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GASTRORETENTIVE DOSAGE FORMS: CURRENT DEVELOPMENTS IN NOVEL SYSTEM DESIGN AND EVALUATION

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ABSTRACT

This review explains the recent advances in gastroretentive drug delivery systems with special focus on floating drug delivery systems. Oral controlled release (CR) dosage forms (DF) have been extensively used to improve therapy of many important medications. However, in the case of narrow absorption window drugs, this pharmaceutical approach cannot be utilized, as it requires sufficient colonic absorption of the drug (which contradicts the definition of narrow absorption window agents). On the other hand, incorporation of the drug into a CR delivery system, which releases its payload in the stomach over a prolonged time period, can lead to significant therapeutic advantages owing to various pharmacokinetic (PK) and pharmacodynamic aspects. Gastroretentive dosage forms (GRDFs) are a drug delivery formulation that are designed to be retained in the stomach for a prolonged time and release there their active materials and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract. This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and/or their therapeutic outcome. This article reviews some of the latest developments in GRDF technology from a pharmaceutical point of view. It also highlights the PK and/or pharmacodynamic rationale for the development of GRDFs for certain drugs that are either absorbed in the upper GI tract or have local activity there.

Key words: Floating drug delivery systems, single unit, multiple units, gastric resident time, Expandable Systems

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INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa.[1] Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed.

Gastroretentive 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 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 intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents[2,3] that delay gastric emptying.

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.[4] 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 myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington.[5]

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

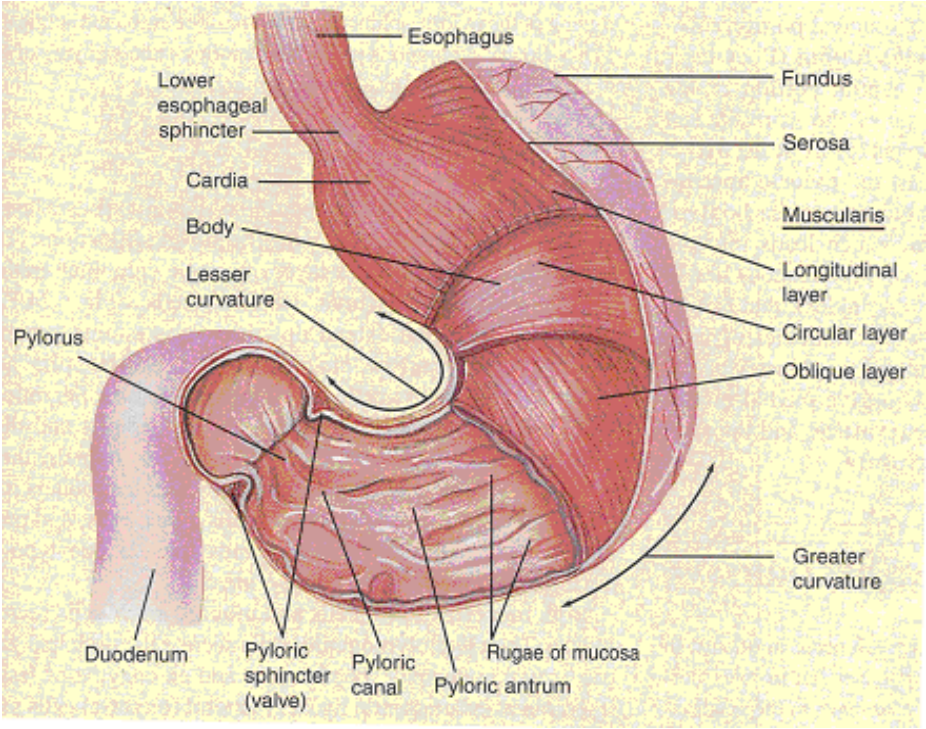


Figure 1: Diagram of human stomach

5.After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.[6]

Advantages of Floating Dosage Form[7]

1. The Principle of HBS may not limited to any particular medicament or class of medicament
2. The HBS formulations are not restricted to medicaments, which are absorbed from stomach, since it has been found that these are equally efficacious with medicament, which absorbed from the intestine.
3. Acidic substances like aspirin cause irritation on the stomach wall when come in to contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.

4. The HBS are advantageous for drugs absorbed through the stomach.e.g. Ferrous salts, antacids.
5. The efficacy of the medicaments administered utilizing the sustained release principle of HBS formulation has been found to be independent of the site of particular medicaments.
6. The HBS are advantageous for drugs meant foe local action in the stomach.e.g.Antacids.
7. Administration of prolongs release floating dosage forms, tablet or capsules, will results 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 the floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
8. When there is vigorous intestinal movement and a shorted 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.

Limitations/Disadvantages

1. These systems require a high level of fluid in the stomach for drug delivery tom float and work efficiently-coat, water.
2. Not suitable for drugs that have solubility or stability problem in GIT.
3. Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
4. Drugs which are irritant to Gastric mucosa is also not desirable or suitable.
5. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
6. The dosage form should be administered with a full glass of water (200-250 ml).
7. These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.

FACTORS AFFECTING GASTRIC RETENTION

Gastric residence time of an oral dosage form is affected by several factors.

pH of the stomach[8]

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.

Gastric emptying[9]

The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Nutritive density of meals helps determine gastric emptying time. 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. 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. 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. Studies have shown that the gastric residence time (GRT) can be significantly increased under the fed conditions since the MMC is delayed. 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." As the units of multiparticulate systems are distributed freely throughout the gastrointestinal tract, their transport is affected to a lesser extent by the transit time of food compared with single unit formulation.

Density[10]

The density of a dosage form also affects the gastric emptying rate. A buoyant dosage form having 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. Density of the dosage form should be less than the gastric contents (1.004gm/ml).

Size and shape of dosage unit[10]

Size and shape of dosage unit also affect the gastric emptying. Several reported shows[10]that tetrahedron- and ring-shaped devices have a better gastric residence time as compared with other shapes. 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.

Fed or Unfed State

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (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.[11]

Nature of the meal

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

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 meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

Age

Elderly people, especially those over 70 years have a significantly longer GRT.

Miscellaneous

Biological factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes, Chron's disease) influence gastric emptying the effect of buoyancy, posture, and nature of meals on the gastric emptying process in vivo using gamma scintigraphy also affects the gastric emptying rate.[10]

Size of the dosage form[12]

To perform these studies, floating and nonfloating capsules of 3 different sizes, 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 nonfloating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase (Figure 1). It was also observed that of the floating and nonfloating units, the

floating units were had a longer gastric residence time for small and medium units while no significant difference was seen between the 2 types of large unit dosage forms. 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.

APPROACHES FOR GRDF DEVELOPMENT

Increasing the GRT of DFs can be achieved in several ways. Naturally, food high in calorie value or containing fats and some amino acids can slow gastric emptying and intestinal transit. Certain drugs such as metoclopramide are known to decrease the gastric motility and thus increase the GRT of drugs that are administered concomitantly. However, it is not acceptable to add a second drug to improve bioavailability. Recently, some sophisticated technologies have been developed to increase the GRT of drug formulations utilizing different features of the stomach anatomy and physiology. Some of these technologies have been adapted by pharmaceutical companies to improve the bioavailability and therapeutic utilization of existing drugs, although it is more likely that the success of these technologies is more valuable in the development of new drugs.

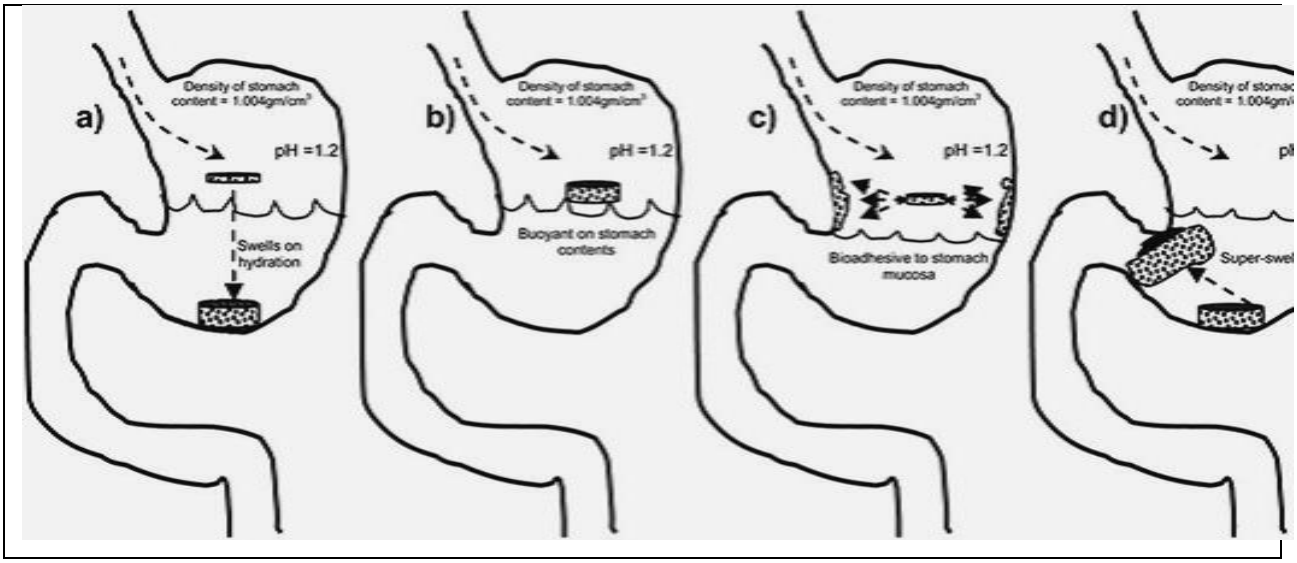


Figure 2 Schematic depicting the mechanisms of retention of a) high density, b) low density, c) bioadhesive and d) swelling/expanding drug delivery systems

Expandable DFs

Expandable DFs are oral delivery devices that increase their size considerably after ingestion; the extended dimensions are aimed to be retained in the stomach and consequently increase their GRT. These DFs are planned to release their drug content in the stomach and be subsequently evacuated owing to the decrease of their dimension and rigidity. Different expandable DFs have

been developed over the last three decades. Originally, these DFs were developed unfolding dosage form by Laby[13] for veterinary use. The design of expandable DFs usually takes into consideration some basic configurations: a small configuration having a suitable size for convenient oral intake, expanded form that is achieved in the stomach and which should have an appropriate size that inhibits its gastric emptying through the pyloric sphincter, and finally a small form achieved after active drug release that allows their evacuation. The expanded device should be rigid enough to remain intact and survive the gastric mechanical forces. Besides, the rate of drug release should be appropriate to achieve optimal absorption of the drug from its absorption window. The first designed GRDF for human use was suggested by Johnson and Rowe[14] on the basis of expansion in the stomach and it was composed of thiolated gelatin, a cross-linking agent, and a drug. Once the device reaches the stomach and is exposed to gastric fluids, the thiolated gelatin hydrates, swells, and cross-links to form a matrix too large to pass through the pylorus. Additives like a nondigestible hydrophilic colloidal material can be added to increase the swelling ratio.

Swelling DFs

The techniques applied for achieving expanding properties for GRDFs are usually swelling or unfolding. Swelling devices are, in most cases, based on a hydrophilic polymer prepared from a combination of polyethylene oxide and hydroxypropyl methyl cellulose that form a hydrogel, which can achieve both CR and swelling properties.

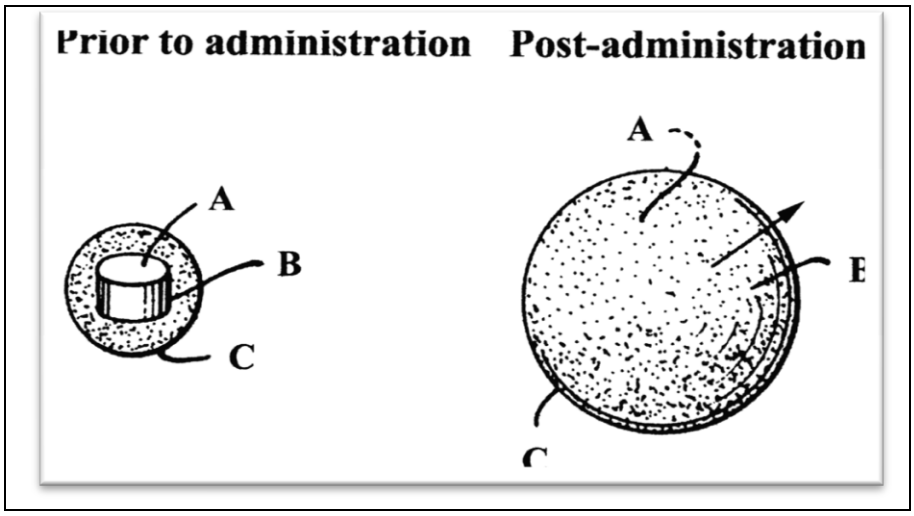


Figure.3: Swelling dosage form modified from Mamajek and Moyer Prior to administration the drug reservoir (A) is surrounded by a swellable expanding agent (B) and the whole enclosed by elastic outer polymeric envelope (C), also controlling drug release rate. Post administration, the pressure of the expanding agent (B) swells the elastic polymer (C). Drug is released from the dosage form through the elastic polymeric envelope (C) as indicated by the arrow.

Mamajek and Moyer[15] have designed a GRDF consisting of a nonhydratable membrane envelope that is drug and fluid permeable; a drug reservoir, an expanding agent, and a swellable resin are enveloped and the whole device expands owing to osmotic pressure. Another swelling device developed exhibits high swelling properties exhibiting 2–50 fold volume increase, which retains device evacuation from the stomach not only because of its large dimension but also because of maintaining the stomach in the fed mode by means of mechanical sensation. By incorporating the active drug into wax-walled tiny pills, a CR of the drug is achieved.

Unfolding DFs

Unfolding GRDFs are usually planned to extend from their initial small configuration to their unfolded large size in the stomach after oral intake. Owing to the mechanical properties of the device, the gastric liquids induce its opening or expanding. Unlike the swelling devices, the unfolding GRDFs are manufactured in their maximal size and are folded into their minimal geometry to enable convenient intake, thus also have to include ‘‘obstructing means’’ that increase their rigidity and thus inhibit their evacuation from the stomach. The effect of size, shape, erodibility, and mechanical shape of the unfolded devices was conducted by Caldwell et al[16] The geometric configurations of the developed devices were continuous stick, ring, tetrahedron, planar disc, planar multilobe, and string. All the devices had the following properties:

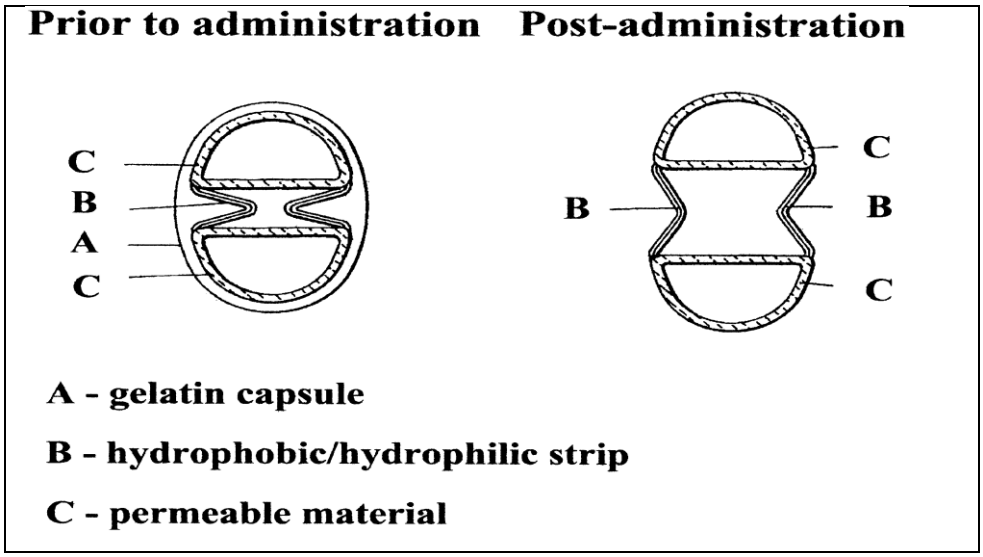


Figure. 4: Unfolding dosage form modified is designed for ruminants. Once the gelatin capsule (A) dissolves in the rumen, the hydrophobic/ hydrophilic strips (B) absorb water and deform, thus causing expansion to a size which prevents regurgitation. The drug diffuses through the permeable material (C) in a controlled manner.

Sufficient resistance to forces applied by the stomach to prevent their rapid passage through the pylorus, their presence in the stomach still allows the free passage of food in the stomach and desired in vivo circumference larger than 5 cm, to ensure gastroretentivity. Studies in beagle dogs have shown that gastroretentivity, assessed as the number of devices retained in the fasting stomach at 24 hr, can remarkably be influenced by the geometry of the unfolded DFs and by the type of test species and increases remarkably as a result of enhanced mechanical properties and decreased polymer erosion.

Floating Formulations

Floating microcapsules were first described by Sheth and Tossounian[17] as forms that can float on the gastric contents wing to their lower bulk density. Usually, floating formulations are prepared from hydrophilic matrices that either have a density lower than one or their density drops below one after immersion in the gastric fluids owing to swelling. Cellulose ether polymers are often used as the floating matrices, and low-density fatty acids can be incorporated as well to decrease hydrating rate and increase buoyancy. More sophisticated devices were developed later and involved the use of various film-coating techniques, incorporation of a floating chamber that is filled with harmless gas or a liquid that gasifies at body temperature. These forms are often called ‘‘hydrodynamically balanced systems’’ (HBS) as they can maintain low density and keep floating even after hydrating. When a floating form is administered with food, the device remains buoyant on the surface of the gastric contents in the upper part of the stomach and moves down toward the pyloric sphincter while the meal empties. The reported GRT of such floating devices varies from 4 to 10 hr. The active drug is progressively released from the formulation matrix and thus introduced to the proximal intestine where it can be absorbed.

Bioadhesive Formulations

Bioadhesive or mucoadhesive formulations were originally developed for increasing GRT and controlling drug delivery of all kinds of drugs. The technique involves coating of microcapsules with bioadhesive polymer, which enables them to adhere to intestinal mucosa and remain for longer time period in the GI while the active drug is released from the device matrix. The cationic chitosan polymers are pharmaceutically acceptable to be used in the preparation of bioadhesive formulations owing to their known ability to bind well to gastric mucosa.[18] taking into consideration the quick turnover of intestinal mucus and the reasonably constant transit time of food and drug in the intestine being independent of size, shape, density or fed state, it is hard to find published data that demonstrate that bioadhesion can actually increase the transit time in

the intestine. Thus, the extended transit of such formulations has yet to be confirmed by direct measurement using abeling methods or scintigraphy rather than using circumstantial methods, such as gastroretentivity, as demonstrated in area under the plasma level vs. time curve.

MECHANISM OF GASTRORETENTIVE DOSAGE FORMS [19]

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 1 (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 (Figure 5b). 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

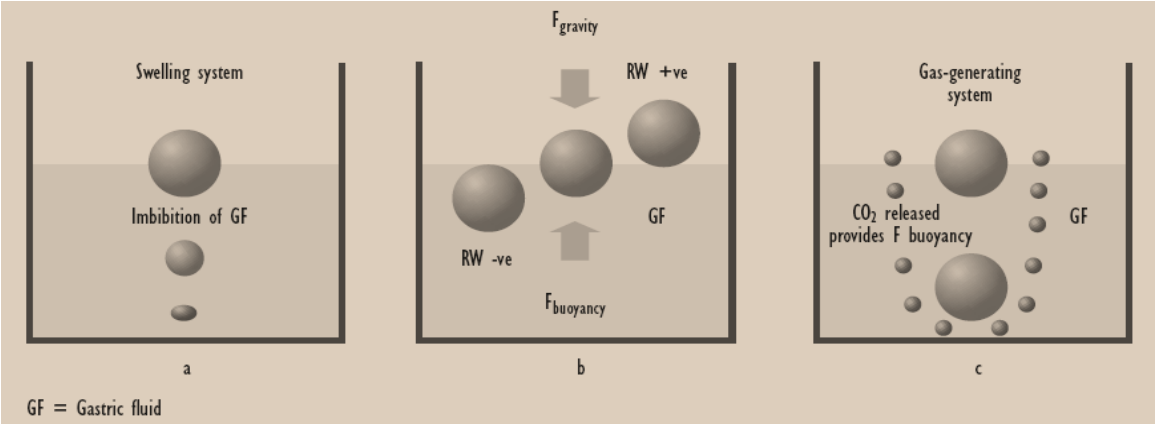


Figure .5) Mechanism of Gastroretentive dosage forms

F = F buoyancy - F gravity

= (Df - Ds) gv--- (1)

Where, F= total vertical force, Df = fluid density,

Ds = object density, v = volume and

g = acceleration due to gravity. g = acceleration due to gravity.

BASED ON THE MECHANISM OF BUOYANCY FDDS CAN BE CLASSIFIED INTO

A.) **Single-Unit Dosage Forms**

I. Effervescent system

II. Non-effervescent system

B**.) Multiple unit dosage form**

I. Effervescent System

II. Non-effervescent system

III. Hollow microsphere

C.) **Raft Forming system**

D.)**Expandable system**

A.) SINGLE-UNIT DOSAGE FORMS

(a) Effervescent systems[20]: 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 gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach.

(i) Volatile liquid containing systems: These have 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 drug-polymer mixture. The polymer of choice can be either ethylcellulose or hydroxypropyl cellulose depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration. drug-polymer mixture. The polymer of choice can be either ethylcellulose or hydroxypropyl

cellulose depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration.

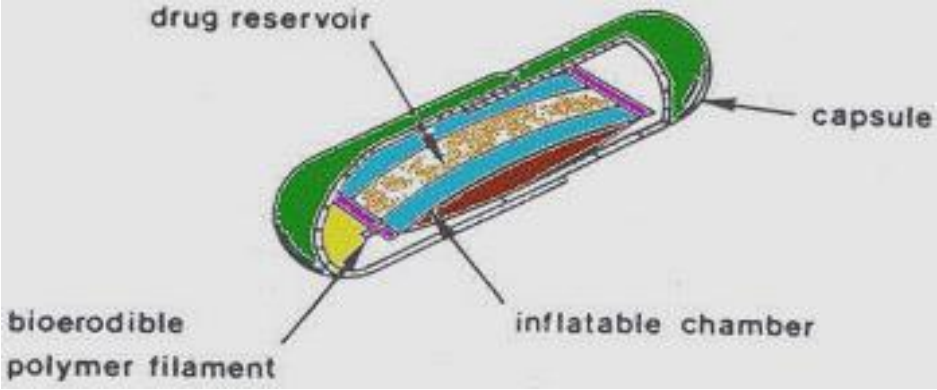


Figure.6 Volatile liquid containing systems

(ii)Gas generating systems[20]: These buoyant systems utilized matrices prepared with swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. 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 approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, that generate carbon dioxide when ingested, floating minicapsules 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.

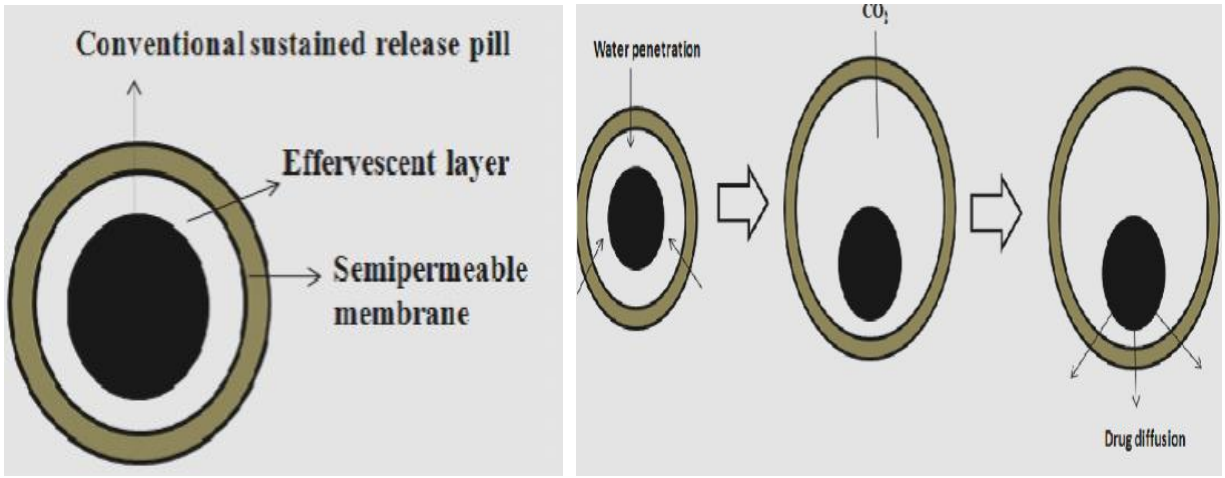


Figure 7. Gas generating systems

(iii) **Matrix Tablets:** Single layer matrix tablet is prepared by incorporating bicarbonates in matrix forming hydrocolloid gelling agent like HPMC, chitosan, alginate or other polymers and drug. Bilayer tablet can also be prepared by gas generating matrix in one layer and second layer with drug for its SR effect. Floating capsules also prepared by incorporating such mixtures. Triple layer tablet also prepared having first swellable floating layer, second sustained release layer of 2 drugs (Metronidazole and Tetracycline) and third rapid dissolving layer of bismuth salt. This tablet is prepared as single dosage form for Triple Therapyof H.Pylori.

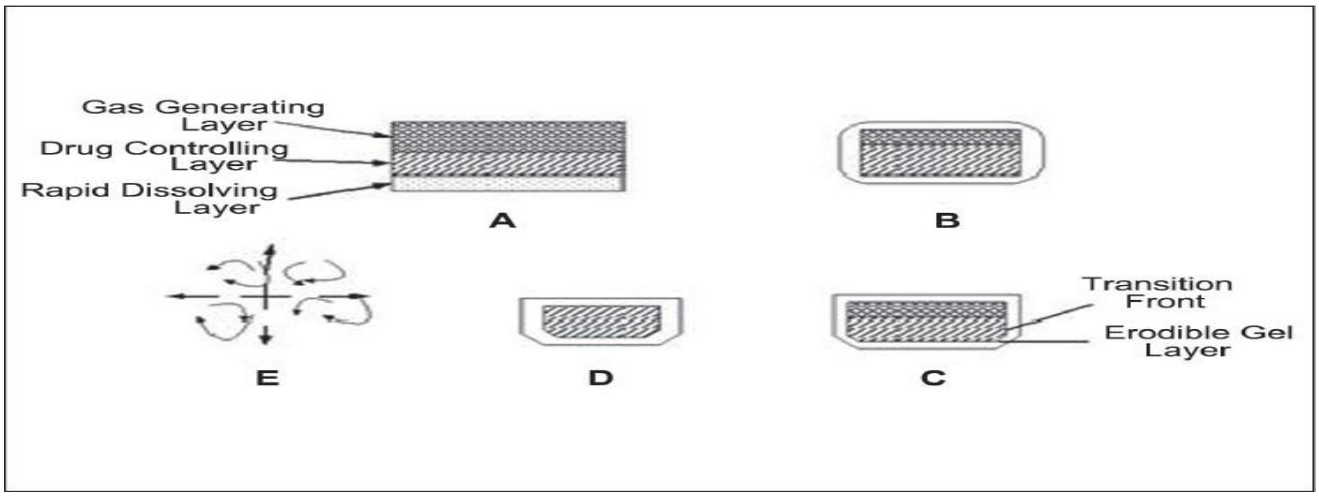


Figure-8 Tripal layer matrix tablet:- Schematic presentation of working of a triple-layer system. (A) Initial configuration of triple-layer tablet. (B) On contact with the dissolution medium the bismuth layer rapidly dissolves and matrix starts swelling. (C) Tablet swells and erodes. (D) and (E)

(b) Noneffervescent system: Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

(i)Hydrodynamically balanced systems: These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl

cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems. The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form. Incorporation of fatty excipients gives low-density formulations reducing the erosion. Effective drug deliveries depend on the balance of drug loadingand the effect of polymer on its release profile several strategies have been tried and investigated to improve efficiencies of the floating hydrodynamically balanced systems[21].

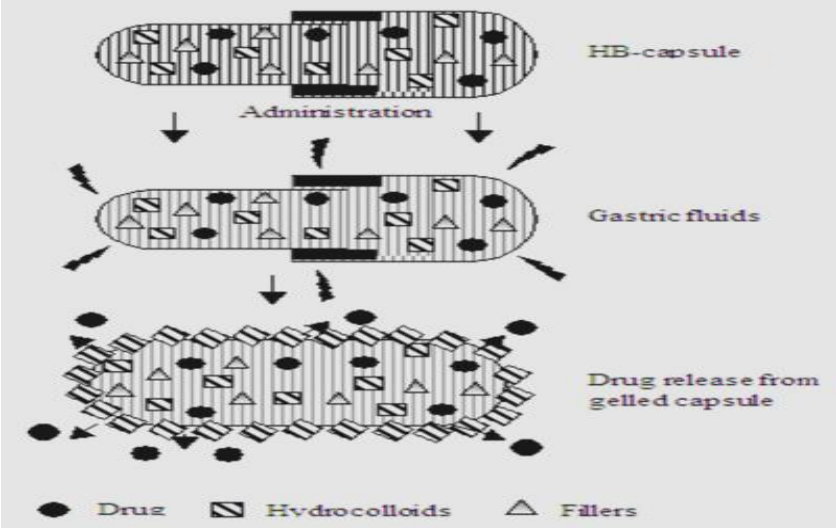


Figure. 9 Working principle of hydrodynamically balanced system.

(iii)Alginate beads: They were made by using Ca2+ and low methoxylated pectin (anionic polysaccharide) or Ca2+ low methoxylated pectin and sodium alginate. In this approach, generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and freeze drying, leading to the formulation of a porous system, which can maintain a floating force for over 12 hrs. These beads improve gastric retention time (GRT) more than 5.5 hrs to 24hrs., Microporous compartment system: This approach is based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the device were completely sealed to present any direct contact of the gastric surface with the undissolved drug. In the stomach the floatation chamber containing entrapped air causes the delivery system to 11float in the gastric fluid. Gastric fluid

enters through the aperture, dissolves the drug and causes the dissolved drug for continuous transport across the intestine for drug absorption.

(B)MULTIPLE-UNIT DOSAGE FORMS

The purpose of 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 pursuit of this endeavor many multiple-unit 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 microsponges, also referred to as "microballoons," have been prepared. In Carbon dioxide–generating multiple-unit oral formulations several devices with features that extend, unfold, or are inflated by carbon dioxide generated in the devices after administration have been described in the recent patent literature. 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.

(a)Effervescent Floating Dosage Form[22]: These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid.

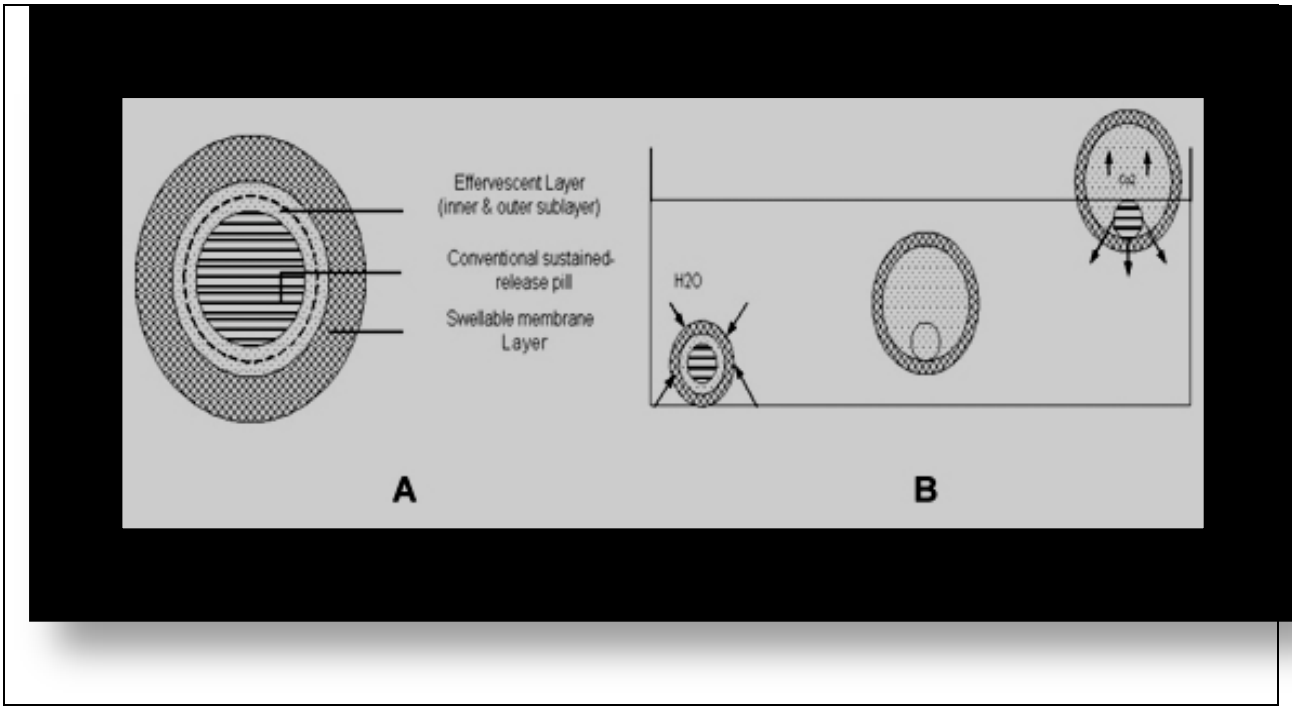


Figure 10. (A) Multiple-unit oral floating drug delivery system. (B) Working principle of effervescent floating drug delivery system

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 provides buoyancy to the dosage forms. A new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sub-layers to avoid direct contact between the 2 agents. These sub-layers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO_2 was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/mL. It was found that the system had good floating ability independent of pH and viscosity and the drug (para-amino benzoic acid) released in a sustained manner. (Figure 10, A and B).

(i)The floating bilayer: The floating bilayer[23]tablets with controlled release for furosemide. The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with β cyclodextrin mixed in a 1:1 ratio. One layer contained the polymers HPMC 4000, HPMC 100, and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid. The in vitro floating studies revealed that the lesser the compression force the shorter is the time of onset of floating, ie, when the tablets were compressed at 15 MPa, these could begin to float at 20 minutes whereas at a force of 32 MPa the time was prolonged to 45 minutes. Radiographic studies on 6 healthy male volunteers revealed that floating tablets were retained in stomach for 6 hours and further blood analysis studies showed that bioavailability of these tablets was 1.8 times that of the conventional tablets. On measuring the volume of urine the peak diuretic effect seen in the conventional tablets was decreased and prolonged in the case of floating dosage form property. Better floating was achieved at a higher HPMC/carbopol ratio and this result demonstrated that carbopol has a negative effect on the floating behavior .A zero-order controlled release multilayer tablet composed of at least 2 barrier layers and 1 drug layer. All the layers were made of swellable, erodible polymers and the tablet was found to swell on contact with aqueous medium. As the tablet dissolved, the barrier layers eroded away to expose more of the drug. Gas-evolving agent was added in either of the barrier layers, which caused the tablet to float and increased the retention of tablet in a patient's stomach.

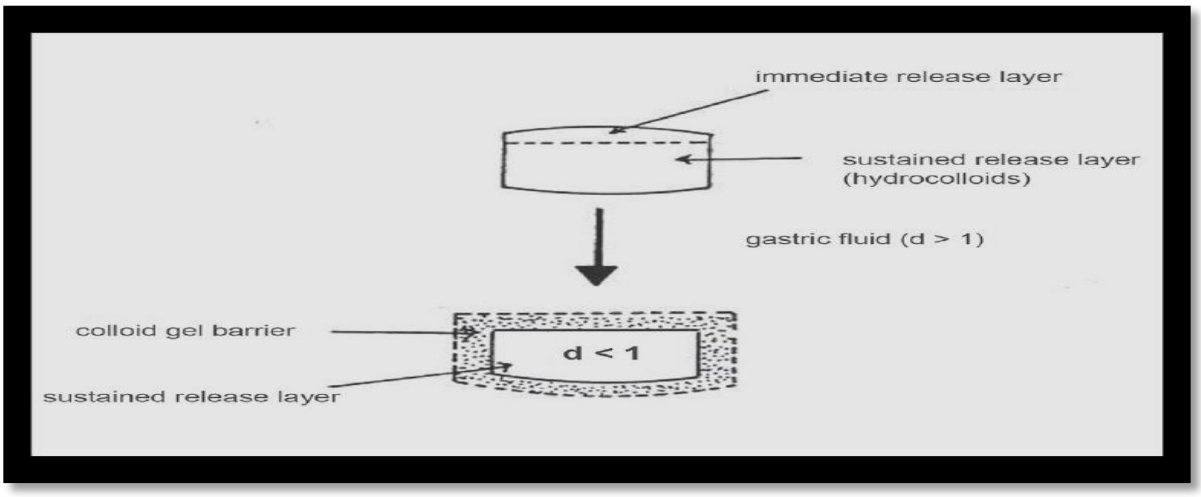


Figure 11. Working principle of floating bilayer drug delivery system

(ii) **Ion exchange resin floating dosage form:** Another type of floating system using ion exchange resin[24] that was loaded with bicarbonate by mixing the beads with 1M sodium bicarbonate solution. The loaded beads were then surrounded by a semi permeable membrane to avoid sudden loss of CO_2. Upon coming in contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO_2 generation thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads. The in vivo behavior of the coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers by gamma radio scintigraphy. Studies showed that the gastric residence time was prolonged considerably (24 hours) compared with uncoated beads (1 to 3 hours).

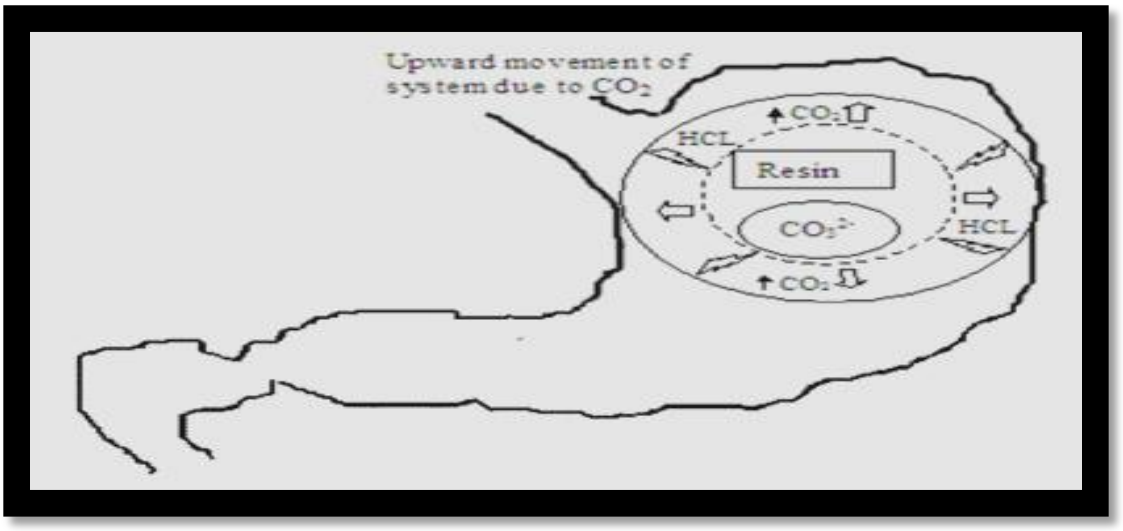


Figure. 12. Pictorial presentation of working of effervescent floating drug delivery system based on ion exchange resin

(iii)Floating alginate beads dosage form: Another preparation of floating delivery system is floating alginate beads using gas-forming agents (calcium carbonate and sodium bicarbonate) and studied the effect of CO_2 generation on the physical properties, morphology, and release rates. The study revealed that the kind and amount of gas-forming agent had a profound effect on the size, floating ability, pore structure, morphology, release rate, and mechanical strength of the floating beads. It was concluded that calcium carbonate formed smaller but stronger beads than sodium bicarbonate. Calcium carbonate was shown to be a less-effective gas-forming agent than sodium bicarbonate but it produced superior floating beads with enhanced control of drug release rates. In vitro floating studies revealed that the beads free of gas-forming agents sank uniformly in the media while the beads containing gas-forming agents in proportions ranging from 5:1 to 1:1 demonstrated excellent floating (100%).

(b) Non-Effervescent Floating Dosage Forms*:* Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene[25]. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass[20].In the approach of hydrodynamically balanced sustained release tablets containing drug and hydrophilic hydrocolloids, which on contact with gastric fluids at body temperature formed a soft gelatinous mass on the surface of the tablet and provided a water-impermeable colloid gel barrier on the surface of the tablets. The drug slowly released from the surface of the gelatinous mass that remained buoyant on gastric fluids.

(c) Microballoons / Hollow microspheres: Microballoons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion evaporation methods 18 (Figure 1) to prolong the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours **[26].** At present hollow

microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good

floating.

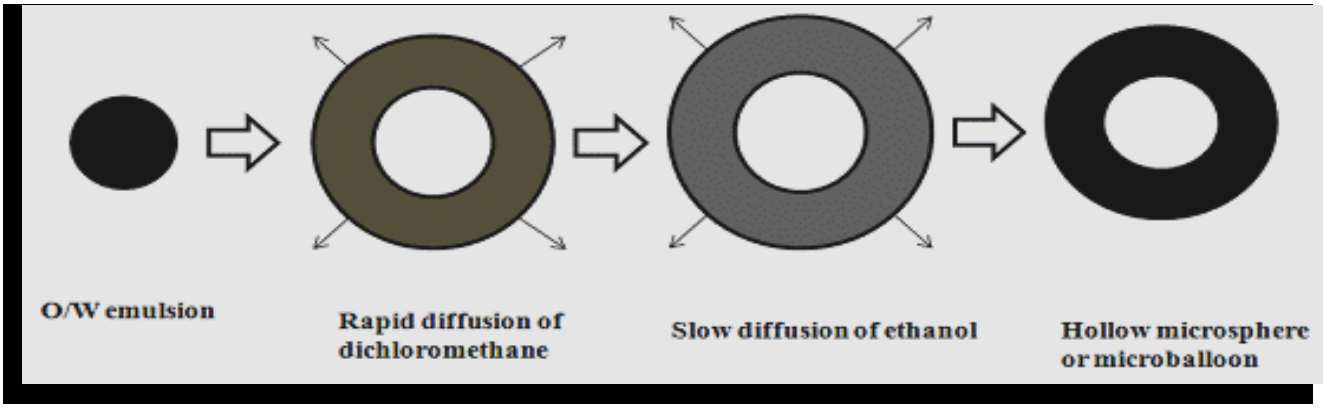


Figure 13. Formulation of floating hollow microsphere or microballoon

C.) RAFT FORMING SYSTEMS[27]

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 CO2.Usually, the system contains a gel forming agent and alkaline bicarbonates orcarbonates responsible for the formation of CO2 to make the system less dense and float on the gastric fluids. The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus. A patent assigned to Reckitt and Colman Products Ltd., describes a raft forming formulation for the treatment of helicobacter pylori (H. Pylori) infections in the GIT. The composition contained drug, alginic acid, sodium bicarbonate, calcium carbonate, mannitol and a sweetener. These ingredients were granulated, and citric acid was added to the granules. The formulation produces effervescence and aerates the raft formed, making it float.

(D) EXPANDABLE SYSTEM

After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems are sometimes referred to as plug type systems because they tend to remain lodged at the

pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. As dosage form coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical-chemical crosslink's in the hydrophilic polymer network[28]. These cross-links prevent the dissolution of the polymer and thus maintain the physical integrity of the dosage form. 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 crosslinking retards the swelling ability of the system and maintains its physical integrity for a prolonged period. On the other hand, a low degree of cross-linking resultsin extensive swelling followed by the rapid dissolution of the polymer. An optimum amount of cross-linking is required to maintain a balance between swelling and dissolution.

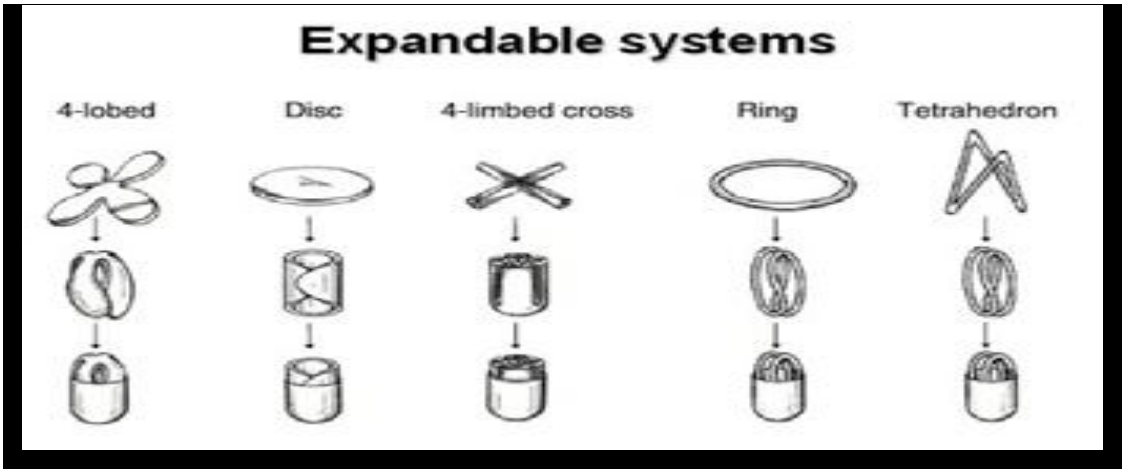


Figure 14. Various types of expandable systems

Table:-01. List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems.

Dosage forms	Drugs
Tablet	Chlorpheniramine maleate, Theophylline, Furosemide, Ciprofolxacin, Pentoxyfillin, Captopril, Acetylsalicylic acid, Nimodipine, Amoxycillin trihydrate, Verapamil HCl, Isosorbide di nitrate, Sotalol, Atenolol, Isosorbide mono nitrate, Acetaminophen, Ampicillin, Cinnarazine, Diltiazem, Florouracil, Piretanide, Prednisolone, Riboflavin- 5′ Phosphate
Capsule	Nicardipine, $_{L}$- Dopa and benserazide, hlordiazepoxide HCl, Furosemide Misoprostal, Diazepam, Propranlol, Urodeoxycholic acid

Microspheres	Verapamil, Aspirin, griseofulvin, and p-nitroaniline, Ketoprofen, Tranilast Iboprufen, Terfenadine
Granules	Indomathacin, Diclofenac sodium, Prednisolone
Films	Cinnarizine
Powders	Several basic drugs

FORMULATION OF FLOATING DOSAGE FORM

Following types of the ingredients can be incorporated in to HBS dosage form [29]

- Hydrocolloids
- Inert fatty materials
- Release rate accelerants
- Release rate retardant
- Buoyancy increasing agents
- Low density material
- Miscellaneous

Hydrocolloids

Suitable hydrocolloids are synthethics, anionic or non ionic like hydrophilic gumes, modified cellulose derivatives. E.g. Accasia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, , Chitosan, Agar, Casein, Bentonite, Veegum, Hydroxy Propyl Methyl Cellulose (HPMC) (K4M, K100M and K15M), Gellan gum(Gelrite®), Sodium Carboxy Methyl Cellulose (CMC), Methyl Cellulose (MC), Hydroxy Propyl Cellulose (HPC)., and Na CMC can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid is having pH 1.2.Although the bulk density of the formulation may initially be more than one, but when gastric fluid is enter in the system, it should be hydrodynamically balanced to have a bulk density of less than one to assure buoyancy.

Inert fatty materials

Edible, pharmaceutical inert fatty material, having a specific gravity less than one can be added to the formulation to decrease the hydrophilic property of formulation and hence increases the buoyancy. Example: Purified grades of beeswax, fatty acids, long chain alcohols, Gelucires® 39/01and 43/01. glycerides, and minaral oils can be used.

Release rate accelerant

The release rate of the medicament from the formulation can be modified by including excipients like lactose and/or mannitol. These may be present from about 5-60% by weight.

Release rate retardant

Insoluble substances such as dicalcium phosphate, talc magnesium strearete decresesd the solubility and hence retard the release of medicaments.

Buoyancy increasing agents

Materials like ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may be adapted up to 80 % by weight.

Low density material- Polypropylene foam powder (Accurel MP 1000®).

Miscellaneous

Pharmaceutically acceptable adjuvant like preservatives, stabilizers, and lubricants can be incorporates in the dosage forms as per the requirements. They do not adversely affect the hydrodynamic balance of the systems.

EVALUATION OF GASTRORETENTIVE DOSAGE FORM

Various parameters that need to be evaluated in gastro retentive formulations which includes floating duration, dissolution profiles, specific gravity, content uniformity, hardness and friability in case of solid dosage forms. In case of multiparticulate drug delivery systems, differential scanning calorimeter (DSC), particle size analysis, flow properties, surface morphology, mechanical properties and x-ray diffraction studies are performed.

1. **Buoyancy Lag Time and Duration of Buoyancy**[30]

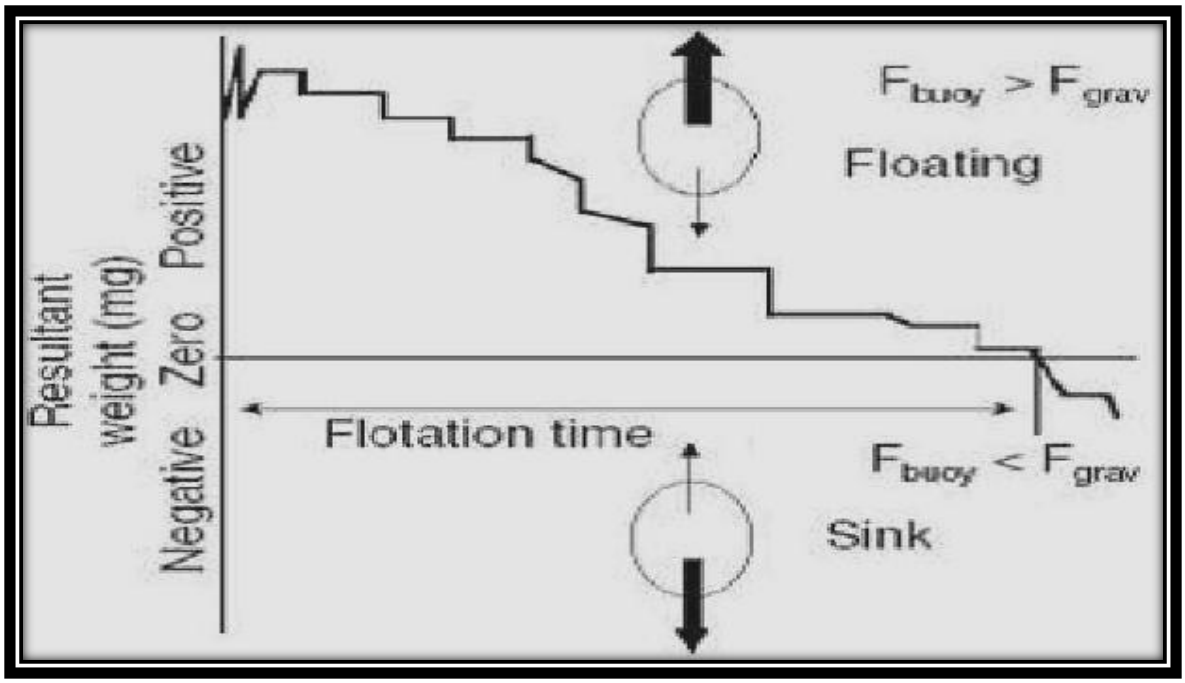
The buoyancy lag time and the duration of buoyancy determine in the U.S.P. dissolution test apparatus II in a acid environment. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of the dissolution medium is taken buoyancy lag time or floating lag time and the duration of buoyancy was observed visually.

2. **Determination of Density**[31]

The tablet density of the floating system was determined by displacement method, using benzene as a displacing medium. A plethysmometer employ to measure tablet density. Firstly, the instrument was calibrated using benzene (density 0.8723g/cc) for its volumetric capacity. Benzene fill till a mark in capillary the instrument. Subsequently, five tablets of known weight were dropped in wider mouth of plethysmometer .The system is kept undisturbed for 1 min, to let benzene displace the air in the pores of the tablets. After that, displacement in the volume of the benzene in the side capillary was noted. Knowing the weight and volume occupied by the tablets, density of five tablets is determine.

3. **Resultant Weight**[32]

Now we know that bulk density and floating time are the main parameters for describing buoyancy. But only single determination of density is not sufficient to describe the buoyancy because density changes with change in resultant weight as a function of time. For example a matrix tablet with bicarbonate and matrixing polymer floats initially by gas generation and entrapment but after some time, some drug is released and simultaneously some outer part of matrixing polymer may erode out leading to change in resultant weight of dosage form. The magnitude and direction of force/resultant weight (up or down) is corresponding to its buoyancy force (Fbuoy) and gravity force (Fgrav) acting on dosage form



F = Fbuoy - FgravF = Df g V – Ds g V F = (Df – Ds) g V, F = (Df – M/V) g V

Where,

F = resultant weight of object

Df = Density of Fluid

DS = Density of Solid object

g = Gravitational force

M = Mass of dosage form

V = Volume of dosage form

So when Ds, density of dosage form is lower, F force is positive gives buoyancy and when it is Ds is higher, F will negative shows sinking.

5. Swelling Index[33]

Tablets weight individually (Wo) and placed in dissolution medium. The temperature is

maintained at 37^{o} C. At regular intervals, the samples remove using a basket and swollen weight(Wt) each tablet was determined at predefined time intervals. The swelling index was calculated by the following equation:

Percentage Swelling Index = (Wt- Wo/ Wo)×100

Where Wo is the is the initial weight of tablet and Wt is the weight of the tablet at time t.

6. **Hardness and Friability**[34]

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet, the resistance of the tablet to chipping, abrasion or breakage under condition of storage, transformation and handling before usage depends on its hardness. Hardness of tablet is measure by using Monsanto Hardness Tester. Friability of the tablets determines using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inch in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed.

The friability (F%) is given by the formula:

F%= (1-W/W) ×100

Where, W is the tablets before the test and W is weight of the tablets after test.

7. Weight Variation

USP provides the weight variation test by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weights to the average The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

8. **In-Vitro dissolution behavior**[35,36]

The release of the medicament was studied by USP-II type dissolution apparatus (Paddle type). Dissolution study is performing at predetermined speed and temperature of about 37^{o}C in an appropriate dissolution medium.5ml of sample withdraw at a predetermined interval and the volume of dissolution medium maintain by adding same volume of dissolution medium. The absorption of withdrawn sample measure spectrophotometrically with suitable dilution and the corresponding concentration was determined from the calibration curve.

A.)In vitro dissolution test is generally done by using USP apparatus with paddle and GRDDS is placed normally as for other conventional tablets. But sometimes as the vessel is large and paddles are at bottom, there is much lesser paddle force acts on floating dosage form which

generally floats on surface. As floating dosage form not rotates may not give proper result and also not reproducible results. Similar problem occur with swellable dosage form, as they are hydrogel may stick to surface of vessel or paddle and gives irreproducible results. In order to prevent such problems, various types of modification in dissolution assembly made are as follows.

B.) To prevent sticking at vessel or paddle and to improve movement of dosage form, method suggested is to keep paddle at surface and not too deep inside dissolution medium.

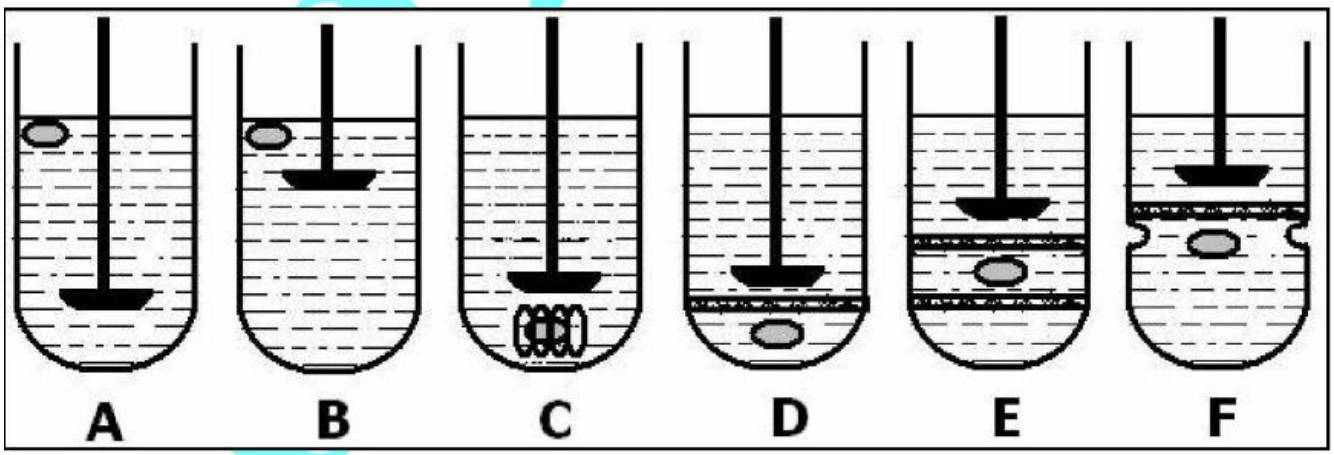


Figure -15 dissolution of floating dosage form

C.) Floating unit can be made fully submerged, by attaching some small, loose, non- reacting material, such as few turns of wire helix, around dosage form. However this method can inhibit three dimensional swelling of some dosage form and also affects drug release.

D.) Other modification is to make floating unit fully submerged under ring or mesh assembly and paddle is just over ring that gives better force for movement of unit.

E.) Other method suggests placing dosage form between 2 ring/meshes.

F.) In previous methods unit have very small area, which can inhibit 3D swelling of swellable units, another method suggest the change in dissolution vessel that is indented at some above place from bottom and mesh is place on indented protrusions, this gives more area for dosage form.

G.) Inspite of the various modifications done to get the reproducible results, none of them showed co-relation with the in-vivo conditions. So a novel dissolution test apparatus with modification of Rossett-Rice test Apparatus was proposed.

IN-VIVO EVALUATION [37]

Radiology

X-ray is widely used for examination of internal body systems. Barium Sulphate is widely used Radio Opaque Marker. So, BaSO4 is incorporated inside dosage form and X-ray images are taken at various intervals to view GR.

Gamma Scintigraphy

This method helps to locate dosage form in the gastrointestinal tract by which we can predict and correlate the gastric emptying time and the passage dosage form in the GIT. The inclusion of radio-opaque material into a solid dosage for m enables it to be visualized by X-rays. Similarly, the inclusion of a γ emitting r radionucleotide in a formulation allows indirect external observation using a γ -camera or scintiscanner. In case of γ -scintigraphy, the γ -rays emitted by the nucleotide are focused on a camera, which helps to monitor the location of the dosage form in the gastrointestinal tract.

Gastroscopy

Gastroscopy is an examination of the inside of the gullet, stomach and duodenum. It is performed by using a thin, flexible fiber-optic instrument that is passed through the mouth Gastroscopy is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS.

Magnetic marker monitoring

It is a method to monitor the passage of an orally applied drug (tablet, capsule, etc.) through the intestinal tract. The dosage form is enriched with a small amount (0.1 – 2 mg) of magnetite (Fe_3O_4), which then is magnetized by a high-energy magnetic field. After application the path of the dosage form can be monitored with special detectors, which contain Superconducting Quantum Interference Devices (SQUIDs). Due to the very low magnetic field of the iron oxide a specially shielded room is necessary in order to eliminate environmental magnetic interference. The method should be able to yield information about why tablets dissolve unequally before or after meals, which may be important for the bioavailability of drugs.

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS[38]

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.

(A)Sustained Drug Delivery: This system 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 <1 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).

(B) 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, eg, 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.

(C) 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. Stomach for 6 hours. It could be concluded that Gelucire 43/01 can be considered as an effective carrier for design of a multi-unit FDDS of highly water-soluble drugs such as diltiazem HCl.

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique. An important feature to take into account is the stomach physiology. The time when the drug is taken (during or apart from the meal) is an important parameter. To develop an efficient gastroretentive dosage form is a real challenge to pharmaceutical technology. Indeed, the drug delivery system must remain for a sufficient time in the stomach, which is not compatible with its normal physiology. All these Gastroretentive drug delivery systems (high density, floating, expandable or unfoldable or swelling, superporous,

bioadhesive, magnetic systems etc.) are interesting and present their own advantages and disadvantages. Now, a lot of work is running to develop different types of gastroretentive delivery systems of various drugs. In the future, it is expected that they will become of increasing importance, ultimately leading to improved efficiencies of various types of pharmacotherapies.

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