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GASTRORETENTIVE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The most Advantageous approach of the Gastro-retentive drug delivery systems improves the drug bioavailability and patient compliance by increasing the gastric residence time and controlling the drug release.These include floating/low density system, swelling and expanding system, bioadhesive/mucoadhesive system, high density system, magnetic system and raft forming system. The present review addresses briefly about the gasroretentive drug delivery system its include physiology of the stomach, objectives, needs, criteria, factors affecting, advantages and disadvantages, approaches, marketed product, evaluation parameters, applications of Gasrtoretentive drug delivery system. In order to understand various physiological difficulties to achieve gastric retention, we have summarized factors influencing gastric retention and also included various strategies for gastric retention. Gastroretentive drug delivery system has become leading methodology in site specific orally administered controlled release drug delivery system. Various drugs, which are unstable in alkaline pH, soluble in acidic pH, having narrow absorption window, site of action specific to stomach can be developed by using this technique.

KEYWORDS: Gastro-retentive drug delivery system, Approaches of gastro-retentive system, Application, Evolution parameters.

INTRODUCTION

Historically, oral drug administration has been the predominant route for drug delivery system. During the past two to three decades, numerous oral delivery systems have been

developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate.

The oral drug delivery system is the most advantageous approach to the Gastroretentive drug delivery system over the Conventional drug delivery system. The oral administration is the most convenient and preferred means of any drug delivery to the systemic circulation. The effective oral drug delivery practice depends on various factors like gastric empting process, gastrointestinal transit time of dosage form, drug release from dosage form and site of absorption of drug·Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms.It has been frequently observed that many drugs which are easily absorbed at upper gastrointestinal tract (GIT), eliminated quickly in to lower GIT because of the peristaltic movement. So it leads to incomplete absorption of drugs from upper part of GIT. To overcome this limitation, the development of oral gastro retentive sustained orcontrolled Release formulation is an attempt to release the drug slowly at upper GIT to maintain effective drug concentration in systemic circulation for a prolonged period. Gastroretentive dosage form are beneficial for such drugs by improving their

- Bioavailability
- Therapeutics efficiency
- Possible reduction of the dose
- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels
- Reduce drug wastage
- Improves solubility of drugs that are less soluble at high pH environment (e.g. weakly basic drug like domperidone,papaverine)[1,2,3]

Physiology of Stomach: The main function of the stomach is to process and transport food. It serves as a short-term storage reservoir, allowing a rather large meal to be consumed quickly. Substantial enzymatic digestion is initiated in stomach, particularly of proteins. Vigorous contractions. of gastric smooth muscle mix and grind foodstuffs with gastric secretions, resulting in liquefaction of food. As food is liquefied in the stomach, it is slowly released into the small intestine for further processing.

Anatomically the stomach is divided into three regions Fundus, Body and Antrum (pylorus) The proximal part made of fundus and body acts as a reservoir for undigested materials, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propellingactions. Gastric emptying occurs in both the fasting and fed states. During the fasting state an interdigestive series of electrical events take place which cycle both through stomach and intestine every 2-3 hrs, which is called as inter digestive myloelectric cycle or migrating myoelectric cycle (MMC).The MMC is further divided into following 4 phases as described by Wilson andWashington.

1. Phase I (Basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (Preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phaseprogresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.[1,3,4,7,9]

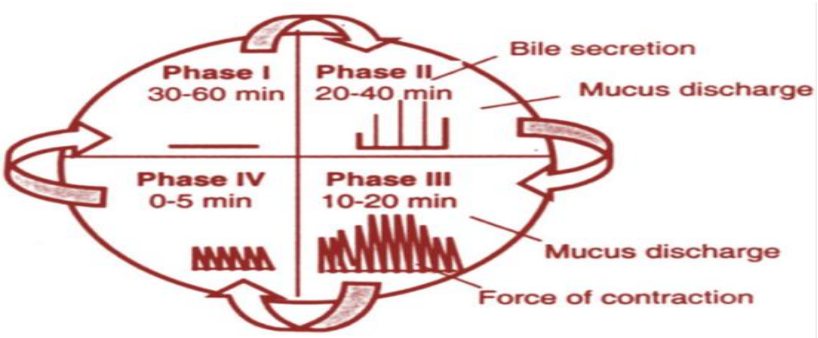

Fig. 1. Motility pattern in gastrointenstinal tract.

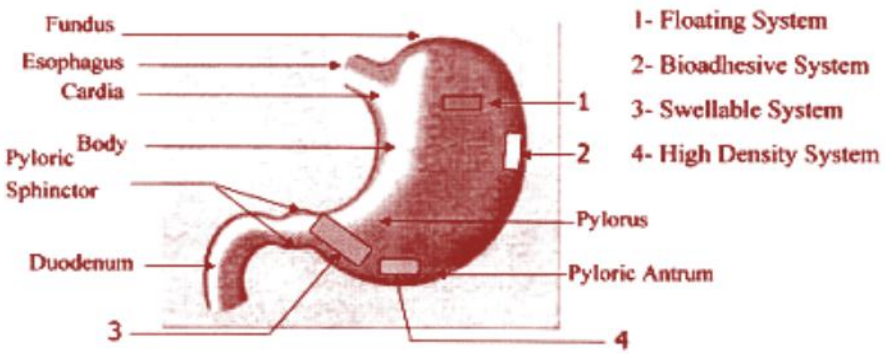

Fig. 2. Physiology of stomach.

Table. 1: Anatomical and Physiological feature of the gastrointestinal tract.

Section	Avg length(m)	Dia (cm)	Villi pre-sent	Absorption mechanim	pH	Major constituts	Food Transit time(Hr)
Oral cavity	15-20	10	-	Convective transport passive diffusion	5.2-6.8	Amylase, mucin, and maltase, ptylin	short
Esophagus	25	2.5	-	Not reported	5.0-6.0	-	Very short
Stomach	20	15	-	Convective transport and passive diffusion mechanism	1.2-3.5	HCl, pepsin, trypsin, ren-nin, lipase	0.25-3.0
Duodenum	25	05	*	Passive diffusion, convective, Active, facili-tated transport, ion pair, pinocytosis mechanism	4.6-6.0	Bile, trypsin, chyotrypsin, amylase, maltase lipase, nuclease, CYP3A4	1-2
Jejunum	300	5	**	Passive diffusion, convective, Active, facili-tated transport	6.3-7.3	Amylase, maltase, lipase, Sucrose, CYP3A5.	Not reported
Ileum	300	2.5-5.0	**	Passive diffusion, convective, active, facili-tated transport, ion pair, pinocytosis	7.6	Nuclease, nucleotidase, enterokinase	1-10
Colon	150	5	*	Passive diffusion, convective transport	7.9-8.0	-	4-20
Rectum	15-19	2.5	-	Passive diffusion, convective transport	7.5-8.0	-	Variable

*- Represents villi are absent, *Represents villi are scarcely present and **Represents villi are abundantly present.*[4]

Drug absorption windows

The drug absorption window of Gastroretentive dosage form is so excellent than that of the conventional dosag form. The absorption windows in the proximal gut can limit the bioavailability of orally administered compounds and can be a major obstacle to the development of controlled or sustained release formulations for important drugs. Methods to increase the residence of drug formulations at or above the absorption window are Gastroretentive dosage forms, that have a slow intestinal transit, in that include the floating system, bioadhesive system, swelling system, and sedimentation system. which is based on multiparticulates or large single unit systems. A good understanding of gastrointestinal transit in humans and the effect of factors such as food can be helpful in the design of rational systems that will have clinical benefit.

Pharmaceutical dosage forms with gastroretentive properties would enable an extended absorption phase of these drugs with narrow absorption window. After oral administration, dosage form would be retained in stomach and release drug there, in a controlled and prolonged manner so that drug could be supplied continuously to its absorption sites in upper GIT.[5,10]

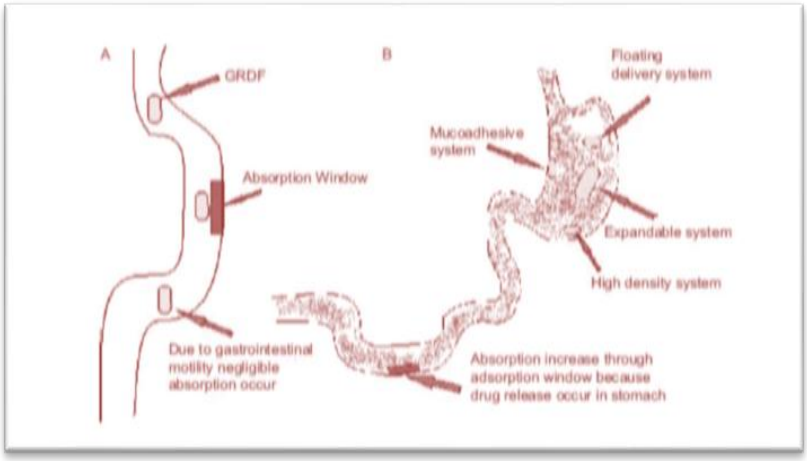

Fig. 3. Drug Absorption Window.

Table. 2: Conventional v/s Gastroretentive drug delivery system.[1,6,10]

Sr. No.	Conventionaldrug delivery system	Gastroretentive drug delivery system
1	High risk of toxicity	Very low risk of toxicity
2	Less patient compliance	Improves patient compliance
3	Not suitable for delivery of drugs with narrow absorption window in small intestine region	Suitable for delivery of drugs with narrow absorption window in small intestine region
4	Not much advantageous for drugs having rapid absorption through GIT	Very much advantageous for drugs acting locally in the stomach
5	Drugs which degrade in the colon	Drugs which degrade in the colon
6	Drugs acting locally in the stomach.	Drugs having rapid absorption through GIT
7	Not much advantageous drugs which are poorly soluble at an alkaline pH	Very much advantageous drugs which are poorly soluble at an alkaline pH
8	No risk of dose dumping	Possibility of dose dumping

Drug selection criteria for Gastroretentive drug delivery system

1. Narrow absorption window in GI tract, e.g., riboflavin and levodopa
2. The drugs basically absorbed from stomach and upper part of GIT, e.g., chlordiazepoxide and cinnarazine.
3. Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.
4. Locally active in the stomach, e.g., antacids and misoprostol.
5. Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole[3,4]

Limitations of gastroretentive drug delivery systems

1. High level of fluid is required in the stomach for drug delivery to float and work efficiently to release of drug.
2. These type of system is not suitable for drug solubility and stability problems in GIT.
3. Drugs such as nifedipine, which under goes first pass metabolism may not be desirable for the preparation of these types of systems.
4. The drugs which produce irritation to Gastric mucosa are not desirable drug candidates for DRDDS.
5. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.[4,9]

Factors affecting gastric retention time of the dosage form

1. Density: the density of the dosage form should be less than that of the gastric contents (1.004g/ml).

2. Size: dosage form having diameter of more than 7.5mm have more gastric residence time than that of 9.9mm diameter dosage form.

3. Shape of the dosage form: the tetra hedron resided in the stomach for longer period than other devices of similar size. Single or multiple unit formulation multiple unit formulation show a more predictable release profile and insignificant impairing of the performance due to failure of the units. , allow coadministration of units with different release profile or containing incompatible substances and permit larger margin of safety against dosage form failure compared with single unit dosage form.

4. Fed or unfed state: under fasting conditions, the gimotility is characterized by periods of strong motaractivity that occurs every 1.5-2 hrs. The MMC sweeps undigested material from the stomach and if the timing of the formulation coincides with that of MMC, the GRT of the unit can be very short, however in fast state MMC is delayed and GRT is longer.

5. Nature of meal: feeding of indigestible polymers or fatty acids can change the motility pattern of the stomach to a fed state, thus decreasing gastric emptying rate and prolonging drug release.

6. Caloric content: GRT can be increased by 4-10 with a meal that is high in protein and fat.

7. Frequency of feed: The GRT can be increase over 400 min when successive meals given are compared with the single meal due to low frequency of MMC.

8. Gender: mean ambulatory GRT in male (3.4hrs) is less compared with the age and race matched female counterparts (4.6hrs) regardless of height, weight and body surface.

9. Age: people with age more than 70 have a significant longer GRT.

10. Concomitant drug administration: anticholinergic like atropine and propetheline, opiates like codeine can prolong GRT.[1,2,3,4,10]

Advantages

1. Delivery of drugs with narrow absorption window in the small intestine region.
2. Longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.
3. Improved bio-availability is expected for drugs that are absorbed readily upon release in the GI tract such as cyclosporine, ciprofloxacin, ranitidine, amoxycillin, captopril, etc.
4. Patient compliance by making a once a day therapy.
5. Improved therapeutic efficacy.
6. Improved bioavailability due to reduced P-glycoprotein activity in the duodenum.
7. Reduces frequency of dosing.
8. Targeted therapy for local ailments in the upper GI tract[1,3,4,7]

Disadvantages

1. Floating systems has limitation, that they require high level of fluids in stomach for floating and working efficiently. So more water intake is prescribed with such dosage form.
2. In supine posture (like sleeping), floating dosage form may swept away (if not of larger size) by contractile waves. So patient should not take floating dosage form just before going to bed.
3. Drugs having stability problem in high acidic environment, having very low solubility in acidic environment and drugs causing irritation to gastric mucosa cannot be incorporated into GRDDS.
4. Bio/mucoadhesives systems have problem of high turnover rate of mucus layer, thick mucus layer & soluble mucus related limitations.

5. Swellable dosage form must be capable to swell fast before its exit from stomach and achieve size larger than pylorus aperture. It must be capable to resist the housekeeper waves of Phase III of MMC.[1,3,4,7]

MECHANISM OF FLOATING SYSTEM

Various approches have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gasgenerating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used. Floating drug delivery systems have a bulk density less than gastric fluids i.e.(1.004g/ml) and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing floating drug delivery system with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.[1]

F = Fbuoyancy – Fgravity = (Df– Ds) gV

Where,

F = Total vertical force in N,

Df = Fluid density in Kg/m^3,

Ds = Density of object in Kg/m^3,

V = Volume of the object m^3,

G = Acceleration due to gravity m/s

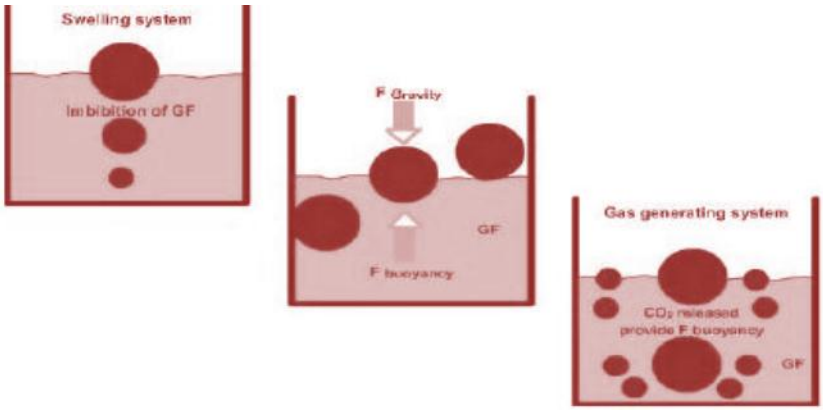

Fig. 4. Mechanism of floating system.

Approaches to Increase Gastric Residence Time Include

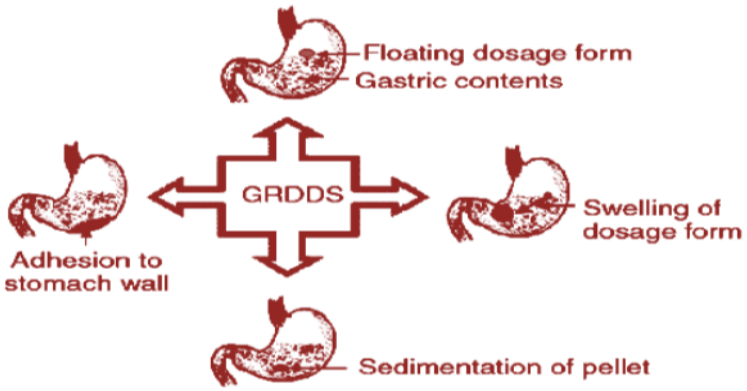

Fig. 5. Approches to Gastroretentive drug delivery system.

Classifications of Gastroretentive Drug Delivery Systems.[1,3,8,6,10]

A. Low-density systems (Floating systems)

a. Non effervances system

1. colloidal gel barrier system/(Hydrodynamically balance system)
2. Intragastric /Microporous compartment system
3. Alginate beds
4. Hollow microsphers

b. Effervances system

1. Volatile liquid containing system
2. Gas generating system
3. Ion exchange regin

B. High-density systems

C. Bioadhesive or Mucoadhesive systems

D. Swelling and Expanding Systems

E. Magnetic system

F. Raft-forming systems

G. Super porous hydrogel system

H. Modified shape systems

Advancements in Gastroretentive drug delivery system

I. Dual working system

J.Floating Osmatic system

K. Floating Pulsatile system

Classifications of Gastroretentive Drug Delivery Systems[1,3,8,6,10]

A.low density system / floating drug delivery system

Floating dosage form is also known as hydrodynamically balanced system (HBS). FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time while the system is floating on the gastric contents, the drug is released slowly at the desired rate. After release of drug, the residual system is emptied from the stomach.

Floating systems can be classified into two distinct categories

a) Non-effervescent system and

b) Effervescent systems

a. Non-effervescent systems

1. Colloidal gel barrier systems[2,3,4]

Hydrodynamically balanced system (HBS) of this type contains drug with gel forming or swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers. They help prolonging the GI residence time and maximize drug reaching its absorption site in the solution form ready for absorption to the absorption window. These systems incorporate high levels (20 to 75 % w/w) ofone or more gel forming highly swellable cellulose type hydrocolloids e.g. hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC) hydroxypropyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (NaCMC) incorporated either in tablets or capsules.

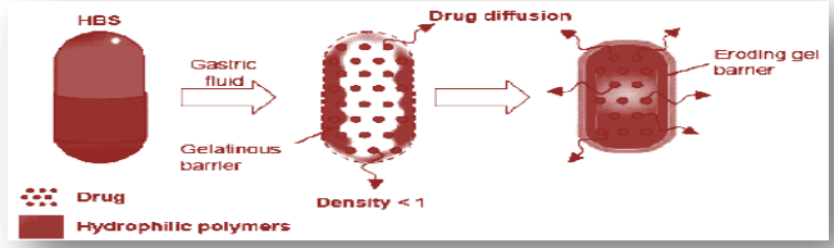

Fig. 6. Colloidal gel barrier system.

2. Micro-porous compartment system: This technology is comprised of encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom surfaces. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric mucosal surface with undissolved drug. In stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the pores, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.[2,3]

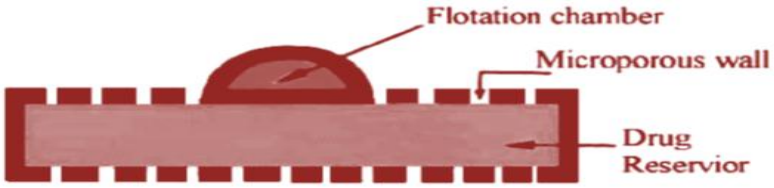

Fig. 7. Floating drug delivery device with microporous membrane and floatation chamber.

3. Alginate beads[2,3]: Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter were prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing a precipitation of calcium alginate. These beads were then separated; snap frozen in liquid nitrogen and freeze-dried at 40ºC for 24 hrs. leading to formation of porous system that maintained floating force for over 12 hrs.

4. Hollow Microspheres: Hollow microspheres (microballoons), loaded with ibuprofen in their outer polymer shells were prepared by novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer were poured into an agitated aqueous solution of PVA that was thermally controlled at 400 C. The gas phase was generated in dispersed polymer droplet by evaporation of dichloromethane and formed an internal cavity in microsphere of polymer with drug.[2,3]

b. Effervescent systems

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas. The gas in floating chamber can be introduced either by volatilization of an organic solvent or by effervescent reaction between organic acids and bicarbonate salts.[2,3]

1. Volatile liquid containing systems

These devices are osmotically controlled floating systems containing a hollow deformable unit that can be converted from a collapsed to an expanded position and returned to collapse position after an extended period. A deformable system consists of two chambers separated by an impermeable, pressure responsive, movable bladder. The first chamber contains the drug and the second chamber contains volatile liquid. The device inflates and the drug is continuously released from the reservoir into the gastric fluid. The device may also consist of bioerodible plug made up of PVA, polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable system from the stomach.[2,3]

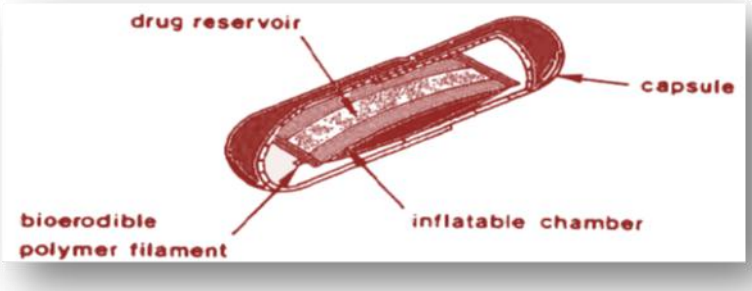

Fig. 8. Gastro inflatable drug delivery device.

2. Gas generating systems: These buoyant delivery systems utilize effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2 which gets entrapped in the jellified hydrochloride layer of the system, thus decreasing its specific gravity and making it float over chyme. These tablets may be either single layered wherein the CO_2 generating components are intimately mixed within the tablet matrix or they may be bilayer in which the gas generating components are compressed in one hydrocolloid containing layer, and the drug in outer layer for sustained release effect. Multiple unit type of floating pills that generates CO2 have also been developed. These kinds of systems float completely within 10 minutes and remain floating over an extended period of 5-6 hrs.[2,3]

3. Ion-Exchange Resins

A coated ion exchange resin bead formulation has been shown to have gastroretentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin, resultant baeds were then encapsulated in a semipermeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach and exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in a membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast the uncoated beads, which will sink quickly.[2,3,7]

B. High density systems

The High density systems in that the dosage forms have a density (3 g/mL) far exceeding that of normal stomach contents (1 g/mL) and thus retained in region of the stomach or sediment of the dosage formand are capable of withstanding its peristaltic movements. High density formulations include coated pellets that have density greater than that of stomach contents (1.004 g/cm3).[2,3,9,10]

C. Bioadhesive or mucoadhesive systems

The term “mucoadhesion” is commonly used to describe an interaction between the mucin layer that lines the entire GIT and a bioadhesive polymer. Bioadhesive drug delivery systems are used as a delivery device within the lumen to enhance drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach.[1,3,9]

D. Swelling and expanding systems

These are the dosage forms, which after swallowing, swell to an extent that prevent their exit from the pylorus. As a result, the dosage form is retained for a longer period of time.[1,3,9,10]

E. Magnetic system

This system is based on the simple idea that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Using a extracorporeal magnet, gastric residence time of the dosage form can be enhanced for a prolonged period of time.[9,10]

F. Raft forming systems: The incorporating alginate gelsreaction with gastric acid, bubbles form in the gel, enabling floating.This raft floats on gastric fluids because of low bulk density created by the formation of CO_2. A patent assigned to Reckitt and Colman Products Ltd., describes for the treatment of Helicobacter pylori (H. Pylori) infections in the GIT a raft forming formulation can be used.[3]

G. Superporous hydrogels

These are swellable systems that differ from conventional types. Absorption of water by conventional hydrogel is very slow process and several hours may be required to reach the equilibrium states during which the premature evacuation of the dosage form may occur. Superporous hydrogel have an pore size >100µm which swell to equilibrium size with in a minutes, due to rapid intake of water by capillary wetting through inter connected open pores. They swell to a larger size and have sufficient mechanical strength to withstand the pressure by gastric contraction. This is achieved by Coformulation of a hydrophilic particulate material, Ac Di- Sol. Several important properties of SPH such as fast swelling, large swelling ratio and surface slipperiness makes SPH as good candidate material for gastric retention devices.[1,3,10]

H.Modified systems: Systems with non disintegrating geometric shape molded from silastic elastomers or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modules of drug delivery device[3,9]

Advancements in Gastroretentive drug delivery system

I.Dual working systems: These systems are based on the two working principles of either floating and bioadhesion or swelling and bioadhesion. FDDS are formulated to persist floating on the gastric fluid when the stomach is full after a meal. However, as the stomach empties and the tablet reaches the pylorus, the buoyancy of the dosage form may be reduced. It may be that the dosage form will then pass through the pylorus into the small intestine. Thus, the buoyancy of an FDDS in the stomach may be limited to only 3–4 h. Furthermore, floating systems do not always release the drug at the intended site. In a bioadhesive drug delivery system, it is quite likely that the system becomes dislodged from the stomach mucosa wall when the system is full and the semiliquid contents are churning around due to the effect of peristalsis. A dual working system would overcome drawbacks associated with bioadhesive, swelling, and floating systems, and would have a significant effect on improving the therapeutic effect of the drug involved.[10]

J.Floating osmotic systems

A floating osmotic drug delivery system employs the principal of osmotic pressure to float on the gastric fluid. Basically these systems comprise of three parts; an osmotic core (containing drug reservoir, osmotic agents, and other excipients), a shape retaining semipermeable membrane; and an outer compression coating consisting of gas generating and gel forming agents. For delivery of drug an orifice is bored through both the outer layers. After administration when this system comes in contact with gastric fluid, initially CO_2 is generated due to the presence of a gas forming agent and this generated gas entraps within the bed of swelled gel, thus the system became buoyant due to diminished density. Delivery of drug then totally depends upon the osmotic pressure generated inside the osmotic core.[10]

K. Floating-pulsatile systems: Pulsatile drug delivery systems release the drug rapidly and completely after certain lag times. However, an uncertainty is always associated with such systems, they may expel out from the body without releasing drug content due to the presence of lag time. Floating pulsatile systems develop to overcome this drawback and have gained increasing interest during recent years for a number of drug therapies.[10]

In Vitro Evalution Parameters of Floating Tablets

A. Pre-compression parameters[2,3,6,7]

1. Bulk density (BD): Weigh accurately 25 g of granules, which was previously passed through 22# sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in gm/ml by the following formula.

Bulk density = Weigh of powder/ Bulk volume

2. Tapped density (TD): Weigh accurately 25 g of granules, which was previously passed through 22# sieve and transferred in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula

Tapped density = Weigh of powder /Tapped volume.

3. Carr's Index: Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which its packed down.The formula for Carr's index is as below

Carr's index= (Tapped density-Bulk density) / Tapped density × 100

4. Hausner's Ratio

Hausner's Ratio is a number that is correlated to the flowability of a powder.

Hausner's Ratio = Tapped density / Bulk density

5. Angle of repose

The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

tan = h/r

B. Post compression parameters[2,3,6,7]

1. Shape of Tablets

Compressed tablets were examined under the magnifying lens for the shape of the tablet.

2. Hardness

The hardness of the tablets was tested by diametric compression using a Monsanto Hardness Tester. A tablet hardness of about 2-4 Kg/cm2 is considered adequate for mechanical stability.

3. Thickness

Thickness of the all tablet formulations were measured using verniercalipers by placing tablet between two arms of the verniercalipers.

4. Friability

The friability of the tablets was measured in a Roche Friabilator. 20 Tablets were taken, Weighed and Initial weight was noted (W0) are dedusted in a drum for a fixed time (100 Freefalls, in a Roche Friabilator) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 % **Friability (%) =[(Initial weight- Final weight) / (Initial weight)] x 100**

5 Tablet density

Tablet density is an important parameter for floating tablets. The tablet will float only if itsdensity is less than that of gastric fluid (1.004). Density (d) was determined using the relationship

d = m/v

where v = πr2h.

6 Content Uniformity

In this test, 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 85% or not more than 115% (100±15%) of the labeled drug content can considered as the test was passed.

7 Assay

The drug content in each formulation was determined by triturating20 tablets and powder equivalent to average weight was dissolvedin 100ml of 0.1N Hydrochloric acid by sonication for 30 min. Thesolution was filtered through a 0.45µ membrane filter, diluted suitablyand the absorbance of resultant solution was measured spectrophotometrically at λmax of API(nm) using 0.1 N Hydrochloricacid as blank.

8 In-Vitro Buoyancy Studies[3]

The tablets were placed in a 100-mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Buoyancy (%) = Wf /Wf+Ws*100

Where, **Wf** are the weights of floating tablet

Ws are settled tablet

9 Swelling Study[2,3]: The swelling behavior of a dosage form was measured by studying its weight gain or wateruntake the dimensional changes could be measured in terms of the increase in tablet diameterand/or thickness over time. Water uptake was measured in terms of percent weight gain, asgiven by the equation.

WU = (W1 – W0) x 100

10 Resultant weight test[2,3,8]: 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 objectwhen 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

Where 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 sinks.

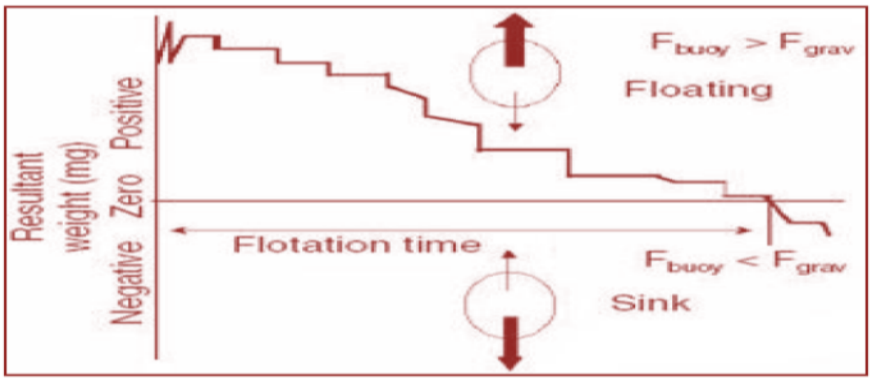

Fig. 9. Effect of various forces on floating system.

11 Weight gain and water uptake (WU)[2,3,8]

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

WU = (Wt – Wo) X 100 / Wo

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

12 Specific Gravity:[2,3] The displacement method is used to determine the specific gravity of floating system using compound benzene as a displacing medium.

13 In-Vitro Dissolution Study[2,3]**:** The In-vitro dissolution study for the Floating tablets were carried out in USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCl as dissolution medium at 50 rpm and temperature 37±0.5°C. At predetermined time

intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at λmax of API(nm) using UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3).

14 *In Vitro* Drug Release Kinetic Studies[2]

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order, first order, Higuchi square root, Korsmeyer- Peppas model[78].The criteria for selecting the most appropriate model was chosen on the basis of goodness of fit test. The data were processed for regression analysis using graph pad prism.

15 Shear stress measurement

The shear stress measures the force that causes a mucoadhesive to slide with respect to the mucus layer in a direction parallel to their plane of contact. Adhesion tests based on the shear stress measurement involve two glass slides coated with a polymer and a film of mucus. Mucus forms a thin film between the two polymer coated slides, and the test measures the force required to separate the two surfaces.

In vivo method

1. X-Ray method[2,3]

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[2,310]

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[2,310]

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[2,3,10]

Ultrasonic waves reflected substantially different acoustic impedances across interface enable the imaging of some abdominal organs. Most DFs do not have sharp acoustic mismatches across their interface with the physiologica milieu. Therefore, Ultrasonography is not routinely usedfor 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.

5. Magnetic marker monitoring[2,3]

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.

6. 13C Octanoic acid breath test[2,3]

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 upto 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.

7. Magnetic resonance imagining (MRI)[2,3,10]

MRI is a non-invasive diagnostic technology. MRI uses a powerful magnetic field, radio frequency pulses, and a computer to produce detailed pictures of organs, soft tissues, bone, and virtually all other internal body structures. The images can then be examined on a computermonitor, transmitted electronically, and printed or copied to a CD. MRI does not use ionizing radiation (x-rays). In the last couple of years, MRI was shown to be a valuable tool in gastrointestinal research for the analysis of gastric emptying, motility, and intra-gastric distribution of macronutrients and drug models. The advantages of MRI include high soft

tissue contrast, high temporal and spatial resolution, as well as a lack of ionizing irradiation. Also, harmless paramagnetic and supra-magnetic MR imaging contrast agents can be applied to specifically enhance or suppress signal of fluids and tissues of interest and thus permit betterdelineation and study of organs (Dorozynski et al., 2007).

Table. 4: Marketed products of Gastroretentive drug delivery system.[2,3,7,9,10]

Sr. No.	Brand Name	Drug	Company, Country	Technology
1	Madopar	Levodopa (100 mg), Benserazide (25 mg)	Roche products, USA	Floating CR capsule
2	Valrelease	Diazepam (15 mg)	Hoffman-Laroche, USA	Floating capsule
3	Liquid gaviscon	Al. Hydroxide (95 mg), Mg. Carbonate (358mg)	Glaxo smith kline, India	Effervescent floating Liquid alginate preparation
4	Topalkan	Al-Mg antacid	Pierre fabre drug, France	Floating liquid alginate preparation
5	Conviron	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
6	Cifran OD	Ciprofloxacin (1 g)	Ranbaxy, India	Gas-generating ® floating tablet
7	Cytotec	Misoprostol (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule
8	Oflin OD	Ofloxacin (400 mg)	Ranbaxy, India	Gas generating floating tablet

Application of Gastro-Retentive Drug Delivery System.[2]

1. Enhance bioavailability: The bioavailability of CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

2. Sustained drug delivery: The Gastroretentive drug delivery system is used for dosage form retained in the stomach for longer period for the drug released in stomach or intestine. In this systems dose large in size and passing from the pyloric opening is prohibited. New sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours). Similarly a comparative study between the Madopar HBS and Madopar standard formulation was done it shown the drug was released up to 8 hours in vitro in the former case and the release completed in less than 30 minutes in the latter case.

3. Site–specific drug delivery systems: These systems are particularly advantageous for drugs those are specifically absorbed from the stomach or the proximal part of the small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. It reduces the side effects which are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.

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

5. Minimize adverse activity at the colon

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that areabsorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

6. Reduce fluctuations of drug concentration

Continuous input of the drug following controlled release gastro-retentive dosage form administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance fordrugs with a narrow therapeutic index.

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