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Review Article

Floating Drug Delivery for Prolonging Gastric Retention of Dosage Form

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ABSTRACT

The purpose of writing this review on floating drug delivery systems (FDDS) was to focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. The purpose of this paper is to review the recent literature and current technology such as several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems (HBS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, and other delayed gastric emptying devices used in the development of gastro retentive dosage forms.

INTRODUCTION

Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is be dilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time (GET) in humans, which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduce efficacy of the administered dose [1].Therefore, control of placement of a drug delivery system (DDS) in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem [2].These types of problem can be overcome by FDDS.

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After oral administration, such a delivery would be retained in the stomach and release the drug in a controlled manner so that the drug could be supplied continuously to its absorption sites. Hence, an advantageous drug delivery system to control and prolong the gastric emptying time and to deliver drugs in higher concentrations to the absorption site necessitates a specialized delivery system. A significant approach in this regard can be achieved by floating drug delivery systems. [3, 4]

BASIC PHYSIOLOGY OF STOMACH[7]

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

The stomach is an expanded section of the digestive tube between the esophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube; with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions. In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds

called rugae. The image of stomach anatomy is depicted in Fig. 1.

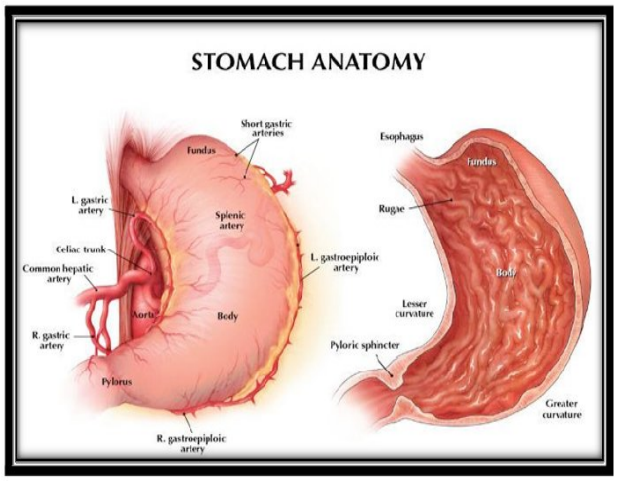

Figure 1: Anatomy of Stomach [8]

GASTRIC MOTILITY

Gastric motility is controlled by a complex set of neural and hormonal signals. Nervous control originates from the enteric nervous system as well as parasympathetic (predominantly vagus nerve) and sympathetic systems. A large battery of hormones has been shown to influence gastric motility for e.g. both gastrin and cholecystokinin act to relax the proximal stomach and enhance contractions in the distal stomach. The bottom line is that the patterns of gastric motility likely are a result from smooth muscle cells integrating a large number of inhibitory and stimulatory signals. Liquid readily pass through the pylorus in spurts, but solids must be reduced to a diameter of less than 1-2 mm before passing pyloric gatekeeper. The gastric volume is important for dissolution of the dosage form in vivo. The resting volume of the stomach is 25-50 ml. There is a large difference in gastric secretion of normal and achlorhydric individuals. Gastric pH also has pronounced effect of absorption of drug from delivery system. The pH of fasting stomach is 1.2-.2.0 and in fed conditions 2.0-6.0[9].

GASTRIC EMPTY RATE (GASTRO-INTESTINAL MOTILITY PATTERN)[10]

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myoelectric cycle or Migrating Myoelectric Cycle (MMC), which is further divided into following 4 phases.

Phase I (Basal phase) lasts from 40 to 60 minutes with rare contractions.

Phase II (Pre burst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

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.

Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

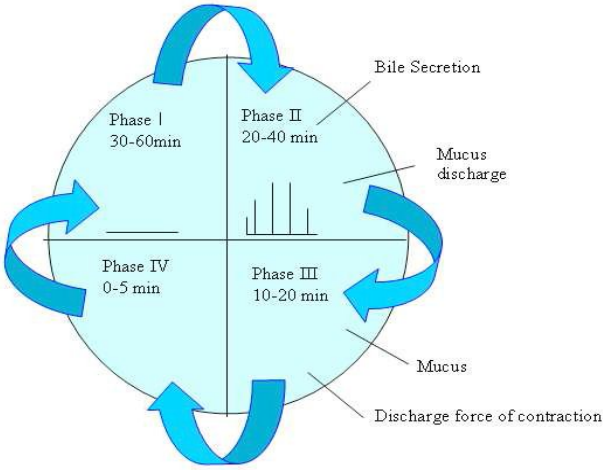

Figure 2: Motility patterns of the GIT in the fasted state.

After the ingestion of a meal, contraction pattern changes from fasted to that of fed state (Fig. 2). This is also known as digestive motility pattern and comprises continuous contraction as in phase II of fasted state. These contractions result in reducing the size of food particles (less than 1mm), which are propelled towards the pylorus in a suspension form. During the fed state, onset of MMC is delayed resulting in slow emptying rate.

FACTORS AFFECTING GASTRIC RETENTION[11-18]

1. Density: GRT is a function of dosage form buoyancy that is dependent on the density of a dosage form, which affects the gastric emptying rate. A buoyant dosage form should have a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.

2. Size: Dosage form units having a diameter of more than 7.5 mm are reported to have an increased gastric residence time compared with those having a diameter of 9.9 mm. Gastric retention time of dosage form in the fed state can also be influenced by its size. Small tablets are emptied from the stomach during the digestive phase while large size units are expelled during the house keeping waves.

3. Shape of dosage form: The six shapes tested (ring, tetrahedron, cloverleaf, disk, string and pellet) displayed different gastric retention times, due to their size and geometry of the systems. The tetrahedron resided in the stomach for longer periods than other devices of a similar size; likewise extended gastric retention was observed with rigid rings. Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) have a better gastric residence time as compared with other shapes and had been reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.

4. 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.

5. Effect of buoyancy: On comparison of floating and non floating dosage units, it was concluded that regardless of their sizes the floating dosage units remained buoyant on the gastric contents throughout their residence in the gastrointestinal tract, while the non floating 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 non-floating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase.

6. 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. In the fed state, MMC is delayed and GRT is considerably longer. It was concluded that as meals were given 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. 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. Studies have revealed that small-size tablets leave the stomach during the digestive phase while the large-size tablets are emptied during the housekeeping waves.

7. 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 increase in acidity and caloric value slows down gastric emptying time.

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

9. 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.

10. Gender: Mean ambulatory GRT in males (3.4Å} 0.6 hours) is less compared with their age and race matched female counterparts (4.6Å} 1.2 hours), regardless of the weight, height and body surface.

11. Age: Elderly people, over 70, have a significantly longer GRT.

12. Posture: GRT can vary between supine and upright ambulatory states of the patient. When subjects were kept in the supine position it was observed that the floating forms could only prolong their stay because of their size; otherwise the buoyancy remained no longer an advantage for gastric retention.

13. Biological factors: Diabetes and Cohn's disease, etc. Stress increases gastric emptying rates while depression slows it down.

14. Concomitant Drug administration & interaction: Anticholinergic like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.

15. Volume of liquids: 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.

In order for a hydrodynamically balanced dosage forms to float in the stomach, the density if the dosage forms should be less than the gastric contents. However, the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyant capabilities. The prolongation of the gastric residence time by food is expected to maximize during drug absorption from the dosage form due to increased dissolution of the drug and longer residence at the most favorable sites of absorption. However, literature data on the relationship between device size and gastric residence time are contradictory.

TECHNIQUES OF GASTRIC RETENTION

Various techniques were used to encourage gastric retention of an oral dosage form. Floating systems have low bulk density, so that they can float on the gastric juice in the stomach. The problem arises when the stomach is completely emptied of gastric fluid in such a situation; there is nothing to float on.

1. High-density systems [18, 19]

Gastric contents have a density close to water (~1.004 g/cm^3). When the patient is upright small high-density pellets sink to the bottom of the stomach (Fig. 3) where they become entrapped in the folds of the atrium and withstand the peristaltic waves of the stomach wall. A density close to 2.5 g/cm^3 seems necessary for significant prolongation of gastric residence time and barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients. Although encouraging results were reported in ruminants effectiveness in human subjects beings was not observed and no system has been marketed.

2. Bioadhesive or Mucoadhesive drug delivery systems [20, 44]

Adhesion as a process is simply defined as the fixing of two surfaces to one another. There are many different terminological subsets of adhesion depending upon the environment in which the process occurs. When adhesion occurs in a biological substrate it is termed bioadhesion, furthermore if this adhesion occurs on mucosal membranes it is termed mucoadhesion.

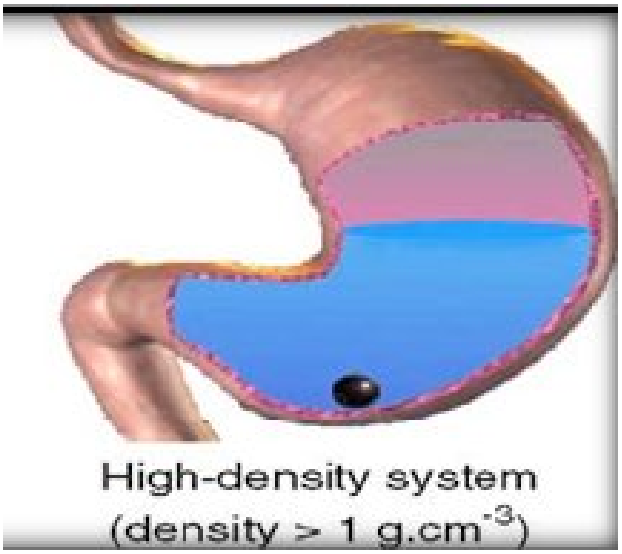

Figure 3: Heavy tablet which is denser than the stomach fluid

Mucoadhesive delivery system remains adhered to mucosal layer and drug is released in controlled manner. Bioadhesive drug delivery systems are used to localize a delivery device within the lumen to enhance the drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the GIT. The proposed mechanism of bioadhesion is the formation of hydrogen and electrostatic bonding at the mucus-polymer junction. Rapid hydration in contact with the muco-epithelial surface appears to favor adhesion, particularly if water can be excluded at the reactive surfaces. These bioadhesive systems do not seem to be in a feasible solution as this bond formation is prevented by the acidic environment and thick mucus present in the stomach at the site. Some of the most promising excipients that have been used commonly in these mocoadhesive systems include polycarbophil, carbopol, lectins, chitosan, tragacanth, sodium alginate, CMC, pectin, gelatin, etc. High turnover of mucus adds to the difficulties in retaining a bioadhesive system at the site.

3. Expandable, unfoldable and swellable systems [8, 21]

This class of gastro retentive system is capable of expanding in stomach. The expanded structure is trapped in stomach for prolong period leading to sustained drug release and subsequent controlled absorption in stomach. One way to retain a dosage form in the stomach is by increasing its size the stomach discharges its contents through the pylorus into the intestine. If

the dosage form is larger in size than that of the pylorus, it can be retained in the stomach for a long time. Swelling type dosage forms are such that after swallowing these products swell to an extent that prevents their exit from the stomach through the pylorus as a result the dosage form is retained in the stomach for along period of time (Fig. 4). These systems may be referred to as plug type systems, since they exhibit a tendency to remain lodged at the pyloric sphincter.

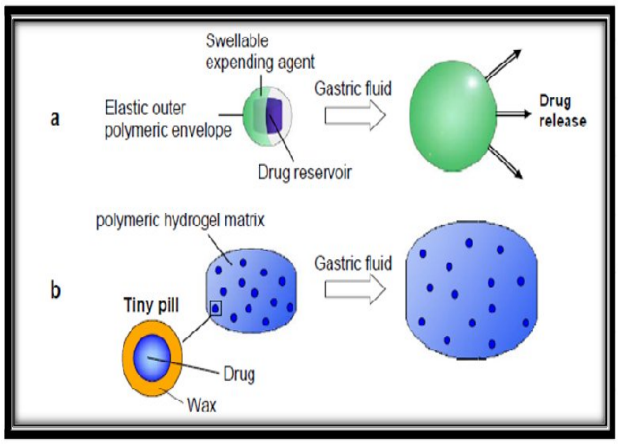

Figure 4: Swellable systems

4. Raft-forming systems [8, 45]

A gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO_2 bubbles (Fig. 5) on contact with gastric fluid. Formulations also typically contain antacids such as aluminum hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastro esophageal reflux treatment as with Liquid GaviconÄ (GSk).

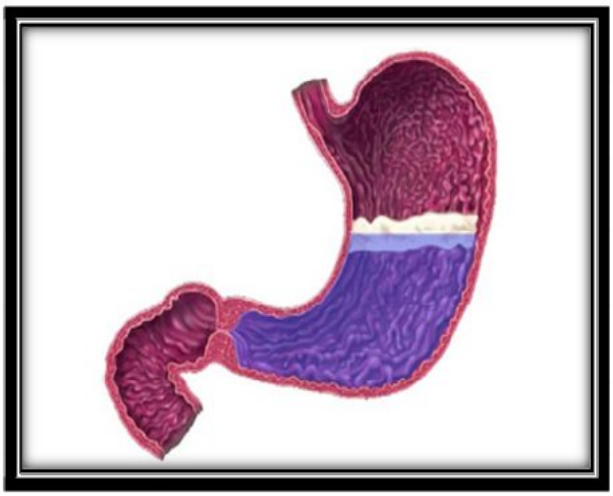

Figure 5: The barrier formed by a raft-forming system

5. Super porous hydrogel systems [12]

These swellable systems differ sufficiently from the conventional types to warrant separate classification. In this approach to improve gastric retention time (GRT) super porous hydrogels of average pore size >100 micro miter, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material.

6. Magnetic systems [19]

This system is based on a simple idea: the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Ito et al. used this technique in rabbits with bioadhesives granules containing ultrafine ferrite (g-Fe_2O_3). They guided them to the esophagus with an external magnet (ÅN1700 G) for the initial 2 min and almost all the granules were retained in the region after2 hrs.
Although these systems seem to work, the external magnet must bepositioned with a degree of precision that might compromise patientcompliance.

DEFINITION OF FLOATING DRUG DELIVERY SYSTEMS (FDDS)

The concept of floating drug delivery system (FDDS)was described in literature as early as 1968. Floating dosage forms are oral dosage forms of tablets [5], capsules, or micro beads and contain hydrocolloids that allow floating by swelling thereby prolong the residence time of dosage form within gastro intestinal tract (GIT) [6].

Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration.

ADVANTAGES OF FDDS [22, 23]

1. The gastro retentive systems are advantageous for drugs absorbed through the stomach, e.g. ferrous salts, antacids.
2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact

with it. Hence, HBS formulation may be useful for the administration of aspirin and other similar drugs.

3. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
4. The gastro retentive systems are advantageous for drugs meant for local action in the stomach. E.g. antacids.
5. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, 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.
6. FDDS improves patient compliance by decreasing dosing frequency.
7. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration are avoided; a desirable plasma drug concentration is maintained by continuous drug release.
8. Better therapeutic effect of short half-life drugs can be achieved.
9. Gastric retention time is increased because of buoyancy.
10. Enhanced absorption of drugs, which solubilize only in stomach.
11. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
12. Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.

DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM [22]

1. Floating system is not feasible for those drugs that have solubility or stability problem in GI tract.
2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.
3. The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, may not be desirable candidate. E.g. Nifedipine.
4. The ability of drug to remain in the stomach depends upon the subject being positioned upright.
5. The residence time in the stomach depends upon the digestive state. Hence, FDDS should be administered after the meal.
6. Not suitable for drugs that cause gastric lesions e.g. Non-steroidal anti-inflammatory drugs. Drugs that are unstable in the strong acidic environment, these systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastro intestinal tract.
7. The mucus on the walls of the stomach is in the state of constant renewal, resulting in the unpredictable adherence.
8. Faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.
9. The ability to float relies in the hydration state of dosage form.
10. In all the above, the most important and primary requirement for the success is the physicalintegrity of the system.

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS

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

A. Effervescent system
   1. Volatile liquid containing systems
   2. Gas generating systems

B. Non-effervescent system
   1. Colloidal gel barrier systems
   2. Microporous compartment system
   3. Alginate beads
   4. Hollow microspheres / Microballoons

A. Effervescent system

These buoyant drug delivery systems utilize matrices prepared with swellable polymers such as Methocel® or polysaccharides, e.g., chitosan and effervescent components .Gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas due to acidity of gastric content and is entrapped in the gellified hydrocolloid, thus reducing the density of the system and making it float on the gastric fluid(Fig. 6). An alternative is the incorporation

of matrix containing portion of liquid, which produce gas that evaporates at body temperature.

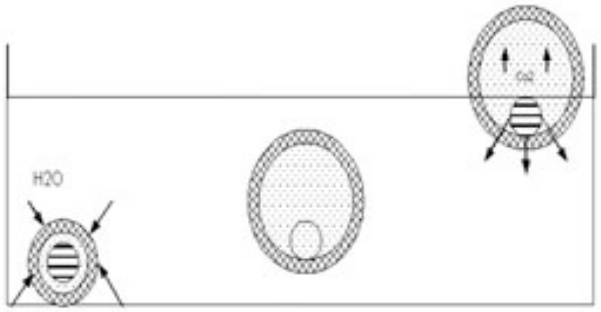

Figure 6: Working principle of effervescent floating drug delivery system

1. Volatile liquid containing systems [24]
The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach.

The device may also consist of a bio erodible plug made up of poly vinyl alcohol, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release the gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable system from the stomach.

I. Intragastric floating gastrointestinal drug delivery system
This system can be made to float in the stomach, because of floating chamber, which may be a vacuum of filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro porous compartment as sawn in fig. 7.

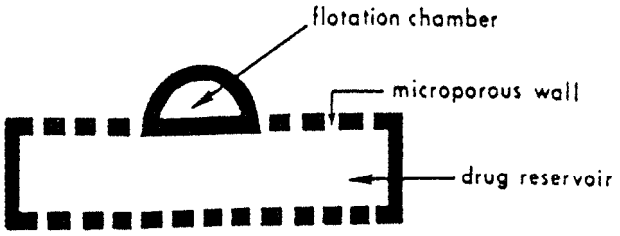

Figure 7: Intra Gastric Floating Gastrointestinal Drug Delivery Device

II. Inflatable gastrointestinal delivery systems [24]
In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflatable in the stomach. These systems are fabricated by loading the chamber with the drug reservoir, which can be a drug impregnated polymeric matrix, than 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 into the gastric fluid.

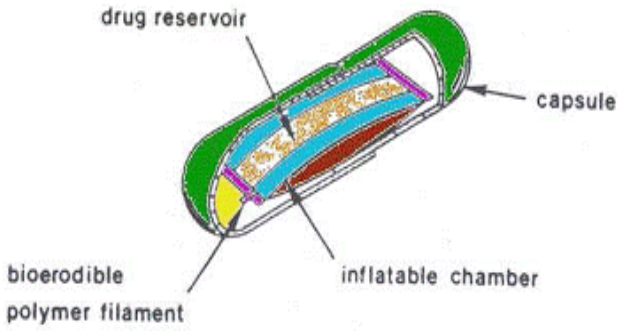

Figure 8: Inflatable gastrointestinal delivery system

III. Intra gastric 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 intra gastric 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 [25].

The osmotic pressure controlled drug delivery device consists of two components, drug reservoir compartment and an osmotically active compartment. A pressure responsive collapsible bag encloses the drug reservoir compartment, which is impermeable to vapor liquid and homo drug delivery orifice. The osmoticallly active compartment contains an osmotically active salt is enclosed within a semi permeable housing. In the stomach, the water in the gastrointestinal fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is then created which acts on the collapsible bag in turn forces the bag reservoir compartment to reduce its volume and activate the drug release through the delivery orifice.

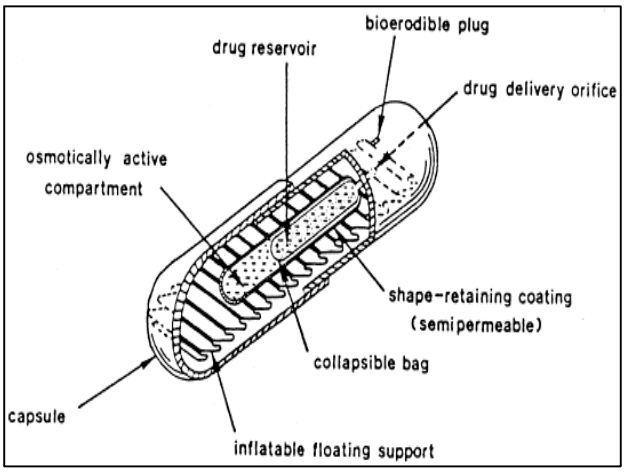

Figure 9: Intragastric osmotically controlled drug delivery system

These buoyant delivery systems utilize effervescent reaction between carbonate or bicarbonate salts and citric or tartaric acid to liberate carbon dioxide. The liberated carbon dioxide gets entrapped in the hydrocolloid layer of the system. Thus the specific gravity decreases and the system begins to float [2, 26]. The common approach used for the preparation of these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus carbon dioxide is released, causing the beads to float in the stomach. Other reported approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating mini-capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology etc. These kinds of systems float completely within 10 minutes and remain floating over an extended period of 5-6 hrs [27].

2. Gas – Generating Systems [18, 19]

These are matrix type of systems prepared with the help of swellable polymers such as Methylcellulose and chitosan and various effervescent compounds, e.g., sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provide buoyancy to the dosage forms.

I. Intra gastric single layer floating tablets or Hydrodynamically balanced system (HBS)

These are formulated by intimately mixing the CO_2 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.

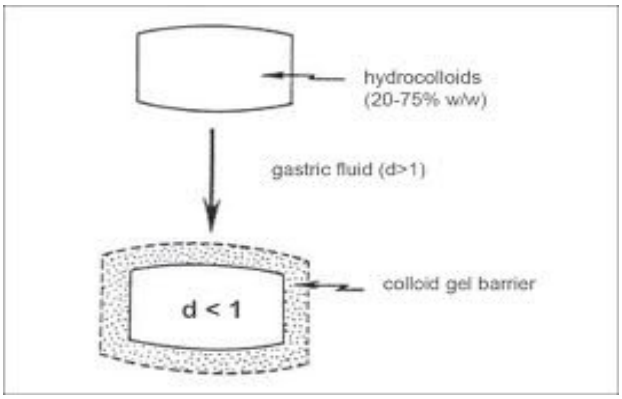

Figure 10: Intra gastric single layer floating tablet

II. Intra gastric bilayer floating tablets

Bilayer or multilayer systems have also been designed. Drug and excipients can be formulated independently and the gas-generating unit can be incorporated into any of the layers (Fig. 11). Further refinements involve coating the matrix with a polymer, which is permeable to water, but not to CO_2. The main difficulty of such formulation is to find a good compromise between elasticity, plasticity and permeability of the polymer.

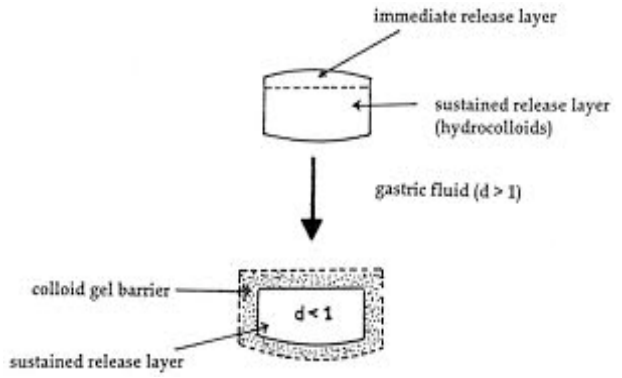

Figure 11: Intra gastric bilayer floating tablets

B. Non effervescent FDDS [24, 28-30]

These systems may be referred to as the "plug type system" since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact after oral administration and maintains a relative integrity of shape and a bulk density of less than 1. This is based on the mechanism of swelling of polymer or bio adhesion to mucosal layer in GIT. The most commonly used excipients are gel forming materials such as polycarbonate, poly acrylate, polystyrene etc. this hydrocolloid starts to hydrate by first forming a gel at the surface of the dosage form. The resultant gel structure then controls the rate of diffusion of solvent-in and drug-out of the dosage form. The various types of this system are as follows:

1. Hydrodynamically Balanced Systems [18,19, 43]

This system was first developed by Sheth and Tossounian [27]. These are single-unit dosage forms, containing one or more gel forming hydrophilic polymers. Hydroxypropylmethylcellulose (HPMC) is the most common used excipient, although Hydroxyethylcellulose (HEC), Hydroxy-propylcellulose (HPC), Sodium Carboxy methylcellulose (NaCMC), agar, carrageenan or alginic acid are also used. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid, and hydration and swelling of the surface polymers produces a floating mass. Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy (Fig. 12).

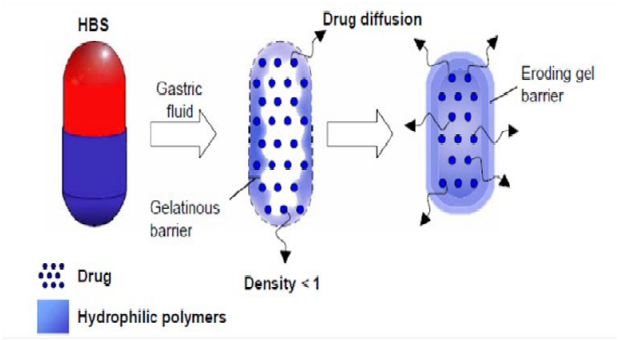

Figure 12: Hydrodynamically balanced system (HBS)

2. Hollow microspheres / Microballoons [31, 32, 39-42]

Hollow microspheres are considered as one of the most promising buoyant systems, as they possess the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere. The general techniques involved in their preparation include simple solvent evaporation and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polycarbonate, Eudragit® Sand cellulose acetate were used in the preparation of hollow microspheres, and the drug release can be modulated by optimizing the polymer quantity and the polymer-plasticizer ratio. Employing solvent evaporation technique developed sustained release floating microspheres using polycarbonate. Aspirin, griseofulvin and p-nitroaniline were used as model drugs. Dispersed phase containing polycarbonate solution in dichloromethane, and micronized drug, was added to the dispersion medium containing sodium chloride, polyvinyl alcohol and methanol. The dispersion was stirred for 3-4h to assure the complete solvent evaporation, and the microspheres obtained were filtered, washed with cold water and dried. The spherical and hollow nature of the microspheres was confirmed by Scanning electron microscopic studies. The microspheres showed a drug payload of more than 50%, and the amount of drug incorporated is found to influence the particle size distribution and drug release. The larger proportion of bigger particles was seen at high drug loading, which can be attributed to the increased viscosity of the dispersed phase. Hollow microspheres (micro balloons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method [12].

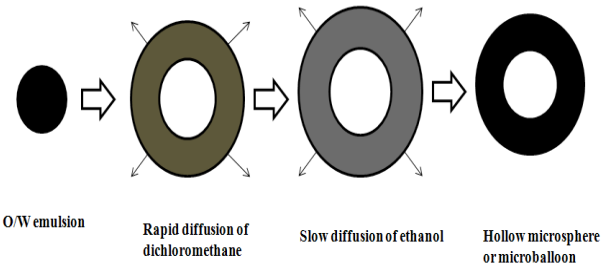

Figure 13: Formulation of floating hollow microsphere or microballoon

3. Alginate beads [46]

Multi-unit 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 sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -400C for 24 hrs. leading to the formation of a porous system, which can maintain a floating force for over 12 hrs. These floating beads gave a prolonged residence time of more than 5.5 hrs.

4. Microporous compartment system

This technology is based on the encapsulation of drug reservoir inside a microporous compartment with aperture along its top and bottom wall (34). The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the un-dissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolved drug for continuous transport across the intestine for absorption.

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery offers several applications for drugshaving poor bioavailability because of the narrow absorptionwindow in the upper part of the gastrointestinal tract.It retains the dosage form at the site of absorption andthus enhances the bioavailability. These are summarizedas follows.

1. Sustained Drug Delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of G1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

Recently sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. 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) [47].

2. Site-Specific Drug Delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide.

Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets [48].

3. Absorption Enhancement

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.

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%) [48].

Table1: List of the drug with floatable delivery system.

Name of Formulation	Name of drugs
Tablets	Ampicillin, Atenolol, Amoxycillin, Chlorpheniramine maleate, Ciprofloxacin, Captopril, Cinnarazine, Diltiazem, Fluoruracil, Isosorbide di nitrate, Riboflavin, Prednisolone, Theophilline.
Capsules	Nicardepine, Diazepam, Misoprostol, Propranolol, Verapamil.
Microspheres/ Floating beads	Aspirin, Verapamil, Ibuprofen, Ketoprofen, Amoxicillin,
Granules	Riboflavin, Meloxicam, Nicardepine Indomethacin, Diclofenac, Prednisolone

CONCLUSION

The FDDS become an additional advantage for drugs that are absorbed primarily in the upper part of gastrointestinal track. Drug absorption in the GIT is a highly variable procedure and

prolonging gastric retention of the dosage form extends the time for drug absorption. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing his technique.

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