GASTRORETENTIVE: A CONTROLLED RELEASE DRUG DELIVERY SYSTEM

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ABSTRACT

There has been a lot of trouble in absorption of drugs having narrow absorption window. Major physiological adversities to overcome include short residence time (GRT) and unpredictable gastric empting time (GET). According to previous studies it has been seen that differences in gastric physiology, such as gastric pH, and motility exhibit both intra as well as inter subject variability demonstrating significant impact on gastric retention time and drug delivery behavior. Various approaches are currently being used in the prolongation of the GRT including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high density systems, modified shape systems and other delayed gastric empting devices. This review article focuses on the current technological development in FDDS with special emphasis on the principal mechanism of floatation and advantages to achieve gastric retention and its potential for oral controlled drug delivery.

Keywords: Gastric Empting Time, Floating Drug Delivery Systems, Short Residence Time.

INTRODUCTION

Drug delivery systems are used for maximizing therapeutic index of the drug and also for reduction in the side effects. The most preferred route is the oral route especially for the administration of therapeutic drugs because low cost of therapy and ease of administration leads to higher level of patient compliance. More than 50% of the drug delivery systems available are to be administered through oral route. Reasons behind using oral route are that it is the most promising route of the drug delivery and effective oral drug delivery may depend upon many factors such as gastric emptying process, gastrointestinal transit time of the dosage form, drug release from the dosage form and site of absorption of drug. High level of patient compliance is the major advantage of using the oral route.

To modify the GI transit time is one of the main challenge in the development of oral controlled drug delivery system. Gastric emptying of pharmaceuticals is highly variable and dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence time usually ranges between 5 minutes to 2 hours. In the fasted state the electrical activity in the stomach – the interdigestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and the transit of dosage forms. It is characterized by four Phases:

Phase I– Period of no contraction (30-60 minutes)
Phase II– Period of intermittent contractions (20-40 minutes)
Phase III– Period of regular contractions at the maximal frequency also known as housekeeper wave (10-20 minutes)
Phase IV– Period of transition between Phase III and Phase I (0-5 minutes) (1).
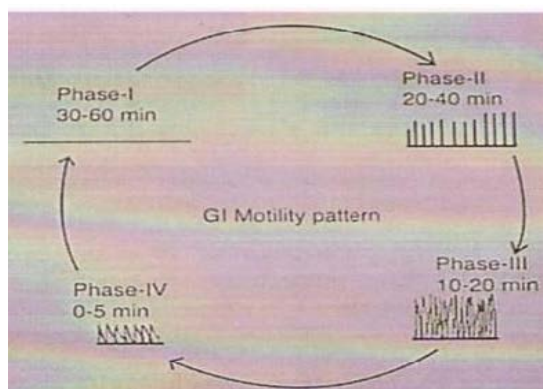

Fig. 1: Gastrointestinal motility pattern

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs (2). Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment.

It has applications also for local drug delivery to the stomach and proximal small intestine. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and patients are highly benefited. Controlled release drug delivery systems that retain in the stomach for a long time have many advantages over sustained release formulations.

Such retention systems (i.e. GRDDS) are important for the drugs that are degraded in intestine or for drugs like antacids or certain enzymes that should act locally in the stomach. Gastric retention may increase solubility for the drugs which are poorly soluble in intestine due to alkaline pH before they are emptied, resulting in improved bioavailability.

These systems also offer advantages in improving GIT absorption of a drug with narrow absorption windows as well as for controlling release of those drugs which are having site-specific absorption limitations.

These systems are useful in case of those drugs which are best absorbed in stomach for eg. Albuterol. From the formulation and technological point of view, floating drug delivery system (FDDS) is considerably easy and logical approach in development of GRDFs. Therefore, this review article focuses on the current technological development in FDDS with special emphasis on the principal mechanism of floatation and advantages to achieve gastric retention and its potential for oral controlled drug delivery (3).

Advantages

- FDDS reduces the drug concentration fluctuation that makes it possible to obtain certain selectivity in the exact pharmacological effect of drugs that are supposed to activate different types of receptors at different concentrations.

- Slow release of the drug into the body reduces the counter activity to minimum level leading to higher drug efficiency.

- Retention of the drug in the gastric formulation at stomach minimizes the amount of drugs that reaches the colon, thereby preventing the degradation of drug that degrades in the colon (1).

- GRDDS is highly advantageous in case of drugs having local action e.g. Antacids

- The bioavailability of many drugs increases when formulated as Floating dosage form .e.g. Riboflavin Controlled release Gastroretentive Dosage form (CR-GRDF) is highly bioavailable than non GRDF-CR polymeric formulations.

- Drugs like aspirin that cause irritation to gastric mucosa when come in contact with it. Therefore to overcome this formulation of such drugs is prepared for administration (4).

Disadvantages

- These systems require a high level of fluid in the stomach for drug delivery the stomach, so that the drug dosage form float and work efficiently.

- Not suitable for drugs that have solubility or stability problem in GIT.

- This system is not suitable for drugs that irritate the gastric mucosa and the drugs that are not stable in the stomach's acidic environment.

- These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract (1).

- Certain drugs get well absorbed along the gastric tract and undergo significant first pass metabolism, may not be suitable for floating systems because of the slow gastric empting that leads to reduced systemic bioavailability (2).

Drug candidates suitable for gastroretention

Drugs having poor colonic absorption but get rapidly absorbed in the upper parts of the GIT are the suitable candidates to be employed for gastroretention.

- Drugs with narrow absorption window. E.g levodopa and riboflavin.

- Drugs that get primarily absorbed in stomach and upper part of stomach e.g. cinnarizine, chlordiazepoxide and calcium supplements.

- Drugs having the property of degrading in stomach e.g. metronidazole and ranitidine HCl.

- Drugs that disturb the normal colonic bacteria e.g amoxicillin trihydrate

- Drugs acting locally in the stomach e.g .antacids and misoprostol (3).

- Drugs that exhibit low solubility at high ph values e.g. diazepam, chlordiazepoxide, verapamil HCl.

Drugs unsuitable for gastroretention

- Drugs having very limited acid solubility. e.g. phenytoin, etc

- Drugs observed with instability in the gastric environment. e.g. erythromycin

- Drugs which should release specifically in the colon. e.g. 5-amino salicylic acid and corticosteroids, etc (5).

Factors affecting gastric retention

Particle size

The particle size of the drug has to be between the ranges of 1 to 2 mm in order to pass through the pyloric valve into the small intestine.

pH

In fasting state, the pH of stomach is approximately 1.5 to 2.0 and in fed state is 2.0 to 6.0. Therefore, a large volume of water has to be administered with an oral dosage form due to which the pH rises from 6.0 to 9.0.

Stomach doesn't get time to produce sufficient acid when the liquid empties the stomach; hence generally basic drugs have a better chance of dissolving in fed state than in a fasting state.

Acidity and caloric value of meal

It does not make any difference whether the meal has high protein, fat or carbohydrate content as long as the caloric content is the same. However, increase in acidity and caloric value slows down gastric emptying time.

Biological factors

Factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes, Chron's disease) influence gastric emptying. In the case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down.

Volume

The resting volume of the stomach is 25 to 50 mL. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster.

Dosage size

According to various studies, it has been seen that gastric empting of a dosage form in the fed state can also be influenced by its size. Tablets having small size leave the stomach during the digestive phase whereas large sized tablets are emptied during the housekeeping waves.

Physical State

There is a difference seen between gastric empting times of liquid, digestible solid, and indigestible solid. It was suggested that the emptying of large (91 mm) indigestible objects from stomach was dependent upon interdigestive migrating myoelectric complex.

When liquid and digestible solids are present in the stomach, it contracts ~3 to 4 times per minute leading to the movement of the contents through partially opened pylorus. Indigestible solids larger than the pyloric opening are propelled back and several phases of myoelectric activity take place when the pyloric opening increases in size during the housekeeping wave and allows the sweeping of the indigestible solids. Studies have shown that the gastric residence time (GRT) can be significantly increased under the fed conditions since the MMC is delayed.

Shape and size

The diameter of the dosage unit is also equally important as a formulation parameter. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm.

Density

Dosage form having density less than that of gastric fluid floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.

Buoyancy

On comparison of floating and nonfloating dosage units, it was observed that regardless of their sizes the floating dosage units remained buoyant on the gastric contents throughout their residence time in the gastrointestinal tract, while the nonfloating dosage units sank and remained in the lower part of the stomach.

Floating units away from the gastro duodenal junction were protected from the peristaltic waves during digestive phase while the nonfloating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase.

It was also observed that out of the floating and nonfloating units, the floating units had a longer gastric residence time for small and medium units while no significant difference was seen between the two types of large unit dosage forms.

Fed & non fed states

The study on this factor revealed that as meals were fed at the time when the previous digestive phase had not completed, the floating

form buoyant in the stomach could retain its position for another digestive phase as it was carried by the peristaltic waves in the upper part of the stomach (2).
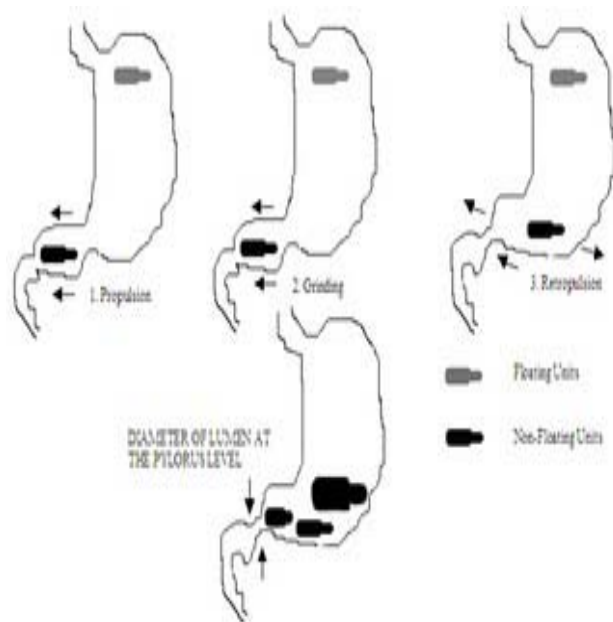

Fig. 2: Intragastric residence positioning of floating and non-floating units.

Techniques involved in designing of floating dosage forms

Two basic approaches used in designing of floating dosage forms are:

a)   Single unit system

b)   Multiple unit system

Single Unit System

The polymers to be used in this approach for preparing the globular shells need to have lower density than the gastric fluid so that they can be used as drug's carrier for controlled release. In coated shells, popcorn, poprice and polystyrol have been used as drug carriers.

For the purpose of undercoating, sugar polymeric materials such as methacrylate polymer and cellulose acetate phthalate can be used. These are further coated with a drug polymer mixture which can be either ethylcellulose or hydroxycellulose depending upon type of desired release. Finally the product was seen to be floating in the gastric fluid while releasing the drug gradually over a prolonged duration. Fluid- filled floating chamber type of dosage forms includes incorporation of a gas-filled floatation chamber into a microporous component that houses a drug reservoir.

Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine.

To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. Various types of tablets

(bilayered and matrix) have been shown to have floatable characteristics. Some of the polymers used are hydroxypropyl cellulose, hydroxypropyl methylcellulose, crospovidone, sodium carboxy methylcellulose, and ethyl cellulose.

The effect of certain polymers like hydroxypropyl methyl cellulose (HPMC) K4M / HPMC K 100 LV ratio (polymer blend) and Sodium lauryl was studied by Patel et al while developing the intra gastric floating system for Cefuroxime Axetil (6). It was observed that HPMC and SLS provided hydrophilic environment and property of wettability to molecules of drug leads to more uniform drug release.

There is a little problem with single unit formulations that is sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation.

Due to unpredictable gastric emptying associated with Migrating Myoelectric complex motility pattern, multiparticulate systems are more advantageous than the single unit systems, as the later ones experience "all or none" emptying pattern from the stomach. Multiple unit dosage forms are claimed to reduce intersubject variability in absorption and lower the probability of dose dumping (4).

Multiple unit system

 The main aim behind designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the above mentioned disadvantages of single-unit formulations. In this regard many multiple units floatable dosage forms have been designed. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate. Spherical polymeric microsponge also referred to as "microballoons," have been prepared.
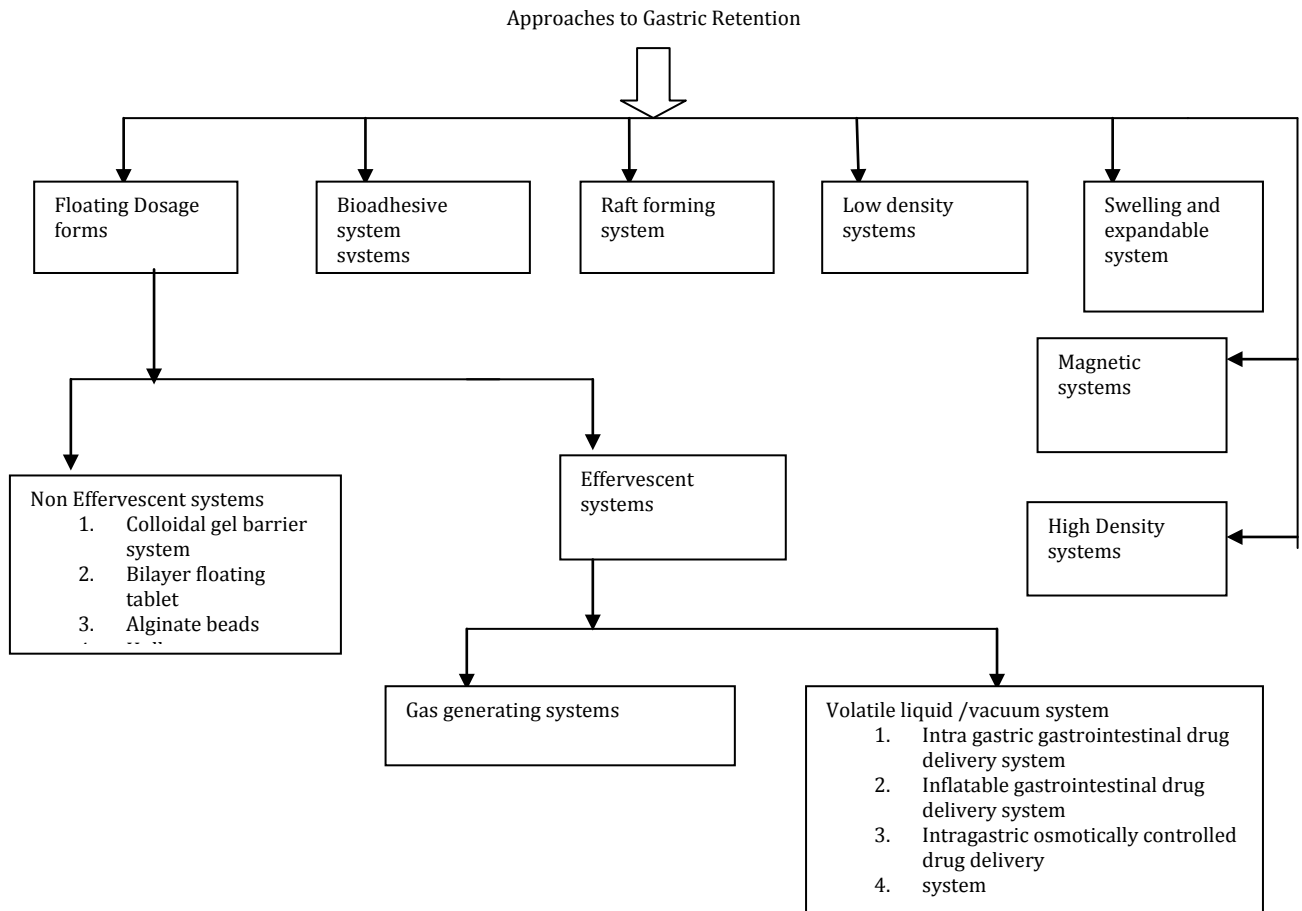
Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability. In Carbon dioxide–generating multiple-unit oral formulations several devices with features that extend, unfold, or are inflated by carbon dioxide aerated in the devices after administration. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to 18 mm in their expanded state is exceeded (7).

Nath et al (2009) designed a sustained release floating microspheres of metformin HCl, using two polymers of different permeability characteristics Cellulose Acetate Autyrate (M.W. of 16000) and Eudragit RL 100 (M.W. of 150,000) using oil in oil emulsion solvent evaporation method. The prepared microspheres were studied for drug release behavior. Polymers were used separately or in combination. Results revealed that microspheres prepared from a single polymer or combination exhibit Higuchi Spherical matrix release, followed by first order and zero order kinetics (8).

Table 1: List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems

Formulation	Drugs
Tablets	Chlopheniramine maleate, Theophylline, Furosemide, Ciprofloxacin, Captopril, Acetylsalicylic acid, Nimodipine, Amoxicillin trihydrate, Verapamil HCl, isosorbide di nitrate, Sotalol, Deltiazem, Prednisolone, piretanide
Capsules	Diazepam, misoprostal, Furosemide, Propranol, Urodeoxycholic acid, benserazide, L-Dopa
Microspheres	Griseofulvin, p-nitroaniline, Ketoprofen, Ibuprofen, Terfenadine , Aspirin, Tranilast
Floating granules	Diclofenac sodium, indomethacin and prednisolone
Films	Cinnarizine

Classification of Floating Drug Delivery System

Approaches to Gastric Retention

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                        ┌──────────────┬──────────────┬──────────────┬──────────────┐
                        ▼              ▼              ▼              ▼              ▼
                  Floating Dosage  Bioadhesive   Raft forming   Low density   Swelling and
                  forms            system        system         systems       expandable
                                   systems                                    system
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Non Effervescent systems
1. Colloidal gel barrier system
2. Bilayer floating tablet
3. Alginate beads

Effervescent systems

Magnetic systems

High Density systems

Gas generating systems

Volatile liquid /vacuum system
1. Intra gastric gastrointestinal drug delivery system
2. Inflatable gastrointestinal drug delivery system
3. Intragastric osmotically controlled drug delivery
4. system

A) Floating Dosage Form

The bulk density of this system is greater than gastric fluids and therefore, remains buoyant in the stomach without causing any effect on the gastric emptying rate for a long time period. The drug releases slowly while the system is floating on the gastric fluid. After drug is released, 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. This can be further divided non-effervescent and gas-generating system.
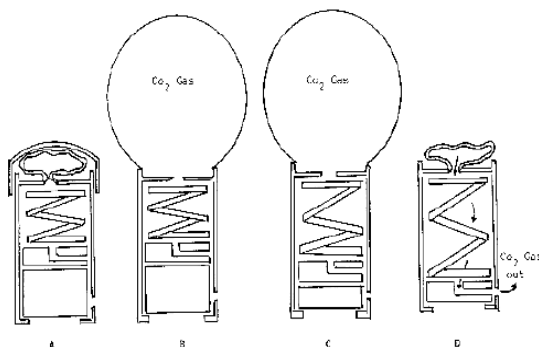

Fig. 3: Mechanism of Effervescent systems (9)

(a) Non – effervescent systems

After swallowing, this system swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. The formulation of such dosage form involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of and a bulk density of less than one within the outer gelatinous barrier (10).The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates (3).

This can again be divided into four sub types:

i) Colloidal gel barrier system

They are also called Hydrodynammically balanced systems (HBS). Such a system drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This helps in prolongation of GRT and maximizes the amount of drug that reaches its absorption 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), polysaccharides 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 (3).
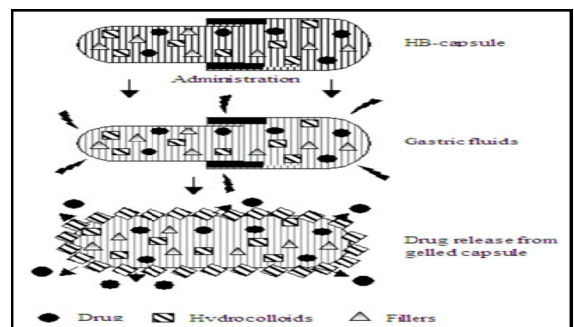

Fig. 4: Working principle of Hydrodynamically balanced system

ii) Bilayer Floating Tablets

A bi-layer tablet contain two layer one immediate release layer which releases 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 (11).
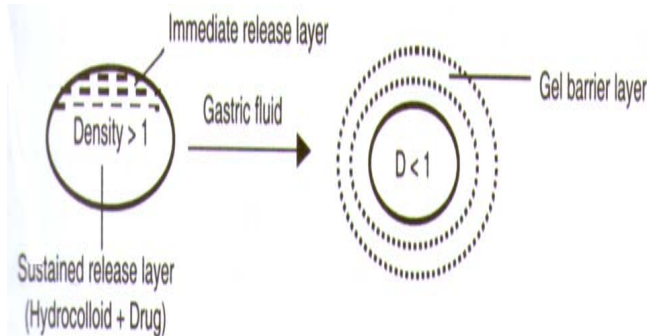

Fig. 5: Bilayered HBS™ showing the gel barrier layer (12)

iii) Alginate Beads

Multiunit floating dosage forms have been developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate.

Floating systems comprising of a calcium alginate core separated by an air compartment from membrane of calcium alginate or calcium alginate /polyvinyl alcohol (PVA) have been developed. The porous structure generated by leaching of PVA, (a water soluble additive in coating composition) was found to increase the membrane permeability preventing the collapse of air compartment.

iv) Hollow Microspheres

Hollow microspheres (microballoons), filled with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40̊. The gas phase generated in dispersed polymer droplet by evaporation of
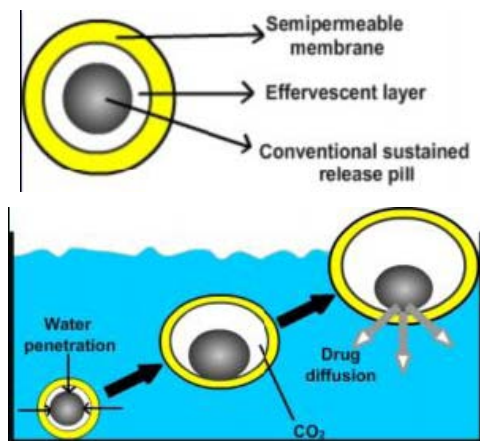

Fig. 6: Mechanism of microballoon

dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro.*

b) Effervescent system

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 the floating chamber can be introduced either by the volatilization of an organic solvent or by the effervescent reaction between organic acids and bicarbonate salts.

Multiple unit type floating pills

The system consists of sustained release pills or seeds surrounded by double layers. The inner layer consists of both sodium bicarbonate and tartaric acid. The outer layer act as swellable membrane layer. Moreover, the effervescent layer was divided into two sub layers to avoid direct contact between sodium bicarbonate and tartaric acid. Sodium bicarbonate was contained in the inner sub layer and tartaric acid was in the outer layer. When the system was immersed in a buffer solution at 37 degree Celsius, it sank at once in the solution and formed swollen pills, like balloons (density < 1 g/ml). Attempt has also been made to develop SR floating tablets using mixture of sodium bicarbonate, citric acid and chitosan.
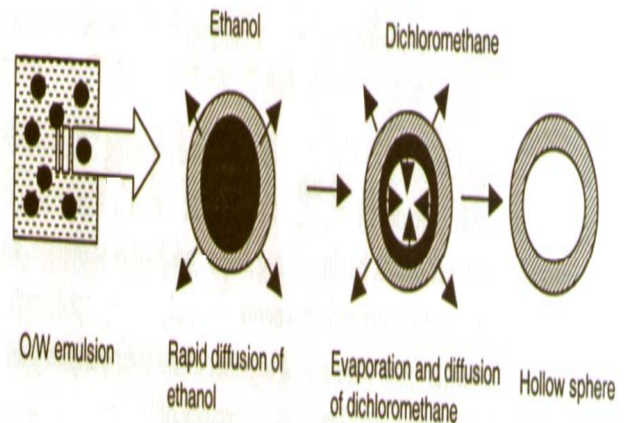

Fig. 7: Multiple unit type of floating pill and its floating behavior

c) Volatile liquid filled system

The GRT of a drug can be sustained by incorporating an inflatable chamber, which contains a liquid e.g, ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. These devices are osmotically controlled floating systems containing a hollow deformable that can convert from a collapsed to an expanded position, and returns to the same position after an extended period. The 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 the volatile liquid. The device may also consist of a biodegradable plug made of PVA, polystyrene etc that gradually dissolves causing the inflatable chamber to release gas and collapse a predetermined time to permit the spontaneous ejection of the inflatable system from the stomach .
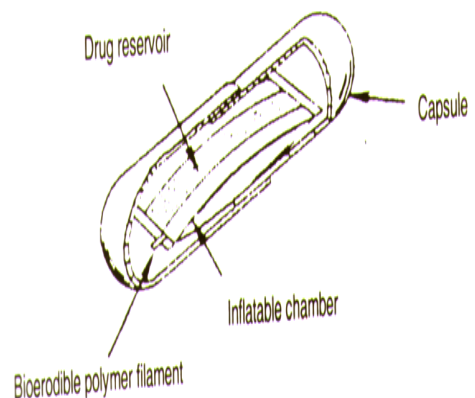

Fig. 8: Osmotically controlled floating systems containing a hollow deformable unit

B) Bioadhesive Systems

The term bioadhesion is defined as adhesion to biological surface i.e. mucus and/or mucosal surface. In instances when the polymeric system interacts with mucus layer only, it is referred as mucoadhesion. In order to develop an ideal oral bioadhesive system, it is important to have a through understanding of mucosa, bioadhesive polymers and mucin-polymer interactions in the physiological environment. Intestinal mucosa is composed of high molecular weight glycoproteins hydrated and covering the mucosa with a continuous adherent blanket. Mucin glycoproteins are rich with fucose and sialic acid groups at the terminal ends which provide a net negative charge in the acidic environment. The thickness of the mucin gel layer varies in different regions of the GIT with thickness ranging between 50-500μm in stomach to 15-150μm in the colon. Cohesion of the mucin gel is dependent upon the glycoprotein concentration. The mucus layer is created biologically to play a number of important functions of protecting the underlying tissues from various diffusing/corrosive elements such as enzymes, acid and other toxic molecules. Also being a visco-elastic gel, it helps in the passage of food over the epithelium, thereby minimizing potential erosive damages. The mucus layer, in addition to providing protection, provides a barrier to drug absorption (13).

C) Raft forming Systems

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO_2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids (12).

D) Low density Systems

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 "microballons" because of the low-density core (Sato and Kawashima, 2004). Generally, techniques used to prepare hollow microspheres involve simple solvent evaporation or solvent diffusion 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.

E) Swellable System

Swellable systems are also retained because of their mechanical properties. The swelling usually results from osmotic absorption of water. The dosage form is small enough to be swallowed, and swells in gastric liquids, the bulk enable gastric retention and maintains the stomach in a 'fed' state, suppressing housekeeper waves.

F) Magnetic System

These systems appear as small gastroretentive capsules containing a magnetic material, whose elimination from the stomach is prevented by the interaction with a sufficiently strong magnet applied to the body surface in the region of the stomach. Despite numerous reports about successful tests, the real applicability of such systems is doubtful because the desired results can be achieved only provided that the magnet position is selected with very high precision. Probably, the development of new conveniently applied magnetic field sources will improve this concept.

G) High Density Systems

Gastric contents have a density close to water (1.004 g /cm³). When the patient is upright small high-density pellets sink to the bottom of the stomach where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. A density close to 2.5 g/cm³ seems necessary for significant prolongation of gastric residence time and barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients.

Table 2: Marketed products of GRDDS

Sr. no	Brand Name	Drug (dose)	Company, Country	Remarks
1.	Madopar	Levodopa(100mg),Benserazide(25mg)	Roche Products, USA	Floating,CR capsule
2.	Valrelease	Diazepam(15mg)	Hoffman-LaRoche	Floating Capsule
3.	Liquid Gaviscon	Al hydroxide(95mg), 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.	Almagate FlotCoat	Al-Mg antacid		Floating dosage form
6.	Conviron	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
7.	Cifran OD	Ciprofloxacin(1gm)	Ranbaxy, India	Gas generating floating form

Method to assess Gastroretentivity of GRDFS

Unlike other formulations, the kinetics of transit of the GRDF along the GI tract, And especially in determining its GRT are very important. It requires, in most cases, an imaging technique that can locate the GRDF *in vivo*. The following method has been used in assessing gastroretentivity.

Gamma Scintigraphy

Gamma Scintigraphy relies on the administration of a dosage form containing small amount of radioisotope e.g., [152]Sm, which is a gamma ray with a relatively short half-life. The isotope has to be incorporated into the GRDF in advance. Then, a short time prior to the study, the formulation has to be irradiated in a neutron source that causes it to emit gamma rays. The emitted ray can be imaged using "gamma camera" – a form of a scintillation counter, combined with a computer to process the image, and thereby the DF can be tracked in the GI tract. This technique is elegant and provides proper assessment of gastroretentivity in humans (15).

Magnetic Resonance Imaging (MRI)

MRI is a noninvasive technique that is not associated with radioactivity and allows observation of the total anatomical structure in relatively high resolution. The visualization of the GI tract by MRI has to be further improved by the administration of contrast media. For solid dosage forms the incorporation of a super paramagnetic compound such as ferrous oxide enables their visualization by MRI. The technique is safe and allows obtaining many pictures from the same subject.

Radiology (X-Ray)

In this technique, a radio-opaque material has to be incorporated in the dosage form, and its location is tracked by X-ray pictures. The technique is used to evaluate gastroretentivity of GRDFs and the disintegration rate of dosage forms in vivo and also to determine the oesophageal transit. Although it is consider cheap and a simple method to use, its major disadvantage is the safety issue owing to repeated exposure to x-ray that increase the risk for the volunteers (14).

Table 3: Different Drugs being administered as GRDDS

Drug	Polymer	Method	Formulation	References
Cefroxime Axetil	Methocel K4M, K100LV	Direct Compression	Tablets	Patel et al, 2006(6)
Domperidone	Poly (ethylene oxide) WSR303 (PEO), HPMC	Direct Compression	Floating matrix tablets	Prajapati et al, 2009 (21)
Cinnarizine HCl	HPMC (K100LV, K4M, K15M, K100MCR)	Direct Compression	Tablet	Nagawal et al, 2010(22)
Diltiazem	Methocel K100M CR , Compritol 888 ATO	Direct Compresion	Tablet	Gambhir et al, 2007 (23)
Captopril	HPMC K4M, K15M , K100M	Direct Compreesion	Tablets	Sharma et al, 2009(24)
Atenolol	HPMC K100M, K4M	Direct Compression	Tablets	Havaldar et al (25)
Dipyradamole	Methocel K15M CR (15000 mPa.s), K4M(4000 mPa.s), K100M CR (100000 mPa.s)	Direct Compression	Tablets	Patel et al (26)
Famotidine	Accurel MP 100, HPMC E₄; 3,500 -6,000 cp, HPC MF(4,000-6500 cp), Sodium CMC (M CMC ; 1,500-2,500)	Direct Compression	Contrilled Release matrix tablets	Elmowafy et al ,2008(27)
Misoprostal	Methocel 4M, Methocel K100	Zanasi LZ64 capsule filling machine	Bilayer Floating Capsule	Oth et al , 1991 (28)
Isosorbite Mononitrate	Carbopol 934P[C934], 971P[C971]and 974P[C974]	Direct Compression	Tablet	Efentakis, 2008(29)
Metoprolol tartarate	HPMC (K4M and K10M)	Direct Compression	Bilayer tablet	Narendra et al 2008(30)
Ranitidine HCl	HPMC K4M , Carbopol 934	Direct compression	Tablets	Kumar et al (31)
Riboflavin	Methocel K4M, Carbopol 971P	Direct Compression	Bilayer Tablets	Masareddy et al (32)
Furosemide	HPMC 4000, HPMC100	Kneading method	Bilayer tablets	Ozdemir et al (33)
Nimodipine	HPMC, PEG 6000	Direct compression	Tablets	Wu et al (34)

Gastroscopy

It is commonly used for the diagnosis and monitoring of the GIT. This technique utilizes fibre optics or video system and can be easily applied for monitoring and locating GRDFs in the stomach. However, it is too inconvenient to conduct the procedure frequently in the same experiment for one subject. In human, the procedure can be applied with or without slight anesthesia while it requires complete anesthesia in dogs.

Evaluation

Evaluation of a drug is a tool to ensure (i) performance characteristics and, (ii) control batch quality. Apart from routine tests like general appearance, hardness, friability, drug content, weight variation, uniformity of content, disintegration time, drug release, etc. Gastroretentive Drug Delivery System needs to be graduated for gastrorentive performance by carrying out specific tests.

1) Measurement of buoyancy capabilities of the FDDS

The floating behaviour was evaluated with resultant weight measurements. The experiment was carried out in two different media like deionised water and simulated meal, in order to monitor possible difference. The results showed that higher molecular weight polymers with slower rate of hydration had enhanced floating behavior and which was more in simulated meal medium compared to deionised water (16).

2) Floating time

The test for floating time is usually performed in simulated gastric fluid or 0.1 N HCl maintained at 37°C, by using USP dissolution apparatus containing 900 ml of 0.1 N HCl as the dissolution medium. 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 (17).

3) In vitro drug release

Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.

4) Drug loading, drug entrapment efficiency, particle size analysis, surface characterization (for floating microspheres and beads)

Drug loading is assessed by crushing accurately weighed sample of beads or microspheres in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by various analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weight of total beads or microspheres. The particle size and the size distribution of beads or microspheres are determined in the dry state using the optical microscopy method. The external and cross-sectional morphology (surface characterization) is done by scanning electron microscope (SEM) (18).

5) Resultant weight

The *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 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 non floating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the Victoria sum of buoyancy (F_{buoy}) and gravity (F_{grav}) forces acting on the objects as shown in the equal,

$F = F_{buoy} - F_{grav}$

$F = dfgV - dsgV = (df-ds) gv$

$F = (df - M/V) gV$

In which the F is total vertical force (resultant weight of the object), g is the acceleration due to gravity, df if the fluid density, ds is the object density is the object mass and V is the volume of the object (19).

6) Specific Gravity

S.Sangekar et al purposed Specific Gravity of the floating system can be determined by the displacement method using benzene as a displacing medium (20).
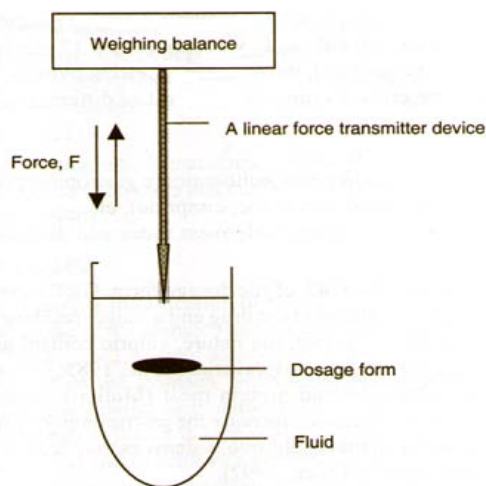
Fig. 9: Schematic view of resultant weight measuring system

CONCLUSION

Gastroretentive Drug Delivery System (GRDDS), comprising mainly of the floating, bioadhesive and swellable systems have emerged as an efficient means of enhancing the bioavailability and controlled release delivery of drugs exhibiting absorption window. By prolonging the gastric emptying time of the dosage form, these systems not only provide controlled release of drug for prolonged period but also present the drug in the absorbable form at regions of optimal absorption. These forms achieve this by retaining the dosage form in gastric region, from where the drug is presented at the 'absorption window'. This ensures maximal absorption of the drug for the desired period. Designing of a GRDDS requires a thorough understanding of physiochemical properties of drug physiological events in GI tract and formulation strategies. A careful consideration of interplay of these parameters can help in designing GRDDS, which meet their objectives successfully. Growing understanding of impact of GI tract physiology on drug delivery and increasing sophistication of this technology will ensure development of an increasing number of GRDDS to optimize drug delivery of molecules exhibiting regional variability in intestinal absorption.

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