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A REVIEW ON FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

Floating drug delivery system are designed to prolong the gastric residence time after oral administration at a particular site and controlling the release of drug especially useful for achieve controlled plasma level,improve bioavailability,reduce drug waste,&enhance the solubility of drugs that are less soluble in high pH environment.Floating drug delivery system(FDDS) is one amongst the gastro retentive drug delivery system(GRDDS) used to achieve prolonged gastric residence time.Various approaches are currently utilized in the prolongation of gastric retention time(GRT) including FDDS,swelling and expandable systems,polymeric bioadhesive systems,high density systems,modified shape systems & other delayed gastric emptying devices.In this review current and recent developments of stomach specific FDDS are discussed that helps to overcome physiological adversities like short gastric residence times & unpredictable gastric emptying times.

KEYWORDS : *GRT,FDDS,GRDDS.*

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INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transittime of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans

because of which wide inter- and intra-subject variations [1] are observed . Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine).The identification of new diseases and the resistance shown towards the existing drugs called for the introduction of new therapeutic molecules.

Since the last three decades many drug molecules formulated as Gastroretentive Drug Delivery System (GRDDS) have been patented keeping in view its commercial success [2]. Oral controlled release (CR) dosage forms (DF) have been extensively used to improve therapy of many important medications.The bioavailability of drugs with an absorption window in the upper small intestine is generally limited with conventional pharmaceutical dosage forms. The residence time of such systems and, thus, of their drug release into the stomach and upper intestine is often short. To overcome this restriction and to increase the bioavailability of these drugs, controlled drug delivery systems, with a prolonged residence time in the stomach, can be used. Incorporation of the drug into a CR-delivery system, which releases its payload in the stomach over a prolonged time period, can lead to significant therapeutic advantages owing to various pharmacokinetic (PK) and pharmacodynamic aspects. Gastroretentive dosage forms (GRDFs) are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract. This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and/or their therapeutic outcome[3] .

ADVANTAGES [4,5]:

Floating drug delivery systems have numerous advantages listed below:

1) The principle of HBS can be used for any particular medicament or class of medicament.

2) The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.

3) The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g.antacids.

4) The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.

5) Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolve drug available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine.

6) When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption is expected under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

7) Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.

8) Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric

retention will extend the time within which drug absorption can occur in the small intestine.

9) Certain types of drugs can benefit from using gastro retentive devices. These include:

- Drugs acting locally in the stomach;
- Drugs those are primarily absorbed in the stomach;
- Drugs those are poorly soluble at an alkaline pH;
- Drugs with a narrow window of absorption;
- Drugs absorbed rapidly from the GI tract; and

Drugs those degrade in the colon.

DISADVANTAGES [6]:

1) There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.

2) Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.

3) Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.

4) It requires sufficient high level of fluids in the stomach for the drug delivery to float.

5) The dosage form should be administered with a full glass of water (200-250 ml.

BIOLOGICAL ASPECTS OF GRDFS [7,8]:

Role of GI tract: Stomach

The stomach is J-shaped organ located in the upper left hand portion of the abdomen, just below the diaphragm. It occupies a portion of the epigastric and left hydrochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area very little absorption takes place from the stomach. It provides barrier to the delivery of drugs to small intestine.

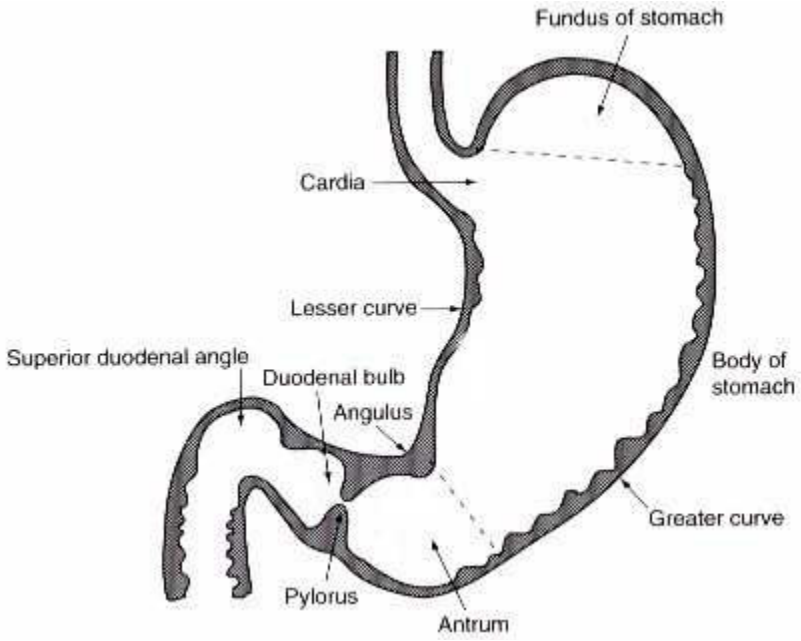


Fig. 1 : anatomy of stomach

The stomach is divided into three anatomical regions. I)Fundus ii) Body and iii) Pylorus (or antrum). The proximal stomach consisted of fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric contents for gastric emptying. Gastric emptying occurs both in

fasting as well as fed states.

The GI tract is always in a state of continuous motility. There are two modes of motility pattern.The digestive mode and interdigestive mode. In case of fasted state an interdigestive series of electrical events occurs in cyclic manner both through stomach and small intestine every 2-3 hr.This electrical activity is termed as interdigestive myoelectric cycle or migrating myoelectric complex (MMC), which is further divided into four phases.

Phase I : Period of no contraction.
Phase II : Period of intermittent contraction.
Phase III : Period of regular contractions at the maximal frequency that
migrate distally.
Phase IV : Period of transition between phase III and phase I.

Phase III has a housekeeping role and serves to clear all indigestible materials from the stomach and small intestine. Consequently, a controlled-release gastrointestinal drug delivery system must be capable of resisting the house keeping action of phase III. Studies revealed that in the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. It can be
concluded that feeding results in a lag time before onset of gastric emptying cycle.

APPROACHES TO GASTRIC RETENTION[9-13]:

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include –

a) Floating Systems:

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus
remain buoyant in the stomach for a prolonged period of time, without affecting the gastric
emptying rate. While the system is floating on the gastric contents, the drug is released slowly at
a desired rate from the system. After the release of the drug, the residual system is emptied from
the stomach. This results in an increase in the GRT and a better control of fluctuations in the
plasma drug concentrations. Floating systems can be classified into two distinct categories, noneffervescent and effervescent systems.

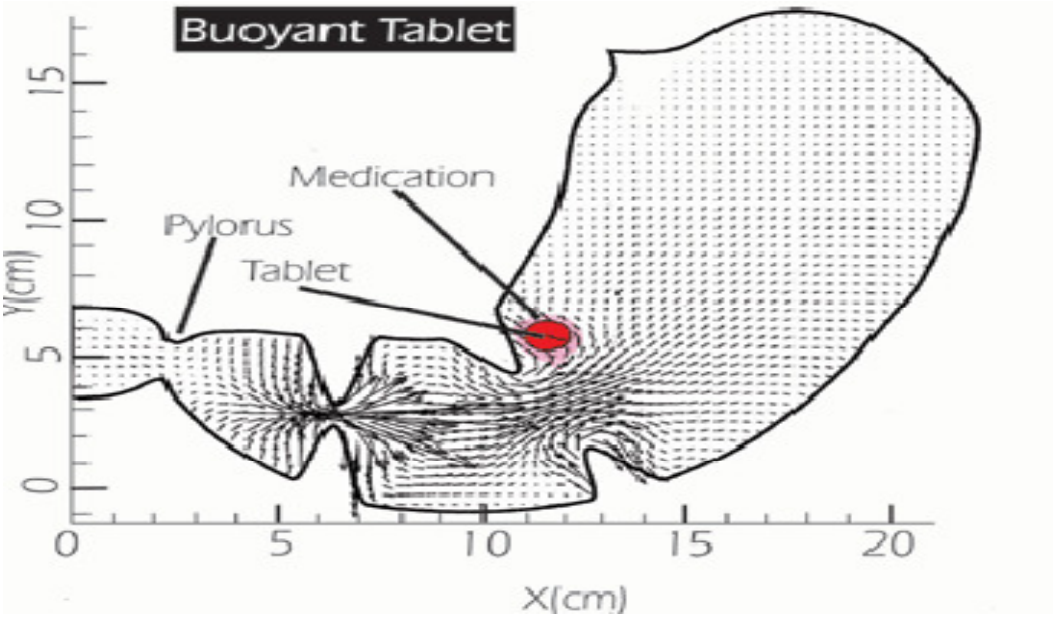


Fig. 2 : graphic of buoyant tablet which is less dense than the stomach fluid and therefore remains in the fundus.

b) Bio/Muco-adhesive Systems:

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the

stomach, by increasing the intimacy and duration of contact of drug with the biological membrane.

The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect. Binding of polymers to the mucin/epithelial surface can be divided into three broad categories :–

- Hydration-mediated adhesion.
- Bonding-mediated adhesion.
- Receptor-mediated adhesion.

c) Swelling and Expanding Systems:

These are the dosage forms, which after swallowing, swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as “plug type system”, since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state.

A balance between the extent and duration of swelling is maintained by the degree of crosslinking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.

d) High Density Systems:

These systems with a density of about 3 g/cm3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm3 acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. They are retained in the antrum of stomach as shown in Fig.3.

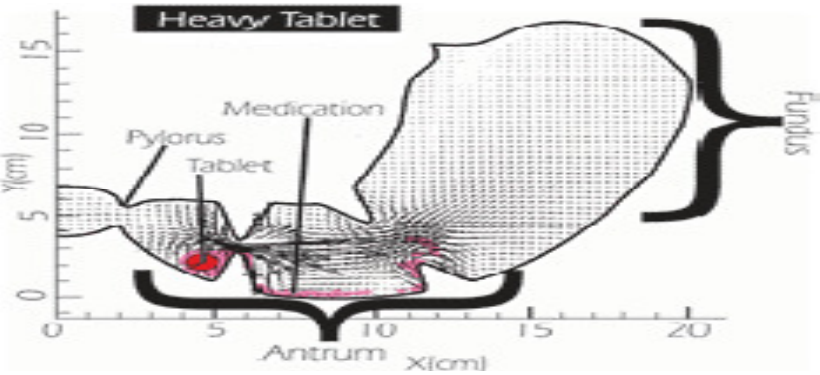


Fig. 3: graphic of heavy tablet which is denser than the stomach fluid and therefore sinks to the antrum

e) Incorporation of Passage Delaying Food Agents:

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C10-C14.

f) Ion Exchange Resins:

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate

and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

g) Osmotic Regulated Systems*:*

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible 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 controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.

TYPES OF FLOATING DRUG DELIVERY SYSTEMS (FDDS)[14,15,16]:

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

A. Effervescent System, and

B. Non- Effervescent System.

A. Effervescent System:-

Effervescent systems include use of gas generating agents, carbonates (ex. 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 the 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.

I. Gas Generating systems

II. Volatile Liquid/Vacuum Containing Systems.

I. Gas – Generating Systems*:*

1. Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced Sysem (HBS):

These are as shown in Fig.4 and formulated by intimately mixing the CO_2 generating agents and the drug with in 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 fluctuations in plasma drug concentration.

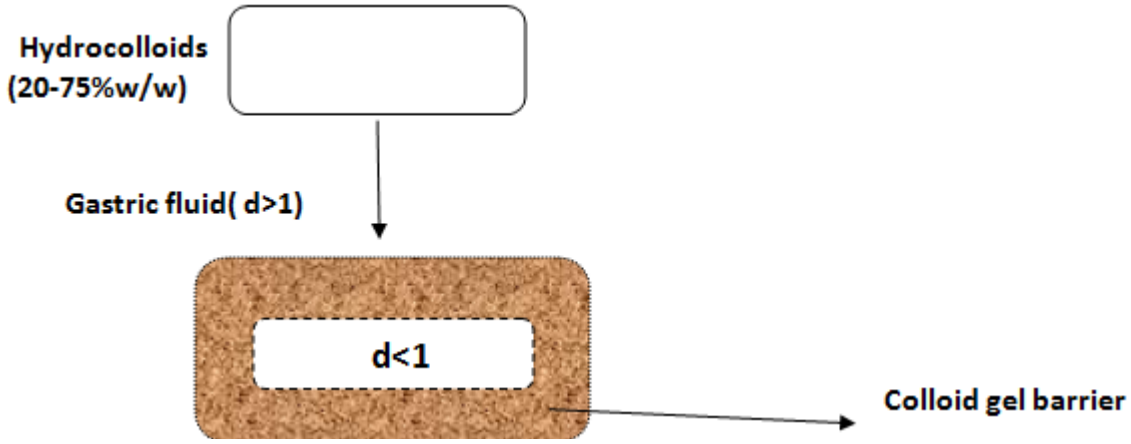


Fig. 4 : intra gastric single layer floating tablet

2. Intra Gastric Bilayer Floating Tablets*:*

These are also compressed tablet as shown in Fig 6 and containing two layer i.e.,

i. Immediate release layer and
ii. Sustained release layer.

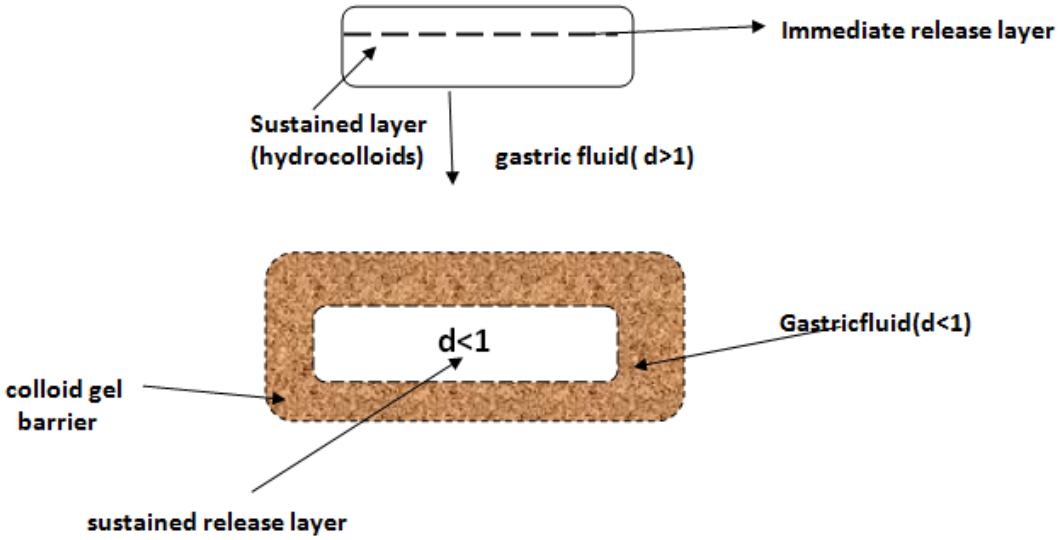
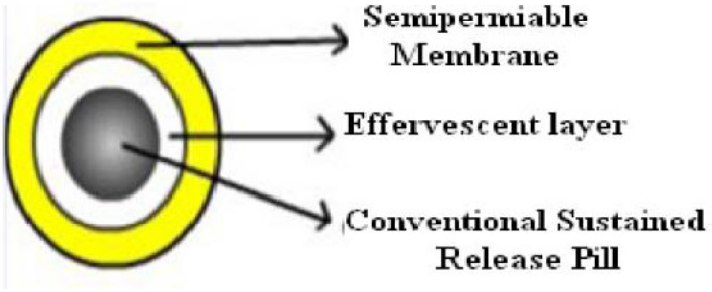


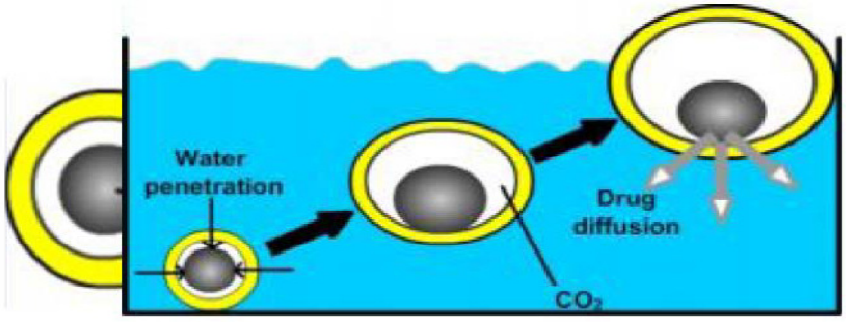
Fig. 5: intra gastric bilayer floating tablet.

3. Multiple Unit type floating pills:

These system consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consist of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, 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 CO2 within the system.



(A)



(B)

Fig. 6 :Gas generating system.

II. Volatile Liquid / Vacuum Containing Systems:

1. Intragastric Floating Gastrointestinal Drug Delivery System:

These system can be made to float in the stomach because of floatation chamber, which may be a vacum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microprous compartment, as shown in Fig.7.

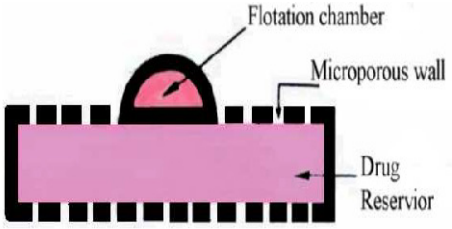


Fig.7 : intra gastric floating gastrointestinal drug delivery device

***2*. 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 capsuledissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid. This system is shown in Fig. 8.

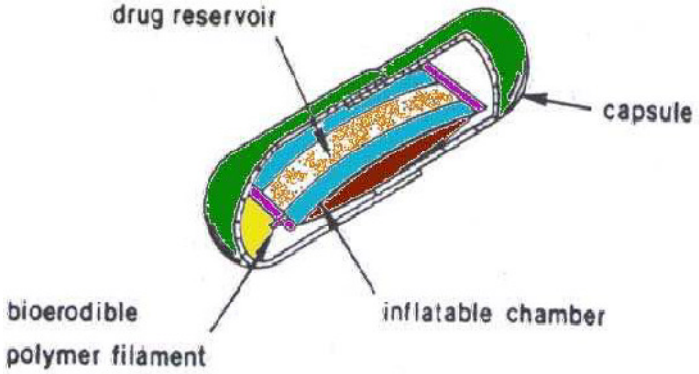


Fig. 8: inflatable gastrointestinal delivery system

3. 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 intragastirc 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 consist 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 semipermeable housing.

In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined

time to deflate the support. The deflated drug delivery system is then emptied from the stomachThis system is shown in Fig. 9

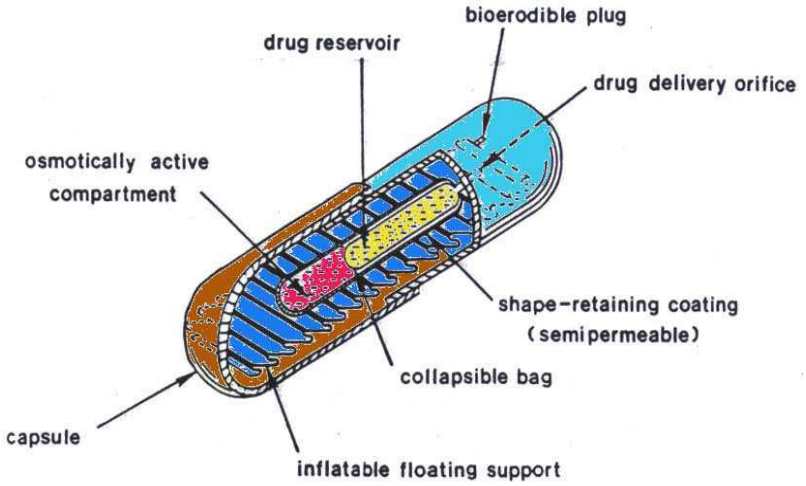


Fig. 9: intragastric osmotically controlled drug delivery system

B. 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 bioadhesive polymer such as chitosan and carbopol. The various types of this system are as:

1. Single Layer Floating Tablets*:*

They are formulated by intimate mixing of drug with a 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.

2. Bilayer Floating Tablets*:*

A bilayer tablet contain two layer one 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.

3. Alignate Beads*:*

Multi unit floating dosage forms were 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, these floating beads gave a prolonged residence time of more than 5.5 hour.

4. Hollow Microspheres*:*

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol:dichloromethane solution ofthe drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 400C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug.

The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*.

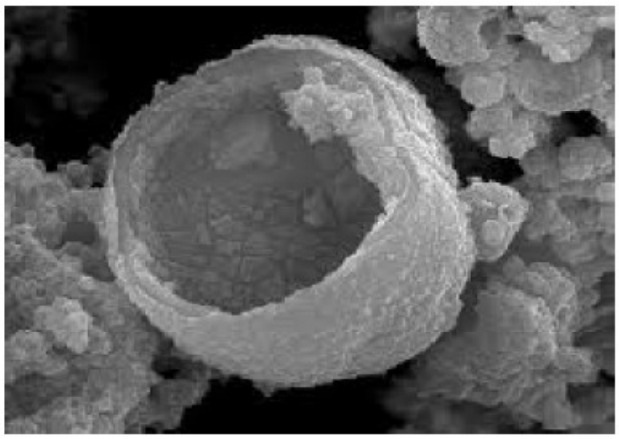


Fig. 10: micro balloons

5.Colloidal gel barrier system

Sheth and Tossounian first designated this 'hydrodynamically balanced system'. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorbtion sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxypropyl cellulose, hydoxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysacharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

6. Microporous compartment system

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

FACTORS CONTROLLING GASTRIC RETENTION TIME OF DOSAGE FORM:

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

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

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

Shape of dosage form – Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GRT. 90% to 100% retention at 24 hours compared with other shapes.

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

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

Nature of meal – Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

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

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

Gender – Mean ambulatory GRT in males (3.4□0.6 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 – Elderly people, especially those over 70, have a significantly longer GRT.

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

Concomitant drug administration – Anticholinergics like Atropine and Propantheline, opiates like Codeine and prokinetic agents like Metoclopramide and Cisapride.

Biological factors – Diabetes and Crohn's disease.

DRUGS USED IN THE FORMULATIONS OF STOMACH SPECIFIC FLOATING DOSAGE FORMS[16,19,20]:

Floating microspheres – Aspirin, Griseofulvin, pnitroaniline, Ibuprofen, Ketoprofen, Piroxicam, Verapamil HCl, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol, Tranilast and Terfinadine

Floating granules - Diclofenac sodium, Indomethacin and Prednisolone

Films – Cinnarizine, Albendazole

Floating tablets and Pills - Isosorbide mononitrate, Diltiazem, Acetylsalicylic acid, Piretanide, Sotalol, carbamazepine, Furosamide, Pentoxyphylline, captopril, Nimodipine. Acetaminophen, Amoxycillin trihydrate, Diazepam.

Floating Capsules -Diazepam, Ursodeoxycholic acid, Verapamil HCl, Nicardipine, Furosemide, Misoprostal.

Table-1: **commercial gastroretentive floating formulations**

Brand name	Delivery system	Drug(dose)	Company name
Valrelease®	Floating capsule	Diazepam (15mg)	Hoffmann-LaRoche, USA
Madopar® HBS (Prolopa® HBS)	Floating, CR capsule	Benserazide (25mg) and L-Dopa (100mg)	Roche Products, USA
Liquid Gaviscon®	Effervescent Floating liquid alginate preparations	Al hydroxide (95 mg), Mg Carbonate (358 mg)	GlaxoSmithkline, India
Topalkan®	Floating liquid alginate preparation	Al – Mg antacid	Pierre Fabre Drug, France
Almagate Flot coat®	Floating dosage form	Al – Mg antacid	_
Conviron®	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India
Cytotech®	Bilayer floating capsule	Misoprostol (100µg/200µg)	Pharmacia, USA
Cifran OD®	Gas-generating floating form	Ciprofloxacin (1gm)	Ranbaxy, India

SUITABLE DRUG CANDIDATES FOR GASTRORETENTION [14]:

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need for repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is
where absorption occurs and contact time is limited. Under normal or average conditions, for example, material passes through the small intestine in as little as 1-3 hours.5 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 GIT, 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.

EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS[20-23]:

Various parameters that need to be evaluated in gastroretentive 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.

A. In Vitro Methods

1) Floating lag time and floating time:

The test for floating time measurement is usually performed in stimulated gastric fluid or 0.1 mole.lit-1 HCl maintained at 370C. It is determined by using USP dissolution apparatus containing 900 ml of 0.1 mole.lit- 1 HCl as a dissolution medium at 370C. The time taken by the dosage form to float is termed as floating lag time and
the time for which the dosage form floats is termed as the floating or flotation time. The system to check continuous floating behavior contains a stainless steel basket connected to a metal
string and suspended from a sartorius electronic balance.The floating object is immersed at affixed depth into a water bath, which is covered to prevent water evaporation. The upward floating force could be measured by the balance and the data transmitted to an online PC through RS232 interphase using a sarto wedge program. A lotus-spread sheet could automatically pick
up the reading on the balances. Test medium used in floating kinetics measurements was 900 ml simulated gastric fluid (pH 1.2) maintained at 37°C, data was collected at 30 sec interval; baseline was recorded and subtracted from each measurement. Dissolution basket had a holder at the bottom to measure the downward force.

2) Dissolution study

Gohel et al proposed a more relevant in vitro dissolution method to evaluate a floating drug delivery system (for tablet dosage form). A 100-mL glass beaker was modified by adding a side arm at the bottom of the beaker so that the beaker can hold 70 ml of 0.1 mole.lit-1 HCl dissolution medium and allow collection of samples. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min to mimic gastric acid secretion rate. The performance of the modified dissolution apparatus was compared with USP dissolution
Apparatus 2 (Paddle). The problem of adherence of the tablet to the shaft of the paddle was observed with the USP dissolution apparatus. The tablet did not stick to the agitating device in the proposed dissolution method. The drug release followed

zero-order kinetics in the proposed method. The proposed test may show good in vitro-in vivo correlation since an attempt is made to mimic the in vivo conditions such as gastric volume, gastric emptying, and gastric acid secretion rate.

3) Resultant weight test:

An in vitro measuring apparatus has been conceived to determine the real floating capabilities of buoyant dosage forms as a function of time. It operates by measuring the force equivalent to the force F required to keep the object totally submerged in the fluid This force determines the resultant weight of the object when immersed and may be used to quantify its floating or nonfloating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the vectorial sum of buoyancy (F bouy) and gravity (F grav) forces acting on the object as shown in the equation

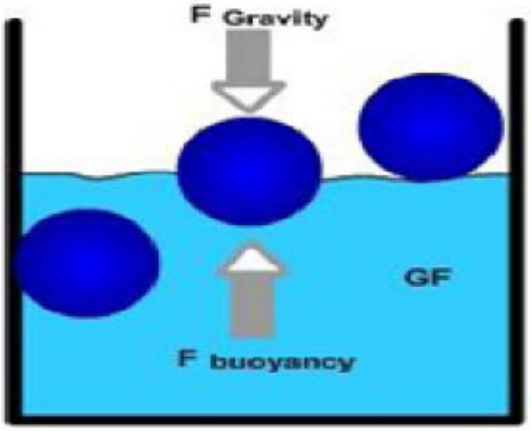
$F = F_{buoy} – F_{grav}$

$F = d_f gV – d_s gV = (d_f - d_s) gV$

$F = (df – M / V) gV$

in which F is the total vertical force (resultant weight of the object), g is acceleration due to gravity, d f is the fluid density, d s is the object density, M is the object mass,

and V is the volume of the object . By convention, a positive resultant weight signifies that the force F is exerted upward and that the object is able to float, whereas a negative resultant weight means that the force F acts downward and that the object sink



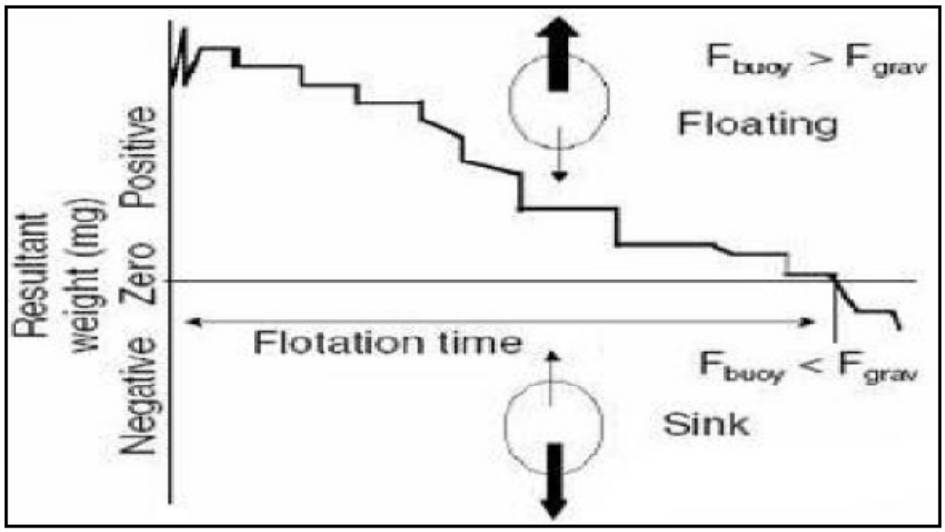


Fig11. effect of various forces on floating system

B. In vivo method

1) X-Ray method

X-Ray is a very popular evaluation parameter for floating dosage form now a day. It helps to locate dosage form in the g.i.t. 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 Xrays.

2) gamma-Scintigraphy

Gamma -Emitting radioisotopes compounded into CR-DFs has become the state-of-art for evaluation of gastroretentive formulation in healthy volunteers. A small amount of a stable isotope e.g. Sm, is compounded into DF during its preparation. The main drawbacks of gamma - scintigraphy are

the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique and the complicated and expensive preparation of radiopharmaceuticals.

3) Gastroscopy

It comprises of peroral endoscopy, used with a fibereoptic and video systems. It is suggested that gastroscopy may be used to inspect visually the effect of prolonged stay in stomach milieu on the FDDS. Alternatively, FDDS may be drawn out of the stomach for more detailed evaluation.

4) Ultrasonography

Ultrasonic waves reflected substantially different acoustic impedances across interface enable the imaging of some abdominal organs57. Most DFs do not have sharp acoustic mismatches across their interface with the physiological milieu. Therefore, Ultrasonography is not routinely used
for the evaluation of FDDS. The characterization included assessment of intragastric location of the hydrogels, solvent penetration into the gel and interactions between gastric wall and FDDS during peristalsis.

PATENTS ON FDDS[24]:

Table 2: patents of fdds

s.no.	Type of formulation	Patent no.	Ref
1	Gastro retentive dosage form	U.S-7,413,752.	Devane et al.,2008.
2	Multiple unit floating dosage form	European patent (EP)10697	Vanderbist etal .,2007
3	Bilayer tablet	EP-002445	Lohrey et al .,2004
4	Floating tablet	U.S-66,352279	Kotler et al.,2003
5	Microspheres	U.S-6207197	IIlum et al.,2001
6	3-layer tablet	U.S-5780057	Conte et al.,1998
7	Foams (or)hollow bodies	U.S-5626876	Muller et al.,1997
8	Floating tablet	U.S-5169639	Baichwal et al .,1992
9	Granule	U.S-4844905	Ichikawa et al .,1989
10	Floating capsules	U.S-4814178	Sheth et al.,1989
11	Tiny pills	U.S-4434153	Urguhart et al .,1978
12	Floating capsule	U.S-4126672	Sheth et al .,1978
13	Floating device	U.S-4055178	Harrigan et al .,1977
14	Empty globular shells	U.S-3976164	Watanable et al.,1976

CONCLUSION:

Drug absorption in GIT is variable process and gastric retention extend the time for drug absorption. Floating dosage form is apotential approach for gastro retentive dosage forms.A huge work has been done in the field of gastro retentive dosage form with the rationale to increase the patient compliances.The review gives idea the progress of FDDS in the literature and market with their advantages,disadvantages.

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