varying between supine and upright state of patient.

Drug administration- anticholinergics, opiates and prokinetic agent can significantly increase GRT.

GENERAL FORMULATION AND DEVELOPMENT[18, 19, 20, 21]:

Knowledge about GI dynamic such as gastric emptying, colonic transit is a key for optimum design of oral controlled release dosage form.

Knowledge about rate and extent of drug absorption from different site of GI tract and factors that governs the absorption assist the design of dosage form.

Three major requirements for FDDS formulations are:

It must forms a cohesive gel barrier

It must maintain specific gravity lower then gastric content (1.004g/cc).

It should release content slowly to serve as a reservoir.

Selection of excipients is important decision for design of dosage form for controlled residence in stomach.

Water soluble cellulose derivatives are best suited polymer for this purpose.

The high molecular weight polymer and slower rate of polymer hydration are usually associated with better floating behavior.

Therefore these polymers are expected to improve floating properties of delivery systems.

It must have full degradation and evacuation of the system once the drug release is over

It must be control the drug release profile

It must have sufficient drug loading capacity

APPROACH TO DESIGN ORAL FLAOTING DRUG DELIVERY SYSTEM:

A number of approaches have been used to increase floating time of a dosage form in stomach which is as follows [22]

a) Hydrodynamically balanced systems: HBS

b) Gas-generating systems

c) Raft-forming systems

d) Low-density systems

Floating systems:

These have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Eventually, the residual system is emptied from the stomach. Gastric emptying is much more rapid in the fasting state and floating systems rely heavily on the presence of food to retard emptying and provide sufficient liquid for effective buoyancy. [23-25] The three approaches used in designing intragastric floating systems will now be described.

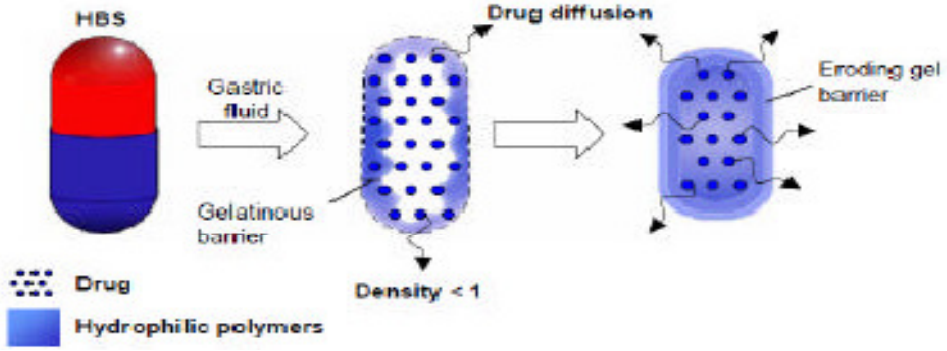
Hydrodynamically balanced systems (HBS):

These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. Hydroxypropylmethylcellulose, Hydroxypropyl methylcellulose (HPMC) is the most common used excipients, although hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), sodium carboxymethylcellulose (NaCMC), agar, carrageenans or alginic acid are also used.

Polysacchacarides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms (Figure 2).[26]

Figure 2: Hydrodynamically balanced system (HBS).

The gelatinous polymer barrier formation results from hydrophilic polymer swelling



Drug is released by diffusion and erosion of the gel barrier.

Gas-generating systems:

Floatability can also be achieved by generation of gas bubbles.CO2 can be generated in situ by incorporation of carbonates or bicarbonates, which react with acid-either the natural gastric acid or co-formulated as citric or tartaric acid. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be **0.76:1.**An alternative is to incorporate a matrix with entrapped of liquid, which forms a gas at body temperature (Figure 3).

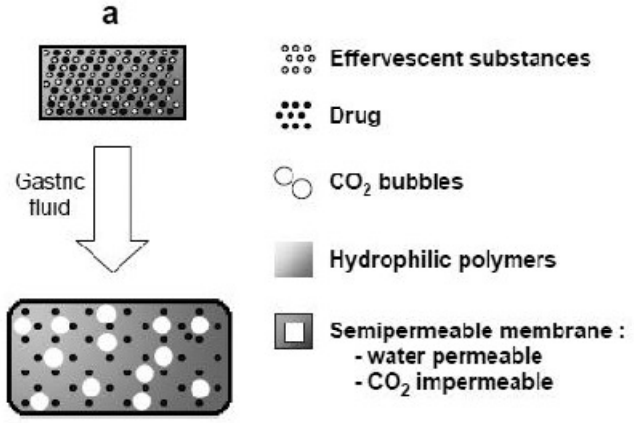


Figure 3: Gas-generating systems

Raft-forming systems:

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment as with Liquid Gavison (GlaxoSmithkline) (Figure 4).[27]

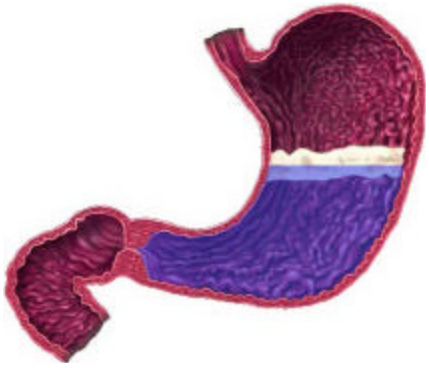


Figure 4: Barrier formed by a raft-forming system

Low-Density System:

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density systems (<1 g/cm3) with immediate buoyancy have therefore been developed. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called ‘‘micro balloons’’

because of the low-density core. Generally, techniques used to prepare hollow microspheres involve simple solvent evaporation or solvent diffusion evaporation methods. Polycarbonate, Eudragit S, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as polymers. Buoyancy and drug release are dependent on quantity of polymer, the plasticizer–polymer ratio and the solvent used (Figure 5).[28-32]

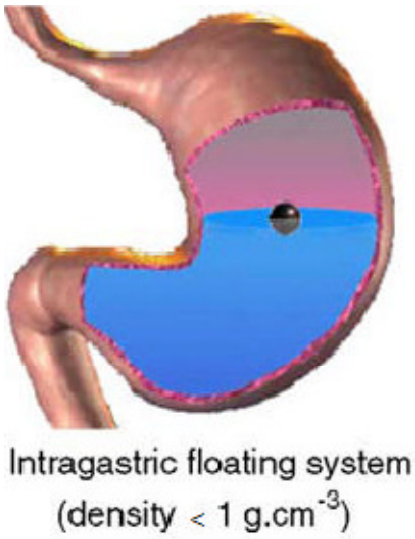


Figure 5: The structure of the low-density, floating matrix tablets.

FlOATING DRUG DELIVERY SYSTEM AND ITS MECHANISM:

Floating drug delivery systems (FDDS) have bulk density lesser than gastric fluids, so they 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, the drug is released slowly at the desired rate from the system as shown in fig. 2(a). 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 as shown in fig. 2(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[33].

F = F buoyancy – F gravity

= (Df – Ds) gv--- (1)

Where, F= total vertical force, Df = fluid density, Ds= object density, v = volume and g = acceleration due to gravity.

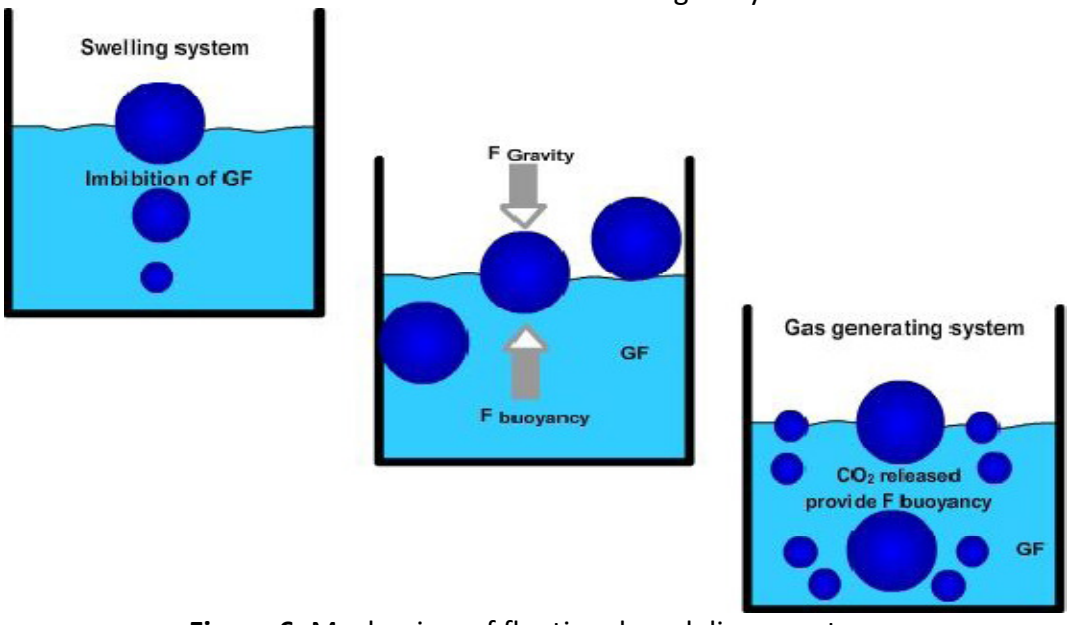


Figure 6: Mechanism of floating drug delivery system

METHOD FOR PREPARING FLOATING DOSAGE FORM:

Following approaches can be used for preparing floating dosage forms:
Using gel forming hydrocolloids such as hydrophilic gums, gelatin, alginates, cellulose derivatives, etc.
Using low density enteric materials such as methacrylic polymer, cellulose acetate phthalate.
By reducing particle size and filling it in a capsule.
By forming carbon dioxide gas and subsequent entrapment of it in the gel network.
By preparing hollow micro-balloons of drug using acrylic polymer and filled in capsules.
By incorporation of inflatable chamber which contained in a liquid e.g. solvent that gasifies at body temperature to cause the chambers to inflate in the stomach.
The factors which govern the effectiveness of active medicaments in HBS are:
Amounts of active medicament to produce therapeutic effect.
Bulk density
Hydrophilic and hydrophobic properties
Stability in gastric fluids.

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM:

Based on the mechanism of buoyancy , two distinctly different technologies have been utilized in the development of FDDs which are:
Non effervescent FDDs
Single layer floating tablet
Bilayer floating tablet
Hydro dynamically balanced capsule
Casein gelatin floating beads
Hollow microspheres/Micro balloons
Effervescent FDDs
Gas generating system
Hydrodynamically balanced system
Intragastric bilayer floating tablet
Multiple unit type floating pills
Volatile liquid system
Intragastric floating drug delivery system-
Inflatable gastrointestinal delivery system-
Intragastric osmotically CDDS-

Non Effervescent FDDs

The non effervescent FDDs based on mechanism of swelling of polymer or bio adhesion to mucous layer in GIT.
The most commonly used excipients in non effervescent FDDs are gel forming or highly swellable cellulose like hydro colloids polysaccharides or matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene.
The various type of these systems are as follow:
Single layer floating tablet
Bilayer floating tablet
Hydro dynamically balanced capsule
Casein gelatin floating beads
Hollow microspheres/Micro balloons

Single layer floating tablet:

They are formulated by intimate mixing of drugs with gel forming hydro colloids which swells in contact with gastric fluids and maintains a relatively integrity of shape and bulk density of lesser than gastric environment.
The air thus entrapped by swollen polymer imparts buoyancy to the dosage form and the gel structure act as reservoir for sustained drug release.

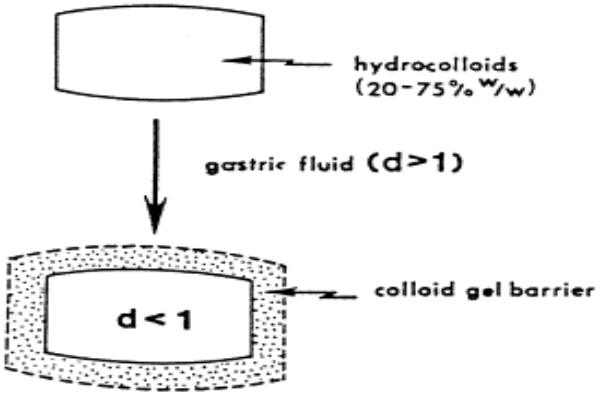


Figure 7: Intragastric Single Layer Floating Tablet

Bilayer floating tablet:

A bilayer tablet containing two layers:
Immediately release layer which release initial dose from the system.
Sustained release layer absorb gastric fluid, forming impermeable colloidal gel barrier on its surface, and maintain a bulk density of lesser than unity, and thereby its remains buoyant in the system.

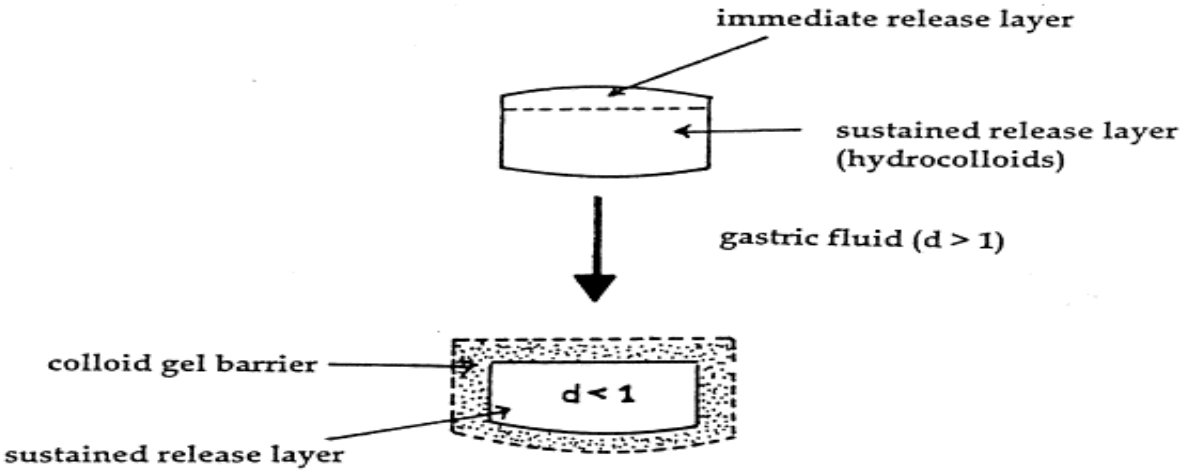


Figure 8: Intragastric Bilayer Floating Tablet

Hydro Dynamically Balanced Capsule:

This system contain drug with gel forming hydro colloid to remain buoyant on stomach content.

Polymers used are HPMC, HEC, HPC, NaCMC, polystyrene, agar etc.

The polymers are mixed with drug and administered in hydro dynamically balanced system capsule.

Capsule shell dissolved when it comes in contact with water and swells to form a gelatinous barrier and imparts buoyancy to dosage form. E.g. bilayer dosage form consisting of capsule. One layer consisting of misoprostol, while other being buoyant layer is responsible for floating of dosage form and remains buoyant in gastric fluid for 13 hour.

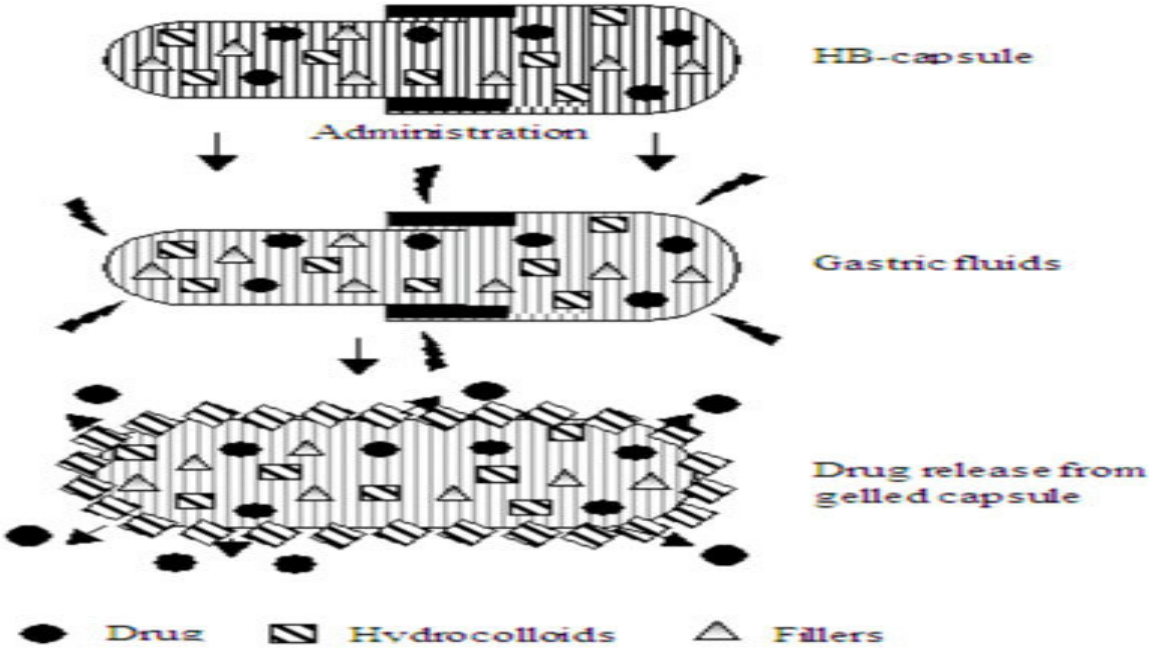


Figure 9: Hydrodynamically Balanced Capsule

Floating Beads:

Spherical beads of approximately 2.5mm diameter can be prepared by dropping a solution of sodium alginate into aqueous solution of calcium chloride, causing a precipitation of sodium alginate leading to formation of porous which can maintain floating force for over 12 hours.

Casein-gelatin floating beads have been prepared for controlled delivery of drug. Casein has

emulsifying property and thus causes air bubbles incorporation that act as air reservoir in floating system.

During the preparation, the application of vacuum develops non floating system.

Hollow Microsphere/Micro balloons:

Polymers used are polycarbonate, cellulose acetate, calcium alginate, Eudragit S and pectin.

Buoyancy and drug release depend on quantity of polymer, the plasticizer polymer ratio, and solvent used for formulation.

They can be prepared by two method:

Solvent evaporation technique

Emulsion solvent diffusion method

Effervescent FDDs:

Includes use of gas generating agents, carbonates and organic acids to produce carbon dioxide, thus reducing density of system and making it float in the gastric fluid.

These effervescent systems classified in 2 types:

Gas generating system

Volatile liquid system

Gas generating system-

Hydronynamically balanced system:

These are formulated by intimately mixing the CO_2 generating agents and the drug within matrix tablet. These have bulk density less then gastric fluid, therefore it float in stomach for prolong periods.

Drug is release slowly at desired rate from the system and after complete release the residual system is expel from the stomach. This lead to increase in GRT and a better control fluctuation in PDC.

Intragastric bilayer floating tablet:

The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with B-cyclodextrin mixed in 1:1 ratio.

One layer containing the polymer HPMC 4000, HPMC 100, CMC (for controlled release) and drug.

The second layer contains the effervescent mixture of sodium bicarbonate and citric acid.

The in vitro floating studies reveal that the lesser the compression force the shorter is the time of onset of floating.

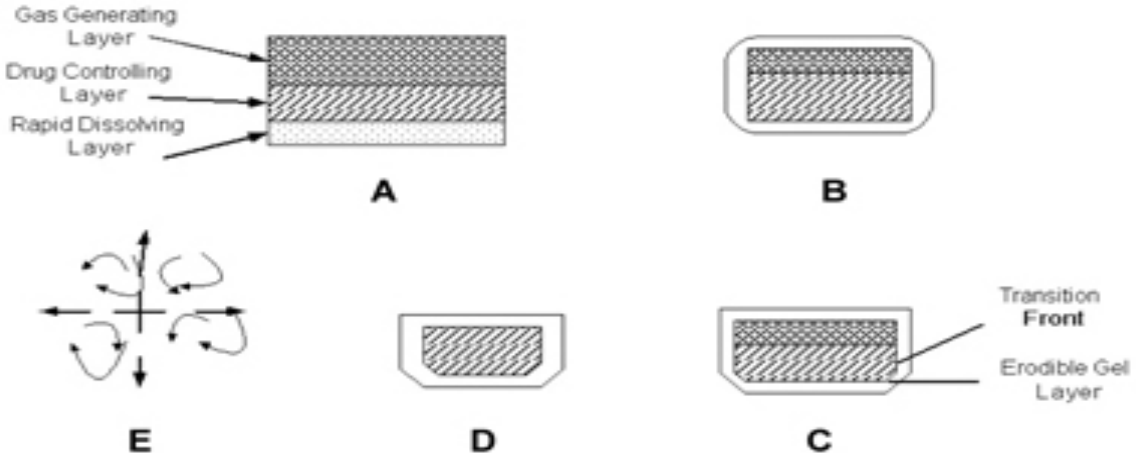


Figure 10: Intragastric Bilayer Effervescent Floating Tablet

Multiple unit type floating pills:

In this system CO_2 gas is generated from the reaction of Na-bicarbonate and tartaric acid.

The system consisted of sustained release pills surrounded by an effervescent layer.

This coated system is further coated with swellable polymer like polyvinyl acetate and purified shellac.

Moreover, the effervescent layer is divided into two sub layers to prevent the direct contact between tartaric acid and sodium bicarbonate. Sodium bicarbonate present in the inner layer surrounded by tartrate.

When the system is exposed to aqueous medium at 37c, the system expand to form a swollen pill with a density lower then 1g/ml.

Carbon dioxide is generated in the inner layer by the diffusion of water through the outer swellable membrane layer.

It is observed that the system start floating within 10 min over the water level for period of 5 hr, independent of the pH and viscosity of medium.

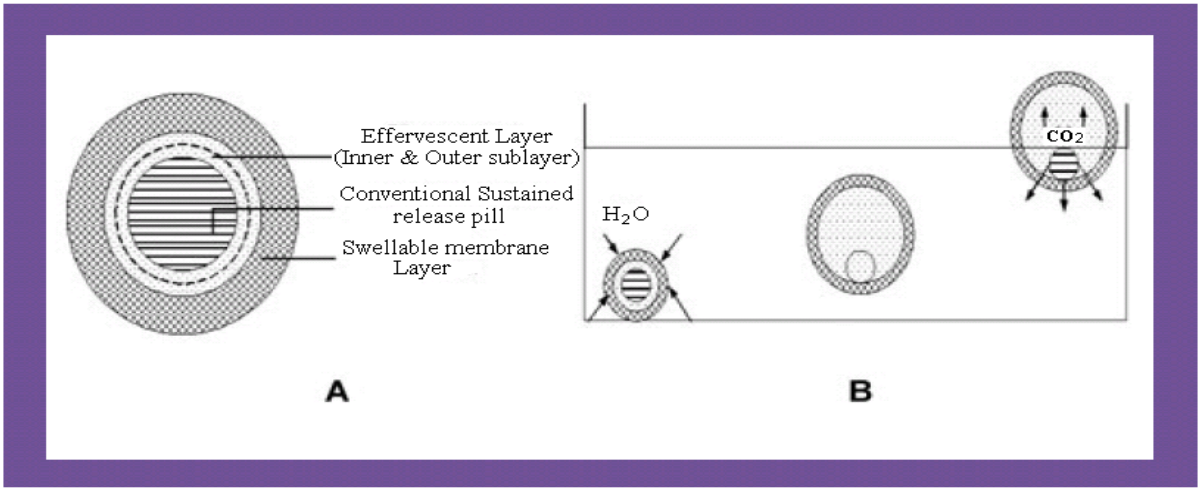


Figure 11: Multiple unit Floating Pill

Volatile liquid system

Intragastric floating drug delivery system-:

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

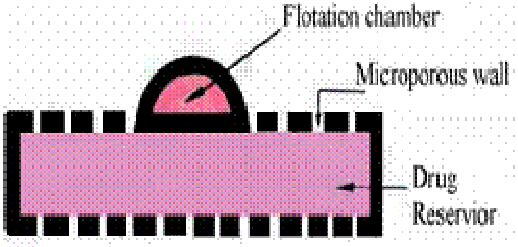


Figure 12: Intragastric Floating Drug Delivery System

Inflatable gastrointestinal delivery system-:

In this system inflatable chamber is incorporated which contain liquid ether that gasified at body temperature which cause chamber to inflate in stomach.

Inflatation chamber with drug reservoir is encapsulated in a capsule.

After oral administration, capsule dissolves to release drug together with inflatable camber in the gastric fluid.

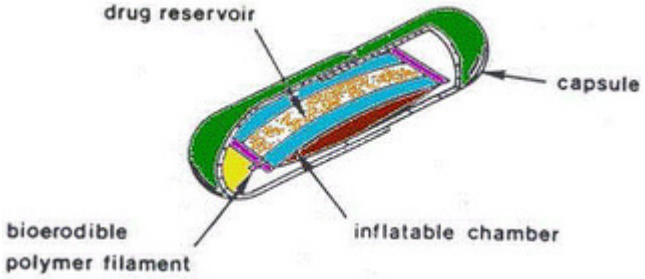


Figure 13: Inflatable Gastrointestinal Delivery System

Intragastric osmotically CDDS-:

Comprise of an osmotic pressure CDDD and inflatable floating support in a capsule. In the stomach, capsule disintegrates to release osmotically CDDD.

The inflatable support inside forms a hollow polymeric beg that contain liquids that gasified at body temperature to inflate the beg.

The osmotic pressure CDDD consists of two component: drug reservoir compartment and osmotically active compartment. Drug reservoir compartment is impermeable to vapor and liquids and hence drug delivery orifice and osmotically active compartment have osmotically active salt which imbibes water from GIT and release drug.

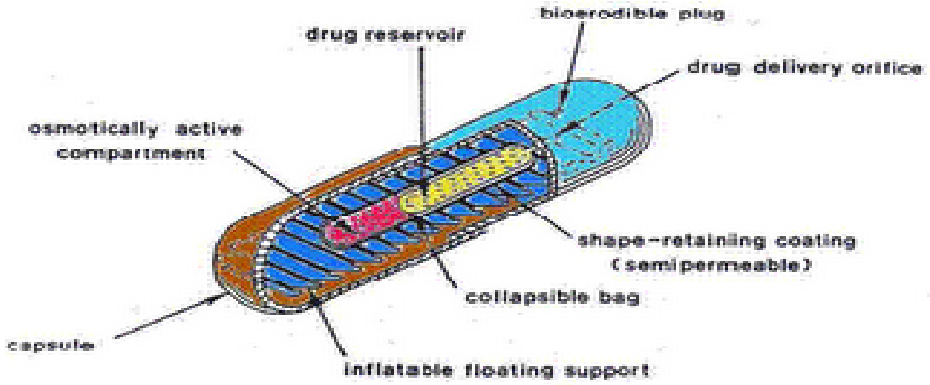


Figure 14: Intragastric Osmotically CDDS

FORMULATION OF FLOATING DOSAGE FORM

The following types of the ingredients can be incorporated in to FDDS [39]

Hydrocolloids
Inert fatty materials
Release rate accelerants
Release rate retardant
Buoyancy increasing agents
Miscellaneous

Hydrocolloids: Suitable hydrocolloids are synthetics, anionic or non ionic like hydrophilic gums, modified cellulose derivatives. Eg. Accasia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, MC, HPC, HEC, and Na CMC can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid is having pH 1.2.Although the bulk density of the formulation may initially be more than one, but when gastric fluid is enter in the system, it should be hydrodynamically balanced to have a bulk density of less than one to assure buoyancy.

Inert fatty materials: Edible, pharmaceutical inert fatty material, having a specific gravity less than one can be added to the formulation to decrease the hydrophilic property of formulation and hence increases the buoyancy. Eg. Purified grades of beeswax, fatty acids, long chain alcohols, glycerides, and mineral oils can be used.

Release rate accelerant: The release rate of the medicament from the formulation can be modified by including excipients like lactose and/or mannitol. These may be present from about 5-60% by weight.

Release rate retardant: Insoluble substances such as dicalcium phosphate, talc, magnesium strearete decreased the solubility and hence retard the release of medicaments.

Buoyancy increasing agents: Materials like ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may be adapted up to 80 % by weight.

Miscellaneous: Pharmaceutically acceptable adjuvant like preservatives, stabilizers, and lubricants can be incorporates in the dosage forms as per the requirements. They do not adversely affect the hydrodynamic balance of the systems.

SELECTION OF POLYMERES40,41,42

GAS GENERATING AGENTS

Alkalinizing agents and Acidulent:

Sodium bicarbonate, Calcium carbonates, Citric acid, Tartaric acid, Adipic acid

Rational behind the selection:

Effervescent compound generally use for this purpose. Sodium bicarbonate, calcium carbonate with citric acid and tartaric acid. When these compounds come in contact with the acidic gastric contents, carbon dioxide is liberated and gets entrapped in swelled hydrocolloids, which provide buoyancy to the dosage forms. Sodium bicarbonate induced CO2 generation in the presence of dissolution medium (0.1 N HCL). The gas generated trapped and protected with in the gel, formed by the hydration of polymer, thus decreasing the density of the tablet as the density of the tablet falls below 1, the tablet become buoyant.

Acidulent is used; since the pH of the stomach is elevated under fed condition (~3.5). Acidulent (Citric acid, Tartaric acid, Adipic acid) was incorporate in the formulation to provide an acidic medium for sodium bicarbonate.

Viscolyzing agent

Sodium alginate, Carbopol 934

Rational behind the selection:

They used to increase the viscosity in the system. Carbopol is being used in the controlled release solid dosage formulations since last four decades. The numbers of manufacturers commercializing controlled release tablets using carbomers are increasing considerably in recent period of development. Tablet formulations using Carbopol polymers have demonstrated zero-order and near zero-order release kinetics. These polymers are effective at low concentrations (less than 10%). Still they show extremely rapid and efficient swelling characteristics in both simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). The Carbopol polymers produce tablets of excellent hardness and low friability. These polymers can be successfully formulated into a variety of different tablet forms, including the traditional swallowable tablets, chewable tablets, buccal tablets, sublingual tablets, effervescent tablets, and suppositories; providing controlled-release properties as well as good binding characteristics. Carbomers show larger dissolution times at lower concentrations than other excipients. Because of these factors Carbopol polymers have greater extent in formulating dosage forms. Because Carbopol polymers swell rapidly in water and absorb great quantities, to avoid the use of flammable solvents, roller compaction is being used as the method to prepare a new form of Carbopol polymer 71G NF.

Carbopol polymer 71G NF is a useful and versatile controlled-release additive for tablet formulations in direct compression.

Drug Dissolution Mechanism from Carbopol Polymers:

In the dry state, the drug is trapped in a glassy core. As the external surface of the tablet is hydrated, it also forms a gelatinous layer upon hydration, however, this gel layer is significantly different structurally from the traditional matrix tablet. The hydrogel are not entangled chains of polymer, but discrete microgels made up of many polymer particles, in which the drug is dispersed. The crosslink network enables the entrapment of drugs in the hydrogel domains. Since these hydrogels are not water soluble, they do not dissolve, and erosion in the manner of linear polymers does not occur.

Rather, when the hydrogel is fully hydrated, osmotic pressure from within works to break up the structure, essentially by sloughing off discrete pieces of the hydrogel. It is postulated that as the concentration of the drug becomes high within the gel matrix and its thermodynamic activity or chemical potential increases, the gel layer around the tablet core actually acts almost like a rate controlling membrane, resulting in linear release of the drug. Because of this structure, drug dissolution rates are affected by subtle differences in rates of hydration and swelling of the individual polymer hydrogels, which are dependent on the molecular structure of the polymers, including crosslink density, chain entanglement, and crystallinity of the polymer matrix. The magnitude and rate of swelling is also dependent on the pH of the dissolution medium. The channels which form between the polymer hydrogels are influenced by the concentration of the polymer, as well as the degree of swelling. Increasing the amount of polymer will decrease the size of the channels, as does an increase in swelling degree. All of these factors must be taken into account to describe the mechanism for release control in tablets formulated with carbopol polymers.

Swelling agent/Gel forming polymer

Hydroxypropylmethylcellulose (HPMC)

Rational behind the selection:

Hypermellose powder is stable material, although it is hygroscopic after drying. Solution is stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypermellose undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gel point 50-90°C, depending upon grade and concentration of

material. Grades which are generally used in floating tablet are which are highly viscous in nature like HPMC K 100, HPMC K 4, and HPMC K 15.

Disintegrating agent

Povidone, Polyplasdone XL and XL-10

Rational behind the selection:

PVP belongs to a class of compounds known as superdisintegrantes. When they comes in contact with the fluid media they provide the swelling properties to the system they used as highly active explosive agent and as an accelerating agent for disintegration of solid medications. In tabletting, povidone solutions are used as binder in the wet granulation processes.

EVALUATION OF FLOATING DRUG DELIVERY SYSTEM: [28, 29]

The various parameters that need to be evaluated for their effect s on the GRT of buoyant formulation can be mainly be categorized into following different classes:

Galenic parameter- Diameter, Size, Flexibility, Density of matrix.

Control parameter- floating time, Dissolution, Specific gravity, Content uniformity, Hardness, Friability. In cash of multiple particulate drug delivery systems, differential scanning colorimetry, particle size analysis, flow properties, surface morphology has been evaluated

Geometric parameter- shape

Physiological parameter – Age, Sex, Posture, Food

Table 1. In Vitro Floating and Dissolution Performance

Drug(Polymer used)	Dissolution Medium and Method	Ref
Pentoxyfillin (HPMC K4 M)	500 mL of artificial gastric fluid pH 1.2 (without pepsin) at 100 rpm using USP XXIII dissolution apparatus. The time taken by the tablet to emerge on the water surface (floating lag time) and time until it floats on water surface was measured.	45
Amoxicillin beads (Calcium alginate)	For dissolution: 900 mL of deaerated 0.1 M HCl (pH 1.2) at 37ºC ± 1ºC in USP XXII dissolution tester at 50 rpm.	46
Ketoprofen (Eudragit S100,Eudragit RL)	20 mL of simulated gastric fluid without pepsin, 50 mg of floating microparticles in 50-mL beakers were shaken horizontally in a water bath. % age of floating micro particles was calculated.	47
Verapamil (Propylene foam, Eudragit RS, ethyl cellulose, poly methyl meth acrylate)	For dissolution: 900 mL of either 0.1 N HCl or the phosphate buffer (pH 6.8) at 37ºC ± 0.1ºC in USP dissolution apparatus (I) at 100 rpm. Verapamil (Propylene foam, Eudragit RS, ethyl cellulose, poly methyl meth acrylate) 30 mL of 0.1 N HCl (containing 0.02% wt/wt Tween 20), pH 1.2. Floatation was studied by placing 60 particles into 30-mL glass flasks. Number of settled particles was counted.	48
Captopril (Methocel K4M)	900 mL of enzyme-free 0.1 N HCl (pH 1.2) in USP XXIII apparatus II (basket method) at 37ºC at 75 rpm.	49
Theophylline (HPMC K4M, Polyethylene oxide)	0.1 N HCl in USP XXIII Apparatus II at 50 rpm at 37°C. Its buoyancy to upper 1/3 of dissolution vessel was measured for each batch of tablet.	20
Furosemide	For dissolution: continuous flow through cell gastric	50

(β Cyclodextrin, HPMC 4000, HPMC 100, CMC, Polyethylene glycol)	fluid of pH 1.2, 45–50 m N/m by adding 0.02% Polysorbate 20 (to reduce the surface tension), the flow rate to provide the sink conditions was 9mL/min.	
Piroxicam (microspheres) (Polycarbonate) .	For dissolution: 900 mL dissolution medium in USP paddle type apparatus at 37ºC at 100 rpm	51
Ampicillin (Sodium alginate)	For dissolution: 500 mL of distilled water, JP XII disintegration test medium No.1 (pH 1.2) and No.2 (pH 6.8) in JP XII dissolution apparatus with paddle stirrer at 50 rpm.	52
Sulphiride (CP 934P)	For dissolution: 500 mL of each JP XII disintegration test medium No. 1 (pH 1.2) and No. 2 (pH 6.8) in JP XII dissolution apparatus at 37º C at 100 rpm.	53
Isardipine (HPMC)	300 mL of artificial gastric fluid in a beaker, which was suspended in water bath at 37ºC agitated by magnetic stirrer and by bubbling CO2 free air.	54
Sotalol	Lag time required for the tablet to start floating on the top of the basket in dissolution apparatus was measured	55
Furosemide	Tablet were placed in a 400-mL flask at pH 1.2 and both the time needed to go upward and float on surface of the fluid and floating duration were determined.	56

Table 2. In Vivo Evaluation

Drug(polymer)	Method	Ref
Tranilast (Eudragit S (BaSo4))	Two healthy male volunteers administered hard gelatin capsules packed with microballoons (1000 mg) with 100 mL water. X-ray photographs at suitable intervals were taken.	57
Isardipine (HPMC)	Two phases: Phase I (fasted conditions):Five healthy volunteers (3 males and 2 females) in an open randomized crossover design, Capsules ingested in sitting position with 100 mL of tap water. Phase II (fed states): Four subjects received normal or MR capsules in a crossover design after standard breakfast. Venous blood samples were taken in heparinized tubes at predetermined time intervals after dosing.	54
Amoxicillin trihydrate	Six healthy fasted male subjects were selected; serum drug levels were compared in a single dose crossover study following administration of tablets/capsules.	46

Floating beads	Gamma scintigraphy: In vivo behavior of coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers of mean age 34 yrs (22–49).	58
Pentoxyfillin	Four healthy beagle dogs (fasted for 24 hours). Tablet was administered with 100 mL of water for radiographic imaging. The animal was positioned in a right lateral/ventrodorsalrecumbency.	45
Furosemide	Six purebred young male beagle dogs (9.6 to 14.3 kg), a 4-period crossover study balanced by residual effects was employed. Dogs were fasted overnight (water ad libitum), a catheter was inserted into right and left cephalic vein with 0.3 mL heparin lock, blood sampling was done at appropriate intervals.	56
Piroxicam	Nine healthy male albino rabbits weighing 2.2–2.5 kg were divided into 3 groups and were fasted for 24 hours. First batch: fed with 20 mg of Piroxicam powder in a gelatin capsule. Second batch: 67% Piroxicam loaded Piroxicam microspheres (~20mg of drug). Third batch: 7 mg of Piroxicam and 67% Piroxicam-loaded Piroxicam microspheres (~20 mg of drug).	51
Sulphiride	Three 3.5-kg white male rabbits 10 mg of the drug/kg body weight was administered in a crossover manner with a 14-day washout period between dosing. Both IV and oral dosage form were given.	53

IN-VITRO EVALUATION, [59,60,61,62]

Floating systems

Buoyancy Lag Time:

It is determined in order to assess 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:

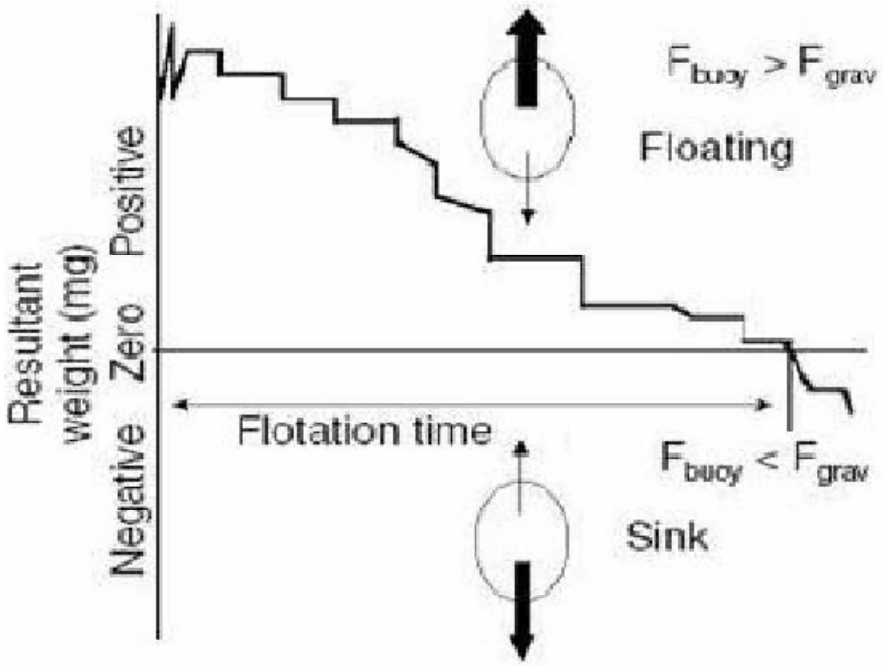
Test for buoyancy is usually performed in SGF-Simulated Gastric Fluid maintained at 370C.The time for which the dosage form continuously floats on the dissolution media is termed
as floating time.

Specific Gravity / Density:

Density can be determined by the displacement method using Benzene as displacement Medium.

Resultant Weight[63]**:**

Now we know that bulk density and floating time are the main parameters for describing buoyancy. But only single determination of density is not sufficient to describe the buoyancy because density changes with change in resultant weight as a function of time. For example a matrix tablet with bicarbonate and matrixing polymer floats initially by gas generation and entrapment but after some time, some drug is released and simultaneously some outer part of matrixing polymer may erode out leading to change in resultant weight of dosage form. The magnitude and direction of force/resultant weight (up or down) is corresponding to its buoyancy force (Fbuoy) and gravity force (Fgrav) acting on dosage form.



F= Fbuoy - FgravF = Df g V – Ds g V F = (Df – Ds) g V
F = (Df – M/V) g V
Where,
F = resultant weight of object
Df = Density of Fluid
DS = Density of Solid object
g = Gravitational force
M = Mass of dosage form
V = Volume of dosage form
So when Ds, density of dosage form is lower, F force is positive gives buoyancy and when it is Ds is higher, F will negative shows sinking.

Swelling systems

Swelling Index:

After immersion of swelling dosage form into SGF at 370C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness / diameter with time.

Water Uptake:

It is an indirect measurement of swelling property of swellable matrix. Here dosage form is removed out at regular interval and weight changes are determined with respect to time. So it is also termed as Weight Gain.

Water uptake = WU = (Wt – Wo) * 100 / Wo

Where,
Wt = weight of dosage form at time t
Wo = initial weight of dosage form

IN-VITRO DISSOLUTION TESTS [63]:

In vitro dissolution test is generally done by using USP apparatus with paddle and GRDDS is placed normally as for other conventional tablets. But sometimes as the vessel is large and paddles are at bottom, there is much lesser paddle force acts on floating dosage form which generally floats on surface. As floating dosage form not rotates may not give proper result and also not reproducible results. Similar problem occur with swellable dosage form, as they are hydrogel may stick to surface of vessel or paddle and gives irreproducible results. In order to prevent such problems, various types of modification in dissolution assembly made are as follows.

To prevent sticking at vessel or paddle and to improve movement of dosage form, method suggested is to keep paddle at surface and not too deep inside dissolution medium.

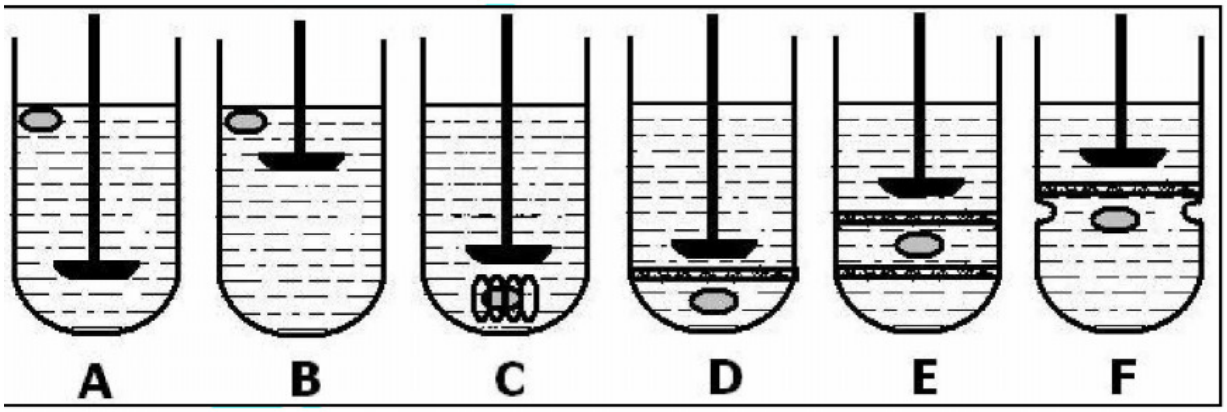


Figure 15- Dissolution of Dosage form

Floating unit can be made fully submerged, by attaching some small, loose, non- reacting material, such as few turns of wire helix, around dosage form. However this method can inhibit three dimensional swelling of some dosage form and also affects drug release.

Other modification is to make floating unit fully submerged under ring or mesh assembly and paddle is just over ring that gives better force for movement of unit.

Other method suggests placing dosage form between 2 ring/meshes.

In previous methods unit have very small area, which can inhibit 3D swelling of swellable units, another method suggest the change in dissolution vessel that is indented at some above place from bottom and mesh is place on indented protrusions, this gives more area for dosage form.

Inspite of the various modifications done to get the reproducible results, none of them showed co-relation with the in-vivo conditions. So a novel dissolution test apparatus with modification of Rossett-Rice test Apparatus was proposed.

IN-VIVO EVALUATION 64, 65, 66

Radiology:

X-ray is widely used for examination of internal body systems. Barium Sulphate is widely used Radio Opaque Marker. So, $BaSO_4$ is incorporated inside dosage form and X-ray images are taken at various intervals to view GR.

Scintigraphy:

Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is 99Tc.

Gastroscopy:

Gastroscopy is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS.

Magnetic Marker Monitoring:

In this technique, dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment. Advantage of this method is that it is radiation less and so not hazardous.

Ultrasonography:

Used sometimes, not used generally because it is not traceable at intestine.

13C Octanoic Acid Breath Test:

13C Octanoic acid is incorporated into GRDDS. In stomach due to chemical reaction, octanoic acid liberates CO_2 gas which comes out in breath. The important Carbon atom which will come in CO_2 is replaced with 13C isotope. So time up to which $13CO_2$ gas is observed in breath can be considered as gastric retention time of dosage form. As the dosage form moves to intestine, there is no reaction and no CO_2 release. So this method is cheaper than other.

ADVANTAGES[67, 68, 69]

1) Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide

2) Maintenance of constant therapeutic levels over a prolonged period and thus reduction influctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics.E.g. B-lactam antibiotics (penicillin and cephalosporin)

3) For drugs with relatively short half life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient Compliance.

4) They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.

5) Gastro retentive drug delivery can produce prolongs and sustains release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.

6) The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable Effects of side effects.

7) Gastro retentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index.

8) Gastro retentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.

9) Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.

APPLICATION[70, 71, 72, 73]

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:

1. Sustained Drug Delivery:

Hydrodynamicaly Balanced System type dosage forms remain in the stomach for several hours, increase the gastric residence time and thus release the drug over a prolonged period of time. These dosage forms have bulk density less than one, relatively large in size and did not easily pass through pylorus. Madopar HBS formulation has shown to release Levodopa for up to 8 hours in vitro whereas the standard formulation released Levodopa in less than 30 min.

2 . 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, furosemide. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets. Recently , a bilayer floating capsule of misoprostol which is a synthetic analog of prostaglandin E1, was developed and used as a protectant of gastric ulcers caused by administration of NSAIDS.By targeting slow delivery of misoprostol to the stomach the desired therapeutic levels could be achieved and wastage of drug be reduced.

3. Absorption Enhancement:

Drugs that have poor bioavailability because of site specific absorption from the upper parts of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significantly increase in the bioavailability of floating dosage forms(42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%)[49].

4.There are some cases in where the relative bioavailability of floating dosage form is reduced as compared to conventional dosage form e.g. floating tablets of amoxicillin trihydrate has bioavailability reduced to 80.5% when compared with conventional capsule in such cases , the

reduction in bioavailability is compensated by the advantages offered by FDDS.

5. FDDS served as an excellent drug delivery system for the eradication of Helicobacter pylori, which is now believed to be causative bacterium for chronic gastritis and peptic ulcers. The patient requires high concentration to be maintained at the site of infection that is within gastric mucosa. The floating dosage form by virtue of its floating ability was retained in stomach and maintained high concentration of drug in the stomach.

6.Floating system are particularly useful for acid stable drugs, drugs which are poorly soluble or unstable in intestinal fluids and for those which undergo abrupt changes their pH- dependent solubility due to food, age and pathophysiological condition of GIT.

7. Alza corporation has developed a gastro retentive platform for the OROS® system, which showed prolong residence time in a dog model as the product remain in the canine stomach at 12 hrs post dose and was frequently present at 24 hrs

Table 3. List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems.

Dosage Forms	Drugs
Tablets	Chlorpheniramine maleate, Theophylline, Furosemide ,Ciprofloxacin ,Pentoxyfillin ,Captopril Acetylsalicylic acid ,Nimodipine ,Amoxicillin trihydrate ,Verapamil HCl ,Isosorbide di nitrate ,Sotalol ,Atenolol ,Isosorbide mono nitrate Acetaminophen ,Ampicillin ,Cinnarazine ,Diltiazem ,Fluorouracil ,Piretanide ,Prednisolone ,Riboflavin- 5Phosphate
Capsule	Nicardipine ,L- Dopa and benserazide chlordiazepoxide HCl ,Furosemide ,Misoprostal ,Diazepam ,Propranlol ,Urodeoxycholic acid
Microsphere	Verapamil ,Aspirin, griseofulvin,and p-nitroaniline ,Ketoprofen ,Tranilast ,Iboprufen ,Terfenadine
Granules	Indomathacin ,Diclofenac sodium ,Prednisolone
Films	Drug delivery device,cinnarizine
Powders	Several basic drugs

Table 4. Some Marketed Formulation For Floating Drug Delivery System[75]

Sr.no	Product	Drug	Delivery system	Company, Country
1)	Liquid gavison	AluminiumHydroxide, Magnesium Carbonate	Effervescent floating liquid alginate preparation	GlaxoSmithKline, INDIA
2)	Almagate Flatcoat	Aluminium-Magnesium Antacid	Floating dosage form	----------
3)	Topalkan	Aluminum magnesium Antacid	Floating liquid alginate preparation	PierreFabreDrug, FRANCE
4)	Valrelease	Diazepam	Floating capsule	Hoffmann-LaRoche,USA
5)	Madopar	Levodopa and benserzide	Floating CR capsule	Roche Products,USA
6)	Conviron	Ferrous sulphate	Colloidal gel forming FDDS	Ranbaxy, INDIA
7)	Cifran OD	Ciprofloxacin	Gas-generating floating Tablets	Ranbaxy, INDIA
8)	Cytotec	Misoprostal	Bilayer floating Capsule	Pharmacia,USA
9)	Oflin OD	Ofloxacin	Gas generating floating tablet	Ranbaxy , India

Table 5. Patent on FDDS

Drug	Dosage Form	Patent application number
Azithromycin	Swelling type oral CR tablet	US patent Appl 2007196396
Metformin HCl	Swelling type oral CR tablet	US patent US6488962
Rosiglitazone	Swelling type tablet	EP Patent1732513
Heparin& insulin	Bilayered SR tablet	US Patent Appln 2008153779
Levodopa & Carbidopa	Swelling Tablet	EP Patent 1560569
Bupropion HBr	Swelling Tablet	US Patent 7241805
Valsartan	Swelling Tablet	WO PCT Appln 2008027945
Gabapentin	Swelling Tablet	US Patent Appln 2007092565
Ranitidine HCL	Swelling Tablet	US Patent 6340475
Theophylline	Multi-layered tablet	US Patent 5783212
Ciprofloxacin, Acyclovir, Ofloxacin	Buoyant bilayer tablet	US Patent Appln 2006013876
Diltiazem HCl	Buoyant CR tablet	WOPCT Appln 02102415
Glipizide, Nifedipine, Verapamil	Pellets, beads, granules or capsules	WOPCT Appln 0110405
Amoxicillin	SR floating capsule form	US Patent Appln 2006121106
Theophylline, Ampicillin, Captopril	Non-compressed SR floating tablets	US Patent 4814179
Riboflavin, Chlordiazepoxide, Diazepam	HBS of SR Tablet	US Patent 4451260
Misoprostol+Aspirin, Diclofenac,Piroxicam, Ibuprofen or Naproxen	HBS of bilayer capsule	US Patent 5232704
Cimetidine, Ranitidine & Omeprazole	Antacid powders, tablets	US Patent 5288506
Methotrexate	SR Tablet	US Patent Appln 2008268045
Ofloxacin, Acyclovir, Simvastatin, Carbamazepine, Niacin, Cefixime	SR Tablet	Indian Patent IN2002MU00769

LIMITATIONS[34, 65, 74]:

Require a higher level of fluids in the stomach.

Not suitable for Drugs that...

o Have solubility problems in gastric fluid.E.g. phenytoin

o Cause G.I irritation. E.g.NSAIDS.

o Are unstable in acidic environment.

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

The floating systems in patients with achlorhydria can be questionable in case of swellable system.

Retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.

The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.

The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.

FUTURE POTENTIAL[65]

FODDS is novel drug delivery system which is so far limited to the experimental works, but system is having lot of potential. in present era patient compliance is a major issue in front of formulation and development pharmacist. In such situation FODDS will play an important role in following aspects. The reduced fluctuations in the plasma

level of drug results from delayed gastric emptying. Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability. FODDS considered as a beneficial strategy for the treatment of gastric and duodenal cancers. FODDS concept can also be utilized in the development of various anti-reflux formulations.

CONCLUSION:

A novel floating controlled-release drug delivery system was formulated in an effort increase the gastric retention time of the dosage form and to control drug release. One of the most feasible approaches for achieving a prolonged and predictable dug delivery profiles in the gastrointestinal tract is to control the gastric residence time, using gastroretentive dosage forms that will provide us with new and important therapeutic options. Floating matrix tablets are designed to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability

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