FLOATING DRUG DELIVERY SYSTEM: A NOVEL ACCEPTABLE APPROACH

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ABSTRACT
The aim of writing this review on gastroretentive drug delivery systems was to compile the recent literature with special focus on various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled/Sustained release drug delivery. Several approaches are currently utilized 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 emptying devices. In this review, current & recent developments of Stomach Specific floating drug delivery systems are discussed. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.

KEYWORDS
Gastric retention time, Oral controlled release, Floating dosage form, Evaluations and Applications.

INTRODUCTION
Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. One of such difficulties is the ability to confine the dosage form in the desired area of the gastrointestinal tract. To
overcome this physiological problem, several drug delivery systems with prolonged gastric retention time have been investigated. Attempts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady state by delivering drug in a controlled and reproducible manner. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability reduces drug waste and improves solubility of drugs that are less soluble in high pH environment. Gastric retention to provide new therapeutic possibilities and substantial benefits from patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanism of mucoadhesion, sedimentation, floatation, expansion, modified shape systems or by the administration of pharmacological agents, that delaying gastric emptying. Based on these approaches, floating drug delivery systems seems to be the promising delivery systems for control release of drugs.

**Basic Physiology of Stomach**

The GI tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), oesophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum). The wall of the GI tract has the same general structure throughout most of its length from the oesophagus to the anus, with some local variations for each region. The stomach is an organ with a capacity for storage and mixing. The antrum region is responsible for the mixing and grinding of gastric contents. Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50ml and contains a small amount of gastric fluid (pH 1-3) and air. The mucus spreads and covers the mucosal surface of the stomach as well as the rest of the GI tract.

The GI tract is in a state of continuous motility consisting of two modes: interdigestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract. The interdigestive motility pattern is commonly called the ‘migrating motor complex’ (‘MMC’) and is organized in cycles of activity and quiescence. Each cycle lasts 90–120 minutes and consists of four phases. The concentration of the hormone motilin in the blood controls the duration of the phases.

**The four phase’s digestive motility pattern** (Figure No.2)

**Phase I:** - (Basic phase -last from 30-60 minutes with rare contractions.

**Phase II:** - (Preburst phase) -last for 20-40 minutes with intermittent action potential and contractions.

**Phase III:** - (Burst phase) - last for 10-20 minutes which includes intense and regular contractions for short period.

**Phase IV:** - last for 0-5 minutes and occurs between phase 2 and 1of 2 consecutive cycles.

In the interdigestive or fasted state, an MMC wave migrates from the stomach down the GI tract every 90–120 minutes. A full cycle consists of four phases, beginning in the lower esophageal sphincter/gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum, and finishing at the ileum. Phase III is termed the ‘housekeeper wave’ as the powerful contractions in this phase tend to empty the stomach of its fasting contents and indigestible debris. The administration and subsequent ingestion of food rapidly interrupts the MMC cycle, and the digestive phase is allowed to take place. The upper part of the stomach stores the ingested food initially, where it is compressed gradually by the phasic contractions. The digestive or fed state is observed in response to meal ingestion. It resembles the fasting Phase II and is not cyclical, but continuous, provided that the food remains in the stomach. Large objects are retained by the stomach during the fed pattern but are allowed to pass during Phase III of the
interdigestive MMC. It is thought that the sieving efficiency (i.e. the ability of the stomach to grind the food into smaller size) of the stomach is enhanced by the fed pattern and/or by the presence of food. The fasted-state emptying pattern is independent of the presence of any indigestible solids in the stomach. Patterns of contractions in the stomach occur such that solid food is reduced to particles of less than 1mm diameter that are emptied through the pylorus as a suspension. The duration of the contractions is dependent on the physiochemical characteristics of the ingested meal. Generally, a meal of ~450kcal will interrupt the fasted state motility for about three to four hours. It is reported that the antral contractions reduce the size of food particles to ≤1mm and propel the food through the pylorus. However, it has been shown that ingestible solids ≤7mm can empty from the fed stomach in humans.14

Gastro retenive

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retenive dosage form (GRDF or GRDS).

Dosage form with prolonged GRT, i.e. gastro retenive dosage forms (GRDF), will bring about new and important therapeutic options such as15 This application is especially effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To override this problem, erodible, gastroteative dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.

GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the submucosal tissue of stomach) making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).

GRDFs can be used as carriers for drugs with so-called absorption windows. These substances for e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides, tetracyclines etc.), are taken up only from very specific sites of the GI mucosa.

Approaches to gastric retention

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:-

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, non-effervescent and effervescent systems.

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:-
1. Hydration-mediated adhesion.
2. Bonding-mediated adhesion.
3. Receptor-mediated adhesion.

**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 cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.

**High Density Systems**
These systems with a density of about 3 g/cm$^3$ are retained in the range of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm$^3$ 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 No.4.

**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 C$_{10}$-C$_{14}$.

**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.

**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.

**Gastric residence time (GRT) and its effect**
Gastric residence time of an oral dosage form is affected by several factors. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 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. 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. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids. Studies have revealed that gastric emptying of a dosage form in the fed state can also be influenced by its size. Small-size tablets leave the stomach during the digestive phase while the large-size tablets are emptied during the housekeeping waves.
According to the current research the effect of size of floating and nonfloating dosage forms on gastric emptying and that the floating units remained buoyant on gastric fluids. These are less likely to be expelled from the stomach compared with the nonfloating units, which lie in the antrum region and are propelled by the peristaltic waves. Several formulation parameters can affect the gastric residence time. More reliable gastric emptying patterns are observed for multiparticulate formulations as compared with single unit formulations, which suffer from “all or none concept”. The units of multiparticulate systems are distributed freely throughout the gastrointestinal tract.

The most important parameters affecting gastric emptying and, hence, the gastric retention time of oral dosage forms include:

**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 7.5mm are reported to have an increased GRT compared with those with a diameter of 9.9mm.

**Shape of dosage form:** - tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds 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±0.6hours) 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; and

**Biological factors:** - diabetes and Crohn’s disease, etc.

**FLOATING DRUG DELIVERY SYSTEMS**

**Definition**
Floating systems or dynamically controlled systems or low-density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time (Figure No. 3). This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hallow Microspheres.

**The major requirements for floating drug delivery system are**

It should release contents slowly to serve as a reservoir.
It must maintain specific gravity lower than gastric contents (1.004 - 1.01 gm/cm3).
It must form a cohesive gel barrier.

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Advantages of floating drug delivery system\textsuperscript{19}

Floating drug delivery systems have numerous advantages listed below:

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

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.

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.

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.

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.

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.

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

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.

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 of floating drug delivery systems\textsuperscript{19}

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.

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

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.

Mechanism of floating systems\textsuperscript{20}

Various attempts 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 (gas-generating 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 (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 (given in the Figure No.5 (a)), the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably...
buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to $F$ (as a function of time) that is required to maintain the submerged object. The object floats better if $F$ is on the higher positive side (Fig No.5 (b)). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

$$F = F_{buoyancy} - F_{gravity} = (D_f - D_s) g v$$  \(1\)

Where,
- $F$ = total vertical force,
- $D_f$ = fluid density,
- $D_s$ = object density,
- $v$ = volume and
- $g$ = acceleration due to gravity.

**Methods for preparing floating dosage form:**

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

**Types of floating drug delivery systems (FDDS)**

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

1. Effervescent System, and
2. Non-Effervescent System.

**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.

- Gas generating systems
- Volatile Liquid/Vacuum containing systems.

**Gas - Generating Systems**

**Intra Gastric Single Layer Floating Tablets or Hydro dynamically Balanced System (HBS)**

These are as shown in Figure No.6 and formulated by intimately mixing the CO2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

**Intra Gastric Bilayer Floating Tablets**

These are also compressed tablet as shown in Figure No.7 and containing two layer i.e. immediate release layer and Sustained release layer.

**Multiple Unit type floating pills**

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

**Volatile Liquid / Vacuum Containing Systems**

**Intragastric Floating Gastrointestinal Drug Delivery System**

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment, as shown in Figure No.9.
Inflatable Gastrointestinal Delivery Systems
In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid. This system is shown in Figure No. 10.

Intragastric Osmotically Controlled Drug Delivery System
It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a 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.

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, polycrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol. The various types of this system are as:

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.

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.

Alginate 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, and these floating beads gave a prolonged residence time of more than 5.5 hour.

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 of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40°C. 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 invitro.

**Polymers and other ingredients:**

Following types of ingredients can be incorporated into HBS dosage form in addition to the drugs:

- **Hydrocolloids (20%-75%):** They can be Synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives. E.g. Acacia, pectin, Chitosan, agar, casein, bentonite, veggum, HPMC (K4M, K100M and K15M), Gellan gum (Gelrite®), Sodium CMC, MC, HPC.
- **Inert fatty materials (5%-75%):** Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. E.g. Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.
- **Effervescent agents:** Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine).
- **Release rate accelerants (5%-60%):** e.g. lactose, mannitol
- **Release rate retardants (5%-60%):** e.g. Dicalcium phosphate, talc, magnesium stearate
- **Buoyancy increasing agents (upto 80%):** e.g. ethyl cellulose
- **Low density material:** Polypropylene foam powder (Accurel MP 1000®).

**Applications of Floating Drug Delivery Systems:**

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

- **Enhanced bioavailability**

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

- **Enhanced first-pass biotransformation**

  When the drug is presented to the metabolic enzymes (cytochrome P-450, in particular CYP-3A4) in a sustained manner, the presystemic metabolism of the tested compound may be considerably increased rather than by a bolus input.

- **Sustained drug delivery/reduced frequency of dosing**

  The drugs having short biological half-life, a sustained and slow input from FDDS may result in a flip-flop pharmacokinetics and it reduces the dose frequency. This feature is associated with improved patient compliance and thus improves the therapy. HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time.

- **Targeted therapy for local ailments in the upper GIT**

  The prolonged and sustained administration of the drug from FDDS to the stomach may be useful for local therapy in the stomach.

- **Reduced fluctuations of drug concentration**

  The fluctuations in plasma drug concentration are minimized, and concentration-dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

- **Improved receptor activation selectivity**

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

- **Reduced counter-activity of the body**

  Slow release of the drug into the body minimizes the counter activity leading to higher drug efficiency.

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Extended time over critical (effective) concentration
The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

9. Minimized adverse activity at the colon
Retention of the drug in GRDF at stomach minimizes the amount of drugs that reaches the colon and hence prevents the degradation of drug that degraded in the colon.

10. Site specific drug delivery
A floating dosage form is a widely accepted approach especially for drugs which have limited absorption sites in upper small intestine. These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g. riboflavin and furosemide.

Table No.1: Commonly used drug in formulation of gastro retentive dosages forms

<table>
<thead>
<tr>
<th>S.No</th>
<th>DOSAGE FORMS</th>
<th>DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Floating Tablets or pills</td>
<td>Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbide mononitrate, p-Aminobenzoic acid(PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil HCL.</td>
</tr>
<tr>
<td>2</td>
<td>Floating Capsules</td>
<td>Chlordiazepoxide HCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin.</td>
</tr>
<tr>
<td>3</td>
<td>Floating Microspheres</td>
<td>Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast.</td>
</tr>
<tr>
<td>4</td>
<td>Floating Granules</td>
<td>Diclofenac sodium, Indomethacin, Prednisolone.</td>
</tr>
<tr>
<td>5</td>
<td>Floating powders</td>
<td>Several basic drugs.</td>
</tr>
<tr>
<td>6</td>
<td>Floating films</td>
<td>Cinnerzine.</td>
</tr>
</tbody>
</table>
Table No.2: Marketed Products of gastro retentive dosages forms\(^{19, 24, 25}\)

<table>
<thead>
<tr>
<th>S.No</th>
<th>BRAND NAME</th>
<th>DRUG (DOSE)</th>
<th>COMPANY, COUNTRY</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Glumetza GRTM</em></td>
<td>Metformin HCL</td>
<td>Bioavail oin, north America; LG life sciences, korea</td>
<td>Metformin HCL Floating Extended release tablet</td>
</tr>
<tr>
<td>2</td>
<td>Modapar®</td>
<td>Levodopa (100 mg), Benserazide (25 mg)</td>
<td>Roche Products, USA</td>
<td>Floating CR capsule</td>
</tr>
<tr>
<td>3</td>
<td>Valrelease®</td>
<td>Diazepam (15 mg)</td>
<td>Hoffmann-LaRoche, USA</td>
<td>Floating capsule</td>
</tr>
<tr>
<td>4</td>
<td>Liquid® Gavison</td>
<td>Al hydroxide (95 mg), Mg carbonate (358 mg)</td>
<td>Glaxo Smith Kline, India</td>
<td>Effervescent floating liquid alginate preparation</td>
</tr>
<tr>
<td>5</td>
<td>Topalkan®</td>
<td>Al-Mg antacid</td>
<td>Pierre Fabre Drug, France</td>
<td>Floating liquid alginate preparation</td>
</tr>
<tr>
<td>6</td>
<td>Conviron</td>
<td>Ferrous sulphate</td>
<td>Ranbaxy, India</td>
<td>Colloidal gel forming FDDS</td>
</tr>
<tr>
<td>7</td>
<td>Cifran OD®</td>
<td>Ciprofloxacin (1 gm)</td>
<td>Ranbaxy, India</td>
<td>Gas-generating floating tablet</td>
</tr>
<tr>
<td>8</td>
<td>Cytotec®</td>
<td>Misoprostal (100 mcg/200 mcg)</td>
<td>Pharmacia, USA</td>
<td>Bilayer floating capsule</td>
</tr>
<tr>
<td>9</td>
<td>Oflin OD®</td>
<td>Ofloxacin (400mg)</td>
<td>Ranbaxy, India</td>
<td>Gas generating floating tablet</td>
</tr>
</tbody>
</table>
Figure No.1: Diagram of human stomach

Figure No.2: gastrointestinal motility pattern

Figure No.3: Graphic of Buoyant tablet which is less dense than the stomach fluid and therefore remains in the fundus

Figure No.4: Graphic of heavy tablet which is denser than the stomach fluid and therefore sinks to the antrum
Figure No.5: Mechanism of floating systems, GF= Gastric fluid

Figure No.6: Intra Gastric Single Layer Floating Tablets

Figure No.7: Intra Gastric Bilayer Floating Tablets
Figure No.8: (A) A multi-unit oral floating dosage system. (B) Stages of floating mechanism: (a) penetration of water; (b) generation of CO$_2$ and floating; (c) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37°C)

Figure No.9: Intra Gastric Floating Gastrointestinal Drug Delivery Device

Figure No.10: Inflatable Gastrointestinal Delivery System
CONCLUSION
The review work was concluded that Gastro retentive drug delivery systems have emerged as a current approach of enhancing bioavailability and controlled delivery of drugs that exhibit an absorption window. The currently available polymer-mediated No effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled/sustained oral drug delivery. The number of commercial products and patents issued in this field are the evidence of it. The FDDS become an additional advantage for drugs that are absorbed primarily in the upper part of GI tract, i.e., the stomach, duodenum, and jejunum. It seems that to formulate an efficient FDDS is sort of a challenge and the work will go on and on until an ideal approach with industrial applicability and feasibility arrives.

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CONFLICT OF INTEREST
We declare that we have no conflict of interest.

REFERENCES