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An Overview of Floating Drug Delivery System

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Abstract: *The goal of Floating Drug Delivery Systems (FDDS) is to arrange the current emphasis on the basic flotation mechanism to attain stomach retention time. The most current advancements in FDDS are thoroughly discussed, including the formulation and physiological factors influencing stomach retention, methods for designing floating systems, and the characteristics of their classification and formulation. Since dosage forms stay in the stomach longer than conventional dosage forms, the capacity to extend and control the gastric emptying time is a major asset. Gastric emptying of dosage forms is a highly variable process. Drugs with gastroretentive systems have a much longer residence time in the stomach area, improving bioavailability, decreasing drug waste, and increasing solubility for medications that are less soluble in high pH environments. These benefits are achieved over a period of many hours. This review provides a brief overview of floating medication delivery devices.*

Keywords: Floating Drug Delivery System, Gastroretentive Drug Delivery System, It's Classification, Application

I. INTRODUCTION

Any drug delivery system's objective is to deliver a therapeutic dose of the medication to the right location in the body in order to quickly reach and then sustain the appropriate drug concentration. Viable dose options that can be supplied via several routes of administration have been made possible by recent technological advancements. There are several different ways to provide drugs, such as oral, topical, nasal, rectal, vaginal, and ophthalmic, among others. However, among these methods, oral medication delivery is seen to be the most popular and often utilized method for the following reasons:Low cost, simplicity of production, and ease of administration. Drugs that are absorbed from the stomach or have a localized effect ought to be in the stomach for as long as possible.

However, it is shown that with normal dosage forms, this is extremely unlikely to happen. Oral medication administration is seen to be the most promising method. Only when taken numerous times a day can a conventional drug delivery system achieve and sustain the drug concentration within the therapeutically effective range required for treatment. Recently, innovative drug delivery methods have emerged that have the potential to transform medicine delivery and offer several therapeutic advantages. In an effort to release the medication gradually into the Gastrointestinal Tract (GIT) and sustain an effective drug concentration in the systemic circulation for an extended period of time, oral sustained-controlled release formulations have been developed.

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1.1 Gastrointestinal retention:

Gastro retentive devices can stay in the stomach area for a few hours, greatly extending the amount of time that medications can stay there. Extended stomach retention increases the solubility of medications that are less soluble in high pH environments, decreases drug waste, and increases bioavailability. It can also be used to deliver drugs locally to the stomach and the first few inches of the small intestine. Gastro retention contributes to improved pharmaceutical availability with novel treatment opportunities and significant patient benefits. The anatomical and physiological features of the human Gastrointestinal Tract (GIT) must be well understood in order to successfully modulate the gastrointestinal transit time of a drug delivery system through floating drug delivery systems . This will allow for maximum gastrointestinal absorption of drugs and site-specific delivery. These are described and talked about in brief.

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II. ANATOMY OF STOMACH

2.1 Location : The epigastric, unbilical, and left hypochondriac portions of the abdominal cavity are where the stomach is located.

2.2 Anatomical relation:-

- Anteriorly- The anterior abdominal wall and the left lobe of the liver.
- Posteriorly-Left kidney, pancreas, spleen, and abdominal arota.
- Superiorly - oesophagus, left lobe of liver, and diaphragm.
- Inferiorly - Small intestine and transverse colon on the inferior side.
- To the left - Diaphragm and spleen.
- To the right - Liver and duodenum.

The stomach's ugly traits are:

The stomach is a muscular, hollow organ that is made up of the following sections:

1. Fundus: The portion of the stomach above the heart orifice.
2. Body: The stomach's main portion is called the body.
3. Pyloric part :The stomach's lower region, known as the pyloric portion, is separated into the pyloric antrum and pyloric canal. The stomach has developed inner and outer bends, with less curvature and more curvature, as a result of its left dilation.

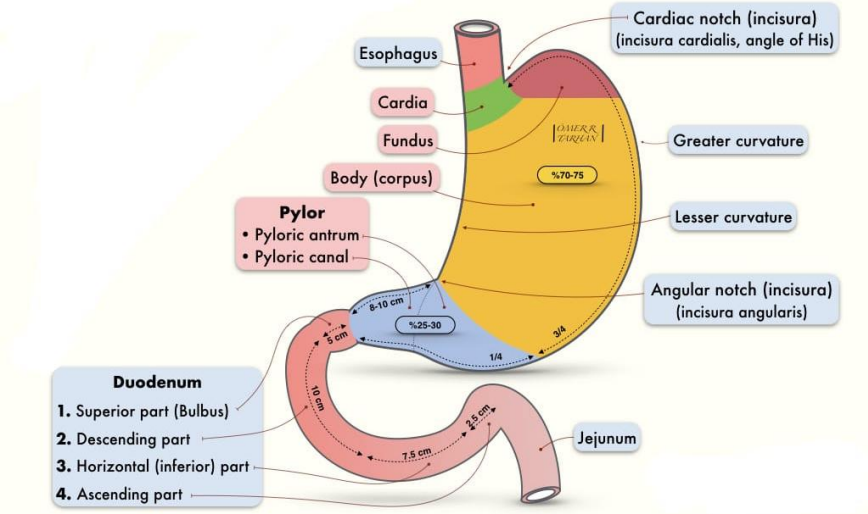

Fig no.01: Anatomy of Stomach

2.3 Structure

1. Similar to how the gastrointestinal tract wall is generally arranged.
2. The pylorus, also known as the pyloric sphincter, is a thicker layer of smooth muscle that divides the stomach and duodenum.
3. The fundus has weak contraction strength because its layers are relatively thin. The strength of contraction is higher in the antrum, where the muscle layers are thicker.
4. The stomach's walls are securely positioned when it is empty. The inner muscle fibers of the stomach extend as food enters, expanding the cavity uniformly to hold the additional contents while maintaining a relatively constant internal pressure.

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2.4 Fundamental Physiology of the Gastrointestinal Tract:

The stomach is composed of three anatomical regions: the fundus, the body, and the antrum (pylorus). The antrum is the primary location for mixing motions and functions as a pump for stomach emptying via thrusting actions, while the proximal portion, composed of the fundus and body, serves as a reservoir for undigested material.

III. PHYSIOLOGY OF STOMACH

The stomach is an enlarged portion of the digestive tract that lies between the small intestine and the oesophagus. With the exception of an additional, oblique layer of smooth muscle inside the circular layer that helps with complex grinding actions, the stomach's wall is physically similar to the other sections of the digestive tube. The stomach contracts when it is empty, causing the mucosa and submucosa to rise into separate folds known as rugae.

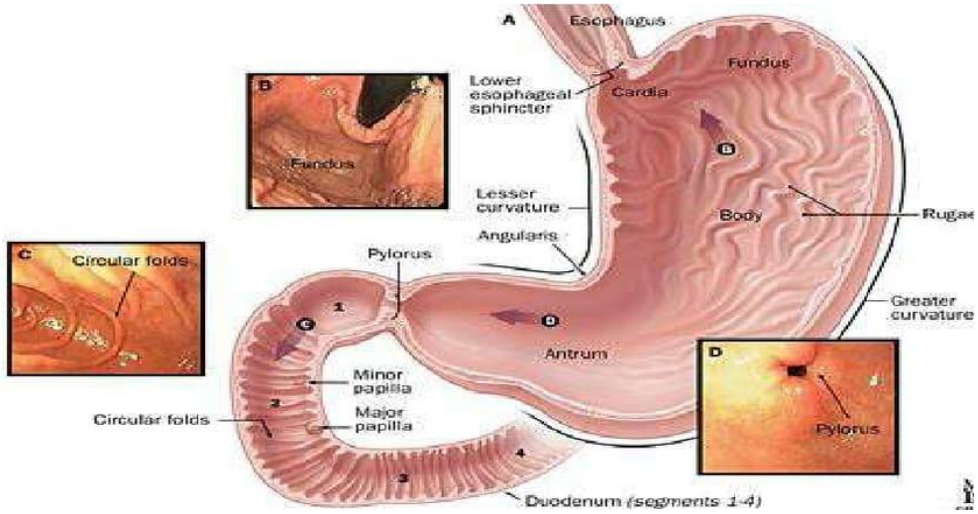

Fig no. 02: Physiology of Stomach

The stomach's surface is covered in secretary epithelial cells, which also extend into gastric pits and glands. There are four main types of these cells:

1. Mucous cells: release an alkaline mucus that shields the epithelium from acid and shear stress.
2. Hydrochloric acid is secreted by parietal cells.
3. Proteolytic enzyme pepsin is secreted by chief cells.
4. G cells: release the gastrin hormone. There are two main reasons why the smooth muscle of the stomach contracts.
5. Chyme is created when food is consumed and is pulverized, combined, and liquefied.
6. Gastric emptying is the process by which chyme is driven into the small intestine through the pyloric canal.

3.1 Gastric motility

A complex network of neuronal and hormonal impulses controls stomach motility. The sympathetic, parasympathetic, and enteric nervous systems—which primarily supply the vagus nerve—are the sources of nervous control. Numerous hormones have been shown to affect stomach motility; for example, cholecystokinin and gastrin both work to relax the proximal stomach and increase contractions in the distal stomach. In summary, the patterns of stomach motility most likely originate from the integration of several inhibitory and stimulatory impulses by smooth muscle cells. While solids must be reduced to a diameter of less than 1-2 mm in order to pass the pyloric gatekeeper, liquids easily pass through the pylorus in spurts. For the dose form to dissolve in vivo, the stomach capacity is crucial. The stomach holds 25 to 50 milliliters at rest. The stomach secretions of those who are achlorhydric and those who are normal differ significantly. The impact of gastric pH on drug absorption via the delivery method is also notable. The stomach's pH ranges from 1.2 to 2.0 when fasting and from 2.0 to 6.0 when eaten.

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3.2 Gastric empty rate

Both when feeding and when fasting, gastric emptying takes place. Nonetheless, the motility patterns in the two states differ. Every two to three hours, an interdigestive sequence of electrical events occurs in the stomach and intestine during the fasting state. This is known as the interdigestive myloelectric cycle, or migrating myloelectric cycle (MMC), and Wilson and Washington have further divided it into the following 4 phases.

The 40–60 minute Phase I (Basal phase) is punctuated by sporadic contractions.

The 40–60 minute Preburst Phase II is characterized by sporadic contractions and action potentials. Both the intensity and frequency steadily rise as the phase goes on.

Three to six minutes make up Phase III, or the blast phase. It consists of brief, strong contractions that occur frequently. All of the undigested material is carried out of the stomach and into the small intestine by means of this wave. Another name for it is the housekeeping wave.

Phase IV, which happens in between phases III and I of two consecutive cycles, lasts from 0 to 5 minutes.

The contraction pattern shifts from the fasted to the fed condition following the consumption of a mixed meal. This pattern, sometimes referred to as the digestive motility pattern, consists of ongoing contractions similar to those seen in Phase II of a fast. Food particles are forced toward the pylorus in a suspension form as a result of these contractions, which cause them to shrink to less than 1 mm in size. The delayed start of MMC during the fed state causes the pace of stomach emptying to slow down. Orally administered controlled release dosage forms are essentially subject to two complications: short gastrointestinal residence duration and unpredictable gastric emptying rate, as shown by scintigraphic investigations determining gastric emptying rates.

IV. FLOATING DRUG DELIVERY SYSTEM

Hydrodynamically controlled systems, also known as Floating Drug Delivery Systems (FDDS), are low-density systems with enough buoyancy to float above the contents of the stomach and stay afloat there for an extended amount of time without slowing down the rate of stomach emptying. The medication is gradually removed from the system at the desired rate while it is floating on the contents of the stomach. The stomach is cleared of any leftover medication after the substance has been released. As a result, the oscillations in plasma drug concentration are better controlled and the gastric retention period is extended.

4.1 Classification of Floating Drug Delivery System:

1. Effervescent system:
   a. Gas generating system
   b. Volatile liquid containing system
2. Non-effervescent System:
   a. Colloidal gel barrier system.
   b. Alginate beds.
   c. Hollow microspheres / Microballons.
   d. Intragastric Floating Drug Delivery Device / Microporous compartment system.

A. Effervescent Systems:

These are matrix-type systems made with the use of effervescent substances like sodium bicarbonate, tartaric acid, and citric acid as well as swellable polymers like methylcellulose and chitosan. They are designed in a way that releases carbon dioxide when it comes into contact with the acidic contents of the stomach and traps gas inside swelling hydrocolloids, giving the dosage forms buoyancy.

Volatile liquid containing systems:

By using an inflatable chamber that is filled with a liquid (such as ether or cyclopentane) that gasifies at body temperature and causes the chamber to inflate in the stomach, a medication delivery system's GRT can be maintained. In order to enable the spontaneous ejection of the inflatable systems from the stomach, the device may also include a

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bio-erodible plug composed of PVA, Polyethylene, etc. that progressively dissolves and causes the inflated chamber to release gas and collapse after a predetermined amount of time.

Gas-generating Systems:

In these buoyant delivery systems, carbonate/bicarbonate salts and citric/tartaric acid undergo effervescent reactions that release CO2, which becomes trapped in the systems' gellified hydrocolloid layer, lowering its specific gravity and causing it to float over chyme. Figure 4 depicts the dose form float in its entirety.

B. Non-effervescent systems

Hydrocolloids of the gel-forming or swellable cellulose type, polysaccharides, and matrix-forming polymers such as polycarbonate, polyacrylate, polymethacrylate, and polystyrene are used in non-effervescent floating dosage forms. The medicine and the hydrocolloid that forms gel are fully mixed as part of the straightforward formulation process. This dosage form swells in contact with gastric juices after oral administration, reaching a bulk density of less than 1. The dose form is buoyant due to the trapped air within the inflated matrix. Through the gelatinous mass, the so-formed swelling gel-like structure serves as a reservoir and permits sustained drug release.

Colloidal gel barrier systems:

Sheth and Tossounian designed the Hydrodymmatic Balance System (HBSTM) for the first time in 1975.These methods include medication that gels hydrocolloids to stay afloat on stomach contents. This system contains a high concentration of one or more matrix-forming polymers, such as polycarbophil, polyacrylates, and polystyrene, as well as gel-forming, highly swellable cellulose type hydrocolloids, such as HEC, HPMC, NaCMC, and polysacchacarides, either in the form of tablets or capsules. The hydrocolloid in the system hydrates when it comes into touch with gastric fluid, forming a colloidal gel barrier surrounding the gel surface. These dose forms are buoyant because of the air retained by the inflated polymer, which retains a density less than unity.

Alginate beads:

Freeze-dried calcium alginate has been used to create multi-unit floating dosage forms. By dropping sodium alginate solution into an aqueous solution of calcium chloride, calcium alginate will precipitate, forming spherical beads with a diameter of around 2.5 mm. Following their separation, the beads are snap-frozen in liquid nitrogen and freeze-dried for 24 hours at -40ºC. This process creates a porous structure that can sustain a floating force for more than 12 hours.

Hollow microspheres :

Using a unique emulsion-solvent diffusion process, hollow microspheres, or microballons, were produced and then loaded with ibuprofen within their outer polymer shells. An agitated aqueous solution of PVA that was thermally regulated at 40°C was filled with the drug's ethanol: dichloromethane solution along with an enteric acrylic polymer. The gas phase that forms in the internal cavity of polymer microspheres containing drugs is produced in scattered polymer droplets through the evaporation of dichloromethane. For more than 12 hours in vitro, the microballons floated constantly on the surface of surfactant-containing acidic dissolving media

Intragastric / Microporous compartment system:

The device is made up of a drug reservoir housed inside a microporous chamber with pores on both the top and bottom surfaces. To avoid any potential physical contact between the undissolved medication and the stomach walls, the reservoir compartment's periphery walls were tightly sealed. A novel levodopa gastro-retentive dosage form with enlarged dimensions and great stiffness is based on unfolding polymeric membranes. The gelatin was folded into big capsules. Within 15 minutes of injection, according to in vitro research, the unfolded state was reached, and this was verified in vivo in beagle dogs. At least two hours were spent maintaining the unfolded form. It was determined that this dose form might enhance the treatment of many medications with narrow absorption windows. Nevertheless, there is a chance that the polymeric films will become lodged in the esophagus, resulting in severe discomfort for the patient or medication-related complications, and prolonged use of the stiff dose form could cause stomach blockage.

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4.2 Factors affecting FDDS:

- Density: dose form buoyancy, which determines GRT, depends on density.
- Size: Compared to dosage form units with a 9.9 mm diameter, those with a diameter of greater than 7.5 mm are reported to increase GRT.
- Shape: When compared to other designs, tetrahedron and ring-shaped devices with flexural moduli of 48 and 22.5 kilo pounds per square inch are said to provide superior GRT and 90%–100% retention at 24 hours.
- Single or multiple unit formulations: Compared to single unit dosage forms, multiple unit formulations allow for a larger margin of safety in the event of a dosage form failure, exhibit more predictable release profiles, and show negligible performance impairment due to unit failures. They also enable co-administration of units with different release profiles or containing incompatible substances.
- Fed or fasted state: When fasting, the GI motility is characterized by bursts of intense motor activity, or the 1.5–2 hour migration of the myoelectric complex (MMC). The MMC removes undigested material from the stomach, and if the formulation is administered at the same time as the MMC, the unit's GRT should be extremely brief. GRT is noticeably longer in the fed state and MMC is delayed.
- Meal type: Eating indigestible polymers or fatty acid salts might cause the stomach to go into a fed state, slowing down the rate at which food is cleared from the stomach and extending the duration of medication release.
- Caloric content: Eating a meal strong in lipids and proteins can raise GRT by 4 to 10 hours.
- Feeding frequency: Because MMC occurs infrequently, the GRT can rise by more than 400 minutes when multiple meals are provided as opposed to a single meal.
- Gender: Regardless of weight, height, or body surface area, the mean ambulatory GRT in males (3.4 ± 0.6 h) is lower than that in females of the same age and race (4.6 ± 1.2 h).
- Age: The GRT is noticeably longer in the elderly, particularly in those over 70. Posture: In supine and upright ambulatory patient states, GRT can differ.
- Concomitant drug administration: The FDDS is impacted by prokinetic drugs like metoclopramide and cisapride, opiates like codeine, and anticholinergics like atropine and propantheline.
- Biological factors: FDDS is also impacted by diabetes and Crohn's illness.

4.3 Evaluation of floating drug delivery system

- Tablet shape: Under a magnifying glass, compressed tablets intended for FDDS are inspected to ascertain their uniform shape.
- Tablet dimensions: In accordance with official compendia, a calibrated Vernier calliper is used to measure the thickness and diameter of tablets in FDDS form, just like for normal tablets. Each formulation's three tablets are chosen at random, and each tablet's thickness is measured separately.
- Measuring tablet hardness: Using a Monsanto-style hardness tester, a random sample of twenty tablets from each batch of formulations should be utilized to determine tablet hardness.
- Weight variation determination: A total of twenty tablets chosen at random are precisely weighed, and the average weight of each tablet is computed. Next, the weight difference between each individual and the average is computed.
- Tablet thickness measurement: For every batch, slide calipers are used to measure the individual crown to crown thickness of 10 tablets.
- Measurement of floating capacity: To measure floating capacity, three separate tablets are added to a single flask that holds 400 milliliters of 0.1(N) HCL solutions. Next, the length of floating (the amount of time that tablets remain on the water's surface) and the floating lag time (the amount of time it takes for each tablet to get from the bottom to the top of the flask in minutes) are calculated. After that, the sample mean and standard deviation are determined.

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- Determining the formulation's density: Three times the volume and mass of each tablet are used to get the tablet's apparent density. Using the formula for a cylinder (V = A × r2 × h), the volume V of the cylindrical tablets is computed from their height h and radius r (both measured with a micrometer gauge).
- Determination of drug content in tablets:Ten tablets are randomly chosen from each batch and placed in a 100 ml volumetric flask that has been loaded with 0.1(N) HCL. After two hours of stirring and waiting, remove one milliliter (ml) from the volumetric flask and place it in the test tube. After that, samples are filtered, appropriately diluted, and spectrophotometrically examined at an appropriate wavelength.
- In vitro dissolution study: The tablet was inserted into the dissolving vessel for the in vitro dissolution research. Samples (5 ml) are taken out every 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, and 12 hours, or more frequently as needed. After each sample, 5 ml of new dissolution medium was added, bringing the total volume of the dissolving fluid to 900 ml. The mean values are plotted against time in the release studies, which were carried out with "n" tablets. Using a UV visible spectrophotometer set to the maximum wavelength for each sample and a reagent blank, the corresponding concentration of each sample is calculated using the associated calibration curve.
- Buoyancy/Floating test: The dosage form's buoyancy on the simulated gastric fluid is introduced, and the dosage form's buoyancy is measured for the duration of that period. Total floating time (TFT) is the amount of time that the dosage form remains buoyant after emerging on the surface of a medium; this is also known as floating lag time (FLT) or buoyancy lag time (BLT).
- Swelling study:Weight increase or water absorption are used to gauge a dose form's swelling behavior. The growth in tablet thickness or diameter over time could be used to quantify the dimensional changes. The following formula can be used to calculate the percentage of weight increase associated with water uptake.

  $$WU = (Wt - Wo)x100$$

  Where,
  WU = Water uptake
  Wt = Weight of dosage form at time t.
  Wo = Initial weight of dosage form [35].

4.4 Mechanism of floating systems:

In an effort to lengthen the retention period, several strategies have been tried, including keeping the dosage form in the stomach. Floating dosage forms (gas-generating and swelling/expanding systems), mucoadhesive systems, high-density systems, specially shaped systems, gastric-emptying delaying devices, and co-administration of gastric-emptying delaying medications are some of the initiatives made in this regard. The floating dosage forms are the most widely utilized of these. Because floating drug delivery systems have a lower bulk density than gastric fluids, they float in the stomach for extended periods of time without slowing down the rate at which the stomach empties.

The drug is removed from the system gradually at the correct rate while it is floating on the stomach contents. The drug's residual system is removed from the stomach following its release. As a result, the variations in plasma drug concentration are better controlled and the GRT is raised. To sustain the buoyancy of the dosage form on the meal's surface, however, a minimum level of floating force (F) is also necessary in addition to the minimal stomach content necessary to permit the correct achievement of the buoyancy retention effect. A unique apparatus for determining the resultant weight has been disclosed in the literature in order to measure the kinetics of the floating force.

The device works by continually measuring the force (as a function of time) equal to F needed to keep an object submerged.

If F is on the upper positive side, the object will float more easily. This device aids in FDDS optimization in terms of sustainability and stability of floating forces generated to avoid any unforeseen fluctuations in intragastric buoyancy.

$$F = Fbuoyancy - Fgravity = (Df - Ds)\, g\, v$$

Where, F= total vertical force,
Df = fluid density,
Ds = object density,
v = volume and

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g = acceleration due to gravity.

FDDS can be divided into two categories according to the buoyancy mechanism:

(A) Single unit floating dosage systems;

(B) Multiple unit floating dosage systems;

(C)Raft forming systems.

Single unit floating dosage systems

Effervescent systems (gas-generating systems):

Utilizing matrices made of swellable polymers (HPMC), polysaccharides (chitosan), effervescent substances (sodium bicarbonate, citric acid, and tartaric acid), or chambers holding a liquid that turns into a gas at body temperature, these buoyant systems function. It is reported that a stoichiometric ratio of 0.76:1 between citric acid and sodium bicarbonate is ideal for gas production. These systems are typically prepared using resin beads coated with ethylcellulose and loaded with bicarbonate. Water is possible to permeate the insoluble but porous covering. The beads float in the stomach as a result of the emission of carbon dioxide.

Additional methods and materials that have been reported include highly swellable hydrocolloids and light mineral oils, a combination of sodium bicarbonate and alginate, multiple unit floating pills that release carbon dioxide upon ingestion, lactose and polyvinyl pyrrolidone coated with HPMC, floating minicapsules with a sodium bicarbonate core, and floating systems based on ion exchange resin technology. The most often utilized excipients in these systems are polycarbonates, agar, sodium alginate, polyethylene oxide, Carbopol®, polyacrylate polymers, polyvinyl acetate, and HPMC.Ozdemir et al. produced floating bilayer pills to provide furosemide with a regulated release. By employing the kneading process and creating a solid dispersion with β cyclodextrin combined in a 1:1 ratio, the drug's low solubility may be improved. The medicine plus the polymers HPMC4000, HPMC100, and CMC (for drug delivery control) were incorporated in one layer. The effervescent concoction of citric acid and sodium bicarbonate was present in the second layer. Six healthy male volunteers underwent radiographic examinations, which revealed that floating tablets were left in the stomach for six hours. Additional blood analysis.

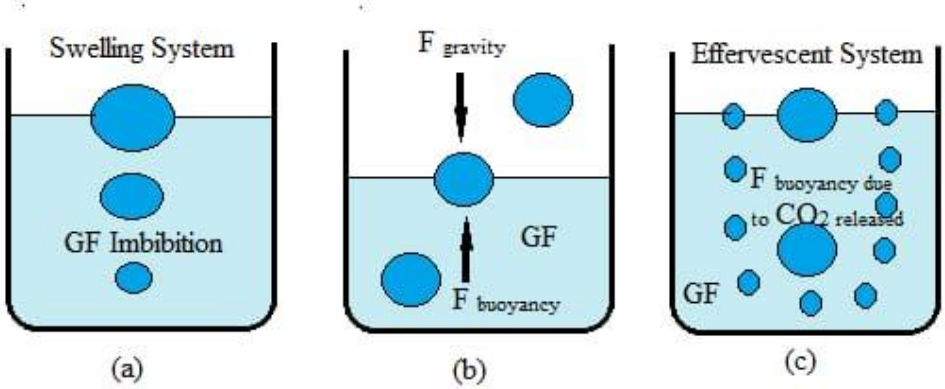

Fig no.03: Mechanism of floating systems.

According to research, these pills had a bioavailability that was 1.8 times higher than that of regular tablets. The peak diuretic effect observed with conventional tablets was both prolonged and lowered when the volume of urine passed was measured in the case of the floating dose form. An expandable tablet made by Penners et al. was made up of a combination of polyvinyl lactams and polyacrylates that expanded quickly in an aqueous environment and stayed in the stomach for a long time. Furthermore, gas-forming chemicals were added such that the system's density decreased as soon as gas was formed, causing the system to tend to float on the contents of the stomach.

A once-daily formulation of ciprofloxacin was produced by Talwar et al. 69.9% ciprofloxacin base, 12.1% cross-linked polyvinyl pyrrolidine, 0.34% sodium alginate, 1.03% xanthum gum, and 13.7% sodium bicarbonate made up the formulation. The pill floated and remained in the stomach because the cross-linked PVP and the gel-forming polymers eventually created a hydrated gel matrix that trapped the gas. The medication was able to diffuse into the hydrated gel matrix, causing a prolonged release of the drug. Baumgartner et al.'s matrix-floating tablet included a large amount of

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medication that was readily soluble. The formulation that yielded the best outcomes included 54.7% medication, HPMC K4 M, Avicel PH 101, and a gas-generating agent. It took thirty seconds for it to float. A longer stomach residence duration was seen in beagle dog in vivo trials when they were fasting. Since there were no discernible differences between humans and dogs in terms of stomach emptying or gastric motility, it seemed possible to compare the experimentally demonstrated longer gastric residence time in beagle dogs to the less than two-hour value reported in the literature for humans.

Non-effervescent systems:

This kind of technology stops the stomach from emptying because it expands uncontrollably after ingesting gastric juice. Since these systems tend to stay positioned close to the pyloric sphincter, they may be referred to as "plug-type systems." One way to formulate these dosage forms is to combine the medication with a gel, which, upon oral administration, swells in contact with gastric fluid and retains a relative shape integrity and bulk density of less than one inside the outer gelatinous barrier. These dose forms become buoyant due to the air retained by the inflated polymer. A colloidal gel barrier, a microporous compartment system, alginate beads, and hollow microspheres are a few instances of this kind of FDDS.A fluid-filled floating chamber is an additional form that has been described. It involves the integration of a gas-filled flotation chamber into a microporous component that contains a drug reservoir. The top and bottom walls have apertures or openings that allow digestive juices to enter and dissolve the medication. To ensure that the medicine remains undissolved, the other two walls that come into contact with the liquid are sealed. Air, a partially vacuum, or any other acceptable gas, liquid, or solid with a suitable specific gravity and inert behavior could be the fluid that is present. It is small enough to be ingested, floats in the stomach for a considerable amount of time, and then the shell breaks down, moves into the intestine, and is eventually expelled.

A 3-layer matrix is used in a more recent self-correcting floatable asymmetric configuration drug delivery devic to regulate the release of the medicament. The invention of an asymmetric configuration drug delivery system has improved the 3-layer principle by enabling zero-order release kinetics and modulating the degree of release by initially keeping a constant area at the

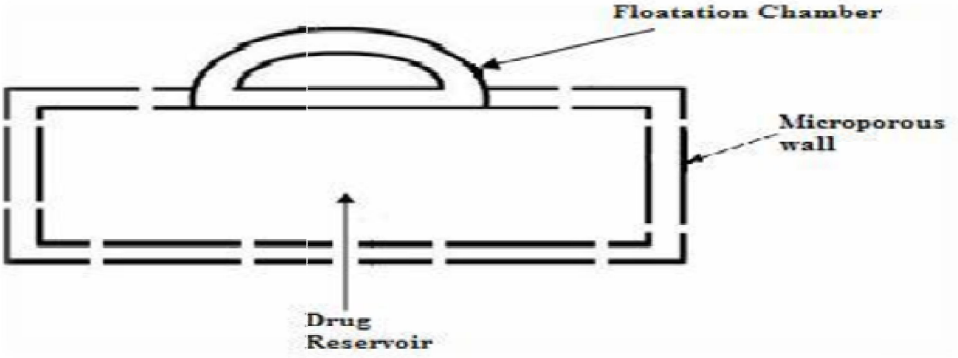

Fig no.04: Gas filled floatation chamber

diffusing front, followed by a dissolution or erosion when the releasing process comes to an end. This system's flotation was intended to extend the in vivo gastric residence time, which in turn produced a longer total transit time with a maximal absorptive capacity and, as a result, increased bioavailability within the gastrointestinal tract. This specific property would apply to medications that are absorbed by active transport from either the proximal or distal section of the small intestine, have a narrow window of absorption, and are pH-dependently soluble.

Using HPMC and poly(ethylene oxide) (PEO) as the rate-controlling polymeric membrane excipients, Yang et al. created a swellable asymmetric triple-layer tablet with floating ability to extend the gastric residence time of a triple drug regimen (tetracycline, metronidazole, and clarithromycin) for the treatment of Helicobacter pylori-associated peptic ulcers. The swellable asymmetric triple-layer tablet technique served as the foundation for the delivery system's architecture. The two main polymeric excipients that controlled the rate were HPMC and polyethylene oxide).

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Bismuth salt was added to one of the outer layers of the triple-layer matrix for immediate release, while tetracycline and metronidazole were added to the core layer for controlled delivery. Using swelleble polymers, a gas-generating layer made of calcium and sodium bicarbonate was incorporated to achieve flotation. This dose form gave continuous distribution of metronidazole and tetracycline for more than 6–8 hours; at the end of this time, it was still floating. Single-unit floating tablets were made by Streubel et al. using a matrix-forming polymer and Accurel MP 1000® polypropylene foam powder.

The density of the matrix tablets was significantly lower than that of the releasing media due to the very porous foam powder therein. The foam powder and matrix-forming polymer ratios might be changed to change the medication release patterns as needed. Hydrodynamically balanced sustained release tablets with drug and hydrophilic hydrocolloids were developed by Sheth and Tossounian. When the tablet surface came into contact with gastric fluids at body temperature, the hydrophilic hydrocolloids formed a soft, gelatinous mass that prevented water from penetrating the surface and created a water-impermeable colloid gel barrier.The gelatinous ball stayed afloat on the gastrointestinal juice, releasing the medication gradually from its surface. Using HPMC and PEG6000, Wu et al. made floating sustained release nimodipine tablets. Nimodipine was first dissolved into a poloxamer-188 solid dispersion and then squeezed straight into the floating tablet formulation itself.

It was discovered that nimodipine's in-vitro release decreased when the HPMC and PEG 6000 content were increased and decreased, respectively. Nur and Zhang [37] used HPMC (4000 and 15000 cps) and carbopol 934P to make floating pills of captopril. They arrived to the conclusion that the hydrocolloid particles' surface swelling upon contact with the gastric fluids and the porosity—the existence of interior spaces in the middle of the tablets—were the two factors controlling the tablets' buoyancy.When compared to conventional tablets, a longer release from these floating tablets was noted, and a regulated release of captopril from the dose form was accomplished within 24 hours. Single-unit formulations have been linked to issues including adhesion or gastrointestinal tract blockage, which can cause irritation locally. The "all or none" problem is these systems' primary flaw. When housekeeper waves are generated, there is a risk that the dose form will enter the intestines in these situations. To solve this issue, several unit dose forms have been developed.

Multiple unit floating systems

Despite much research and development being done on HBS and other floating tablet systems, these all-or-nothing gastric emptying systems have a significant drawback: substantial variability of the gastrointestinal transit time when taken orally. Multiple unit floating systems were created as a solution to this problem, lowering the likelihood of dose-dumping and the inter-subject variability in absorption. The creation of various unit systems that are both effervescent and non-effervescent has been documented in reports [38]. This has received a lot of attention from researchers, who are still delving into the topic of hollow microspheres with enhanced gastric retention qualities and the ability to float on stomach fluid.

Non-effervescent systems:

Compared to effervescent systems, there are very few accounts in the literature on noneffervescent multiple unit systems. Nonetheless, some researchers have noted that chitosan might be used as the polymeric excipient in the development of such a system that contains indomethacin. A report describes the creation of a multiple unit HBS containing indomethacin as a model drug using extrusion. Through the use of a needle, a drug, chitosan, and acetic acid mixture are extruded; the extrudate is then chopped and dried. In acidic environments, chitosan hydrates and floats, and by changing the drug-polymer ratio, the necessary drug release might be achieved.

Effervescent systems (gas-generating systems):

Tetracycline hydrochloride-containing sustained release floating granules were reported by Ikura et al. Drug granulates from stages A and B are combined to create the granules; stage A comprises 60 parts HPMC, 40 parts polyacrylic acid, and 20 parts drug, while stage B contains 70 parts sodium bicarbonate and 30 parts tartaric acid. Stage A granules made up of sixty parts by weight and stage B granules made up of thirty parts by weight are combined with a lubricant and put into capsules. The granules have a sustained drug release of 80% in roughly 6.5 hours and a floating duration of

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more than 8 hours when the capsule shell dissolves and releases the contents into dissolution fluid.Umezawa [41] has described floating minicapsules of pepstatin with a diameter of 0.1–0.2 mm. These minicapsules are composed of a covering and a core. Granules made of lactose, sodium bicarbonate, and a binder coated in HPMC make up the center core. The top layer of the HPMC is covered with pepstatin. The gastric fluid's release of CO2 and the prolonged presence of pepstatin in the stomach are what keep the system afloat. Alginates have drawn a lot of interest in the creation of several unit systems.

Alginates are linear copolymers made of L-mannuronic and L-glucuronic acid residues that are biodegradable and non-toxic. A calcium alginate core and a calcium alginate/PVA membrane are the two components of a multiple unit system that Iannuccelli et al. constructed. They are divided by an air compartment. The PVA leaks out and increases the permeability of the membrane when there is water present, preserving the integrity of the air compartment. Enhancement of the floating qualities of the system was achieved by increasing the molecular weight and concentration of PVA. It has also been reported that floating calcium alginate beads can be prepared by freeze-drying.

The addition of sodium alginate solution drop-wise to an aqueous solution of calcium chloride results in the immediate gelation of the droplet surface because calcium alginate is formed. After being freeze-dried, the resulting beads have a porous structure that helps them float. Using gamma scintigraphy, the researchers examined the behavior of radiolabeled floating beads in human volunteers and contrasted them with nonfloating beads. For floating beads, a longer stomach residence time of over 5.5 hours was noted. The nonfloating beads had a mean onset emptying time of one hour, which was a shorter residence time.

Ichikawa et al. created a novel variety of floating dosage systems with a pill at its center that is made up of layers of swellable membrane and effervescent layer coated on sustained release pills. To prevent direct contact between the two agents, the sodium bicarbonate and tartaric acid-containing effervescent agents' inner layer was split into two sublayers. A swellable polymer membrane made of pure shellac and polyvinyl acetate encircled these sublayers. This system settled when submerged in buffer at 37˚C, allowing the solution to pass through the outer swellable membrane and into the effervescent layer. Then, as a result of the two effervescent agents' neutralizing interaction, CO2 was produced, resulting in enlarged pills that resembled balloons and had a density of less than 1.0 g/ml.

Hollow microspheres:

Because of the center hollow region inside the microsphere, hollow microspheres are thought to be among the most promising buoyant systems , offering the special benefits of multiple unit systems along with improved floating qualities. Simple solvent evaporation as well as solvent diffusion and evaporation are the general methods used in their preparation. The kind of polymer, plasticizer, and solvents used in the preparation process all have a major impact on the drug release and improved floating qualities. Hollow microspheres are made from polymers such polycarbonate, Eudragit® S, and cellulose acetate. The volume of polymer and the ratio of polymer to plasticizer can be adjusted to alter the drug release. Thanoo et al. created sustained release floating microspheres with polycarbonate and the solvent evaporation process. Aspirin, griseofulvin, and p-nitroaniline were utilized as model pharmaceuticals.

The dispersion medium comprising sodium chloride, polyvinyl alcohol, and methanol was supplemented with a dispersed phase that contained a polycarbonate solution in dichloromethane and micronized drug. To guarantee full solvent evaporation, the dispersion was agitated for three to four hours. The resulting microspheres were then filtered, cleaned with cold water, and dried. Scanning electron microscopy analysis verified the microspheres' spherical and hollow structure. More than half of the drug was present in the microspheres, and the amount of drug integrated was found to affect both the drug release and particle size distribution. Because of the higher viscosity of the dispersed phase, a greater fraction of larger particles was seen with high drug loading. A unique emulsion solvent diffusion approach was used to manufacture hollow microspheres, also known as microballoons, with medication contained in their outer polymer shells, as reported by Kawashima et al. The aqueous phase containing polyvinyl alcohol (0.75%, w/v) is supplemented with a medicine and enteric acrylic polymer (Eudragit® S) solution in a mixture of ethanol and dichloromethane, and continuously swirled to form an o/w emulsion. After filtering, a water wash, and drying, the microspheres are produced.

Due to Eudragit® S's insoluble nature in dichloromethane, the diffusion and evaporation profiles of ethanol and dichloromethane indicated a quick diffusion of ethanol from the droplets into the aqueous phase, which may have

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decreased the polymer solubility in the droplets. As a result, the polymer precipitates quickly at the droplet surface, encasing the drug and dichloromethane in a film-like shell. The microspheres exhibited acceptable packing and flow characteristics, and when an acidic solution containing surfactant was present, a floating time of more than 12 hours was achieved.Lee et al. created hollow microspheres by modifying a process and employing model pharmaceuticals such as cyclosporin A, propranolol hydrochloride, tacrine hydrochloride, and theophylline. The preparation process comprised continuously swirling an aqueous solution of polyvinyl alcohol while adding a solution containing the medicament and polymer. Filtration was used to gather the microspheres, which were then dried at 50˚C for 12 hours. The influence of isopropanol and ethanol on microsphere formation was examined by the authors.

The ethanol-prepared microspheres produced a thin coating on the dispersion's surface, which might be the result of ethanol diffusing quickly into the aqueous phase, which solidified the polymer into aggregates that resembled fibers. Because isopropanol diffuses into the aqueous phase more slowly than ethanol does, adding it to the mixture increased the yield of microspheres. Even with a reasonable yield (74%–96%) of microspheres produced at a 5:10 volume ratio between dichloromethane and ethanol, the spheres' uneven shapes and wide size distribution were noticeable. Regarding the quantity and size distribution of microspheres, an ethanol to isopropanol ratio of 8:2 produced satisfactory results. Soppimath et al. used a unique solvent diffusion-evaporation approach to manufacture hollow microspheres of cellulose acetate carrying cardiovascular medicines. The aqueous phase containing polyvinyl alcohol was prepared by adding the polymer and drug solution in ethyl acetate and an acetone combination, then stirring at 500 r/min for 24 hours.

After that, the microspheres were dried and recovered via decantation. Because the organic solvents are soluble, they permeate into the aqueous phase, which causes the interfacial polymer deposition to be induced and hollow microspheres to develop. Since the physical condition of the drug affects the drug release kinetics, tests using scanning electron microscopy revealed the hollowness and lack of drug crystals on the surface of the microspheres, suggesting uniform drug distribution. Good flow qualities (angle of repose 20˚–28˚), a floating period of more than 12 hours under stirred circumstances, and a controlled drug release lasting more than 15 hours were demonstrated by the microspheres. A floating piroxicam dosage form based on hollow polycarbonate microspheres was created by Joseph et al. Through the process of solvent evaporation, the microspheres were created.

A about 95% encapsulation efficiency was attained. Male albino rabbits in good condition were used for in vivo research. The bioavailability of piroxicam microspheres alone was 1.4 times that of the free drug and 4.8 times that of a dosage form that included microspheres plus the loading dose, according to a pharmacokinetic analysis based on a plasma concentration vs. time plot. The sustained delivery of the drug was achieved over an extended period of time.

Fig.（A） Different layers: i) Semi-permeable membrane, ii) Effervescent layer , iii) Core pill layer. (B) Mechanism of floatation via CO2 generation.

Raft forming systems

Raft forming systems have drawn a lot of interest in the administration of medications for gastrointestinal infections and other conditions, as well as antacids. The mechanism underlying the creation of the raft involves the formation of a cohesive gel that is viscous when it comes into contact with stomach fluids. Each part of the liquid expands to form a continuous layer known as a raft. Because CO2 production results in a low bulk density, this raft floats on gastric fluid. In order to make the system less dense and more able to float on the gastric secretions, the system typically consists of an alkaline bicarbonate or carbonate and a gel-forming chemical that causes CO2 to form. Jorgen et al. described a floating mechanism that forms antacid rafts. This contained sodium bicarbonate, an acidic neutralizer, and a gel-forming ingredient (such as alginic acid) that, when in contact with stomach fluid, formed a foamy sodium alginate gel (raft). By functioning as a barrier between the stomach and the esophagus, the raft that had developed in this manner floated on the gastric fluid and stopped the reflux of the gastric contents, or gastric acid, into the esophagus.

Helicobacter pylori (H. Pylori) infections in the gastrointestinal tract can be treated using a raft-forming composition, according to a patent granted to Reckitt and Colman Products Ltd. The mixture included mannitol, sodium bicarbonate, calcium carbonate, alginic acid, and sweetener. These components were ground into granules and then mixed with citric acid. The raft formed and floated because of the formulation's effervescence and aeration.

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4.5 Methods of Developing Floating Drug Delivery Systems:

- **Direct compression technique-**It involves compressing tablets straight from powder without modifying the substance's physical composition. Tricalcium phosphate, dicalcium trihydrate phosphate, and other carriers are the most prevalent ones.
- **Wet granulation technique-**This method involves grinding, drying, and massaging wet powder. Wet granulation creates the particles by binding them together with an adhesive, as opposed to compacting them.
- **Effervescent Technique-**An effervescent reaction between organic acid (citric acid) and bicarbonate salts (CO2) will fill the floating chamber of the drug delivery system with inert gas.
- **Ionotropic Gelation Technique-**In order to produce instantaneous microparticles, the fundamental polymer of natural origin, anionic polysaccharide sodium alginate, was gelled with oppositely charged calcium ions (counter-ions).
- **The method of solvent evaporation:** It is not possible for a continuous phase to eliminate all of the liquid dispersal solvent. Soluble solvent evaporates from the dispersal surface to produce cemented microspheres.
- **Spray drying technique:** This method involves quickly evaporating the coating material to harden the coating by dispersing the core layer into the liquid coating content and spraying the core coating mixture into the environment.
- **Melt solidification technique:** This process involves cooling and hardening the molten mass after emulsifying it in an aqueous phase. This method uses lipids, waxes, polyethylene glycol, and other substances as carriers.
- **Melt Granulation Technique:** This granulation method agglomerates pharmaceutical powders without the use of organic solvents or water by using a meltable binder.

Table 1: Commercially available floating Formulations.

Name of the product	Active Ingredient	Category	Name of the company
Almagate flowcoat	Al-Mgantacid	Antacid	Ranbaxy, India
Liquid Gaviscon	Al hydroxide (95 mg). Mgcarbonate(358mg)	Antacid (in refluxesophagitis)	Glaxo Smithkline, India
Cytotec Bilayercapsule	Misoprostol(100 mcg/200mcg)		Pharmacia, USA

4.6 Advantages of floating drug delivery system :

Drug delivery systems with stomach retentive behavior, or floating dosage systems, have many benefits. Among these are a few of these:

- A straightforward and traditional formulation method.
- Delivery of drugs to particular sites.
- Medication delivery under control.
- Administration of medication for lingering effects at a particular stomach location.
- Increased GRT and prolonged dosing regimen interaction at the intended location result in better medication absorption.
- Reducing the amount that medications with a slow release rate irritate the GIT mucosa. Aspirin and other acidic pharmacological compounds irritate the stomach mucosa when they come into touch with them. Therefore, HBS formulation might be advantageous while administering aspirin and other such medications. When tablets or capsules with prolonged release floating dosage forms are administered, the medication dissolves in the stomach juice. Before being absorbed in the small intestine with the emptying of the stomach, they disintegrate in the gastric fluid. Therefore, it is anticipated that a medication in floating dosage forms will be completely absorbed if it stays in solution form even at the intestinal pH of alkaline.
- Poor absorption is expected since a certain type of diarrhea may arise from a forceful bowel movement with a short transit time. For optimal efficacy in such circumstances, it is beneficial to keep the medication floating in the stomach.
- In the management of GERD, or gastroesophageal reflux disease.

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- Simple administration that encourages better patient compliance.

Additionally, the floating medication delivery device has several drawbacks that restrict its use.

4.7 Disadvantages of floating drug delivery system:

- The main drawback of a floating system is that it requires an adequate amount of stomach contents to float without the aid of a sink. This restriction can be addressed, though, by covering the dose form in bioadhesive polymers, which stick to the stomach mucosa with ease.
- The majority of desirable candidates are those medications that have significant first-pass metabolism and are greatly absorbed throughout the gastrointestinal tract.
- The stomach mucosal linings may get irritated by certain medications found in the floating system.
- The rate at which the stomach of floating systems empties varies greatly depending on their dimensions. As a result, patients shouldn't take their medication before bed.

4.8 Pharmacokinetic aspects of FDDS

Enhanced bioavailability:

The increase in bioavailability of some medications with a limited therapeutic window that are only caused by poor GI absorption owing to multiple variables leading to decreased bioavailability has been expertly explored by FDDS. Among the medications that were thought to have a limited window of absorption, FDDS shown the potential for improved chemical bioavailability to the required site. Control release (CR) floating systems of levodopa and riboflavin have far higher bioavailability when compared to when the traditional formulation is administered. However, CR polymeric forms of several bisphosphonates—among them, alendronate—absorb straight from the stomach. Even in the event that rats' longer stomach retention of the bisphosphonate is achieved through experimental or surgical procedures, the amplitude of this route is still minimal. One may draw the conclusion that a number of concurrent processes pertaining to drug absorption and transit in the gastrointestinal system affect the amount of drug absorption.

Enhanced first-pass biotransformation:

If the drug is delivered to the metabolic enzymes (cytochrome P450, specifically CYP3A4) in a sustained manner as opposed to a bolus input, the pre-systemic metabolism of the tested compound has significantly increased the cause of FDDS, in a manner akin to the increased efficacy of limited capacity active transporters.

Enhanced bioavailability as a result of decreased duodenal P-glycoprotein (P-gp) activity:

P-gp mRNA levels rise longitudinally along the gut, with the colon containing the highest levels, seemingly at odds with the higher density of CYP3A4 at the upper portion of the intestine. Therefore, floating systems may increase absorption in comparison to immediate and controlled release (CR) dose forms for medications like digoxin that are P-gp substrates and do not experience oxidative metabolism.

Reduced frequency of dosing:

Various research indicate that medications having a short biological half-life, sluggish absorption from sustained release, and control release floating system flip-flop pharmacokinetics were shown to have lower dosage frequency. This characteristic is linked to increased patient compliance, which enhances therapy as a result.

Targeted treatment for local illnesses in the upper gastrointestinal tract:

Long-term, continuous medicine delivery from floating devices to the stomach may be helpful for local treatment in the small intestine and stomach.

4.9 Pharmacodynamic aspects of FDDS

Reduced fluctuations of drug concentration:

Comparing the floating system of medication delivery to immediate release dosage forms on continuous drug input, the floating technique yields consistent blood drug concentrations within a tighter range. As a result, pharmacological

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Impact Factor: 7.53
Volume 4, Issue 1, July 2024

effect variations are reduced, and concentration-dependent side effects linked to peak concentrations can be avoided. This particular feature is particularly beneficial for medications with a limited therapeutic index.

Enhanced selectivity in receptor activation:
Reduction of drug concentration fluctuations also allows for some selectivity in the pharmacological effect that is elicited by medicines that activate certain types of receptors at various concentrations.

Decreased body counter-activity:
The pharmacological reaction frequently interferes with natural physiological processes, causing the body to go into rebound mode, which reduces drug activity. It has been demonstrated that introducing a drug gradually into the body, like in the case of FDDS, reduces counteractivity and increases drug efficiency.

Reduced negative effects at the colon:
When a medication is kept in the FDDS, particularly when it is in the stomach in a gastro retentive form, less of the medication travels down the colon. As a result, the drug's unwanted effects on the colon may be avoided. The justification for floating formulation of beta-lactam antibiotics, which are only absorbed from the small intestine and whose presence in the colon promotes the growth of bacteria, comes from this pharmacodynamic feature.

4.10 Application of the Floating Drug Delivery System:
Improved bioavailability: Riboflavin CR-GRDF has a far higher bioavailability when administered in place of non-GRDF CR polymeric formulations.
Drug distribution over an extended period: The GIT encountered problems with oral CR formulations, including stomach residence duration. These problems are typically resolved by HBS systems that have the ability to float on the contents of the stomach, have a bulk density of less than one, and remain in the stomach for lengthy periods of time.
System of site-specific drug delivery: A system of site-specific drug administration delivers the medication to the stomach in a gradual and regulated manner, minimizing systemic exposure and producing the best local therapeutic rates. Dose frequency can be decreased with extended gastrointestinal availability from a site-driven medicine delivery system. Take riboflavin with furosemide, for example.
Enhancement of absorption: Drugs with limited bioavailability from site-specific absorption from the upper section of the GIT could be made into floating drug delivery devices by improving their absorption.
Reduced harmful effects in the colon: HBS keeps medication in the stomach, which lessens the quantity of medication that passes into the colon. Consequently, it is possible to stop undesired medication activity in the colon.
Reduced fluctuations at drug concentration: Following CR-GRDF delivery, continuous drug input leads to a more narrow range of blood drug concentrations than with other instant release dose forms.

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