Review on Gastro Retentive Drug Delivery System

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❖ Abstract

GRDDSs are a cutting-edge strategy in this field (Gastro Retentive Drug Delivery System). By constantly releasing the drug for a lengthy time before it reaches its absorption site, GRDDSs can enhance the controlled delivery of medications with an absorption window. The goal of this study was to look into, gather, and concisely summarize both contemporary and older literatures, with an emphasis on strategies that are currently being used to extend gastric residency time. These include delayed gastric emptying devices such as floating systems, swelling and expanding systems, bio/mucoadhesive systems, high density systems, and others. The classification, formulation considerations for GRDDS, factors affecting gastric retention, benefits, drawbacks, and uses of gastroretentive drug delivery systems are all briefly discussed in this review.

❖ Introduction

Oral drug administration has traditionally been the main method of drug delivery. Numerous oral delivery systems have been created during the last two decades to serve as drug reservoirs from which the active ingredient can be delivered over a certain time period at a planned and controlled pace. However, there are a number of physiological issues with this method. include a variable and unpredictable gastric emptying rate, a short gastrointestinal transit time (8–12 hours), and the existence of an upper small intestine absorption window for a number of medications[1]. Researchers have created a medicine delivery system that can stay in the stomach for a lengthy, predictable amount of time in response to these challenges. An effort is being made to create a drug delivery system that can supply a therapeutically effective plasma drug concentration over a longer period of time, reducing the frequency of dosing and limiting volatility in plasma drug concentration at steady state[2]. As a result, various strategies have been suggested to keep the dosage form in the stomach. These include low density super porous systems, low density floating systems, bioadhesive systems, swelling, expanding, and delayed stomach emptying systems. The most effective method of medication delivery is by the oral route since it is simple to administer, patient-acceptable, non-evasive, and has a flexible formulation[3]. Oral dosage formulations have advanced significantly, going from instant release to site-specific delivery. It is possible to target site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects by using a strategy called gastroretentive drug delivery. The gastric retention time (GRT) of medications can be greatly extended when using gastroretentive dose forms, which can stay in the gastric region for extended periods. Several gastroretentive drug delivery strategies have been created during the past few decades, such as high density (sinking) systems that are retained in the stomach's bottom[4].

❖ Advantages

• Longer stomach residence time may be beneficial for local action in the upper part of the small intestine, such as the treatment of peptic ulcer disease.

• Delivery of medications with a restricted window of absorption in the small intestine region.

• It is anticipated that medications that are quickly absorbed after release in the GI tract, such as,

ranitidine, amoxicillin, cyclosporine, ciprofloxacin, captopril, etc.

• Ensuring once-daily therapy compliance from the patient.

• Increased therapeutic effectiveness.

• Decreases the dosage frequency.

• The bioavailability of therapeutic agents can be greatly increased by using this gastroretentive drug delivery technique in comparison to the administration of non gastroretentive drug delivery, especially for those that get metabolized in the upper GIT.

• Drugs from dosage forms that provide local therapy in the stomach and small intestine can be released from capsules and tablets for a longer period of time and continuously. As a result, they are helpful for treating conditions of the stomach and small intestine.

• Gastro retentive medication administration can reduce the body's defence mechanisms, increasing drug effectiveness.

• Extends the duration the dose form spends at the absorption site.

• First pass metabolism increases medication bioavailability.

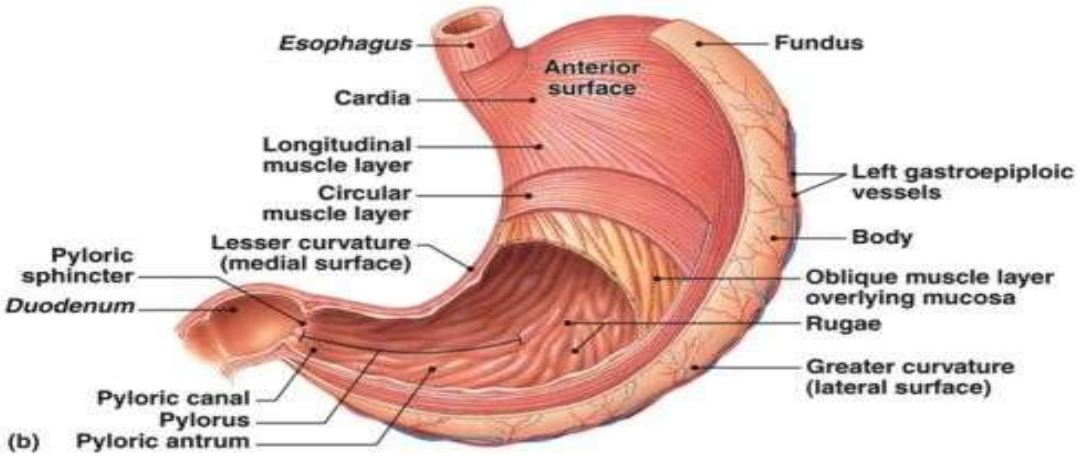
• Drug delivery at a specified site.

• Lessening mucosal irritation caused by medications by releasing them gradually and at a controlled rate[5].

❖ **Disadvantages**

- Unsuitable for medications with a low acid solubility. Unsuitable for medications that are unstable in an acidic environment, such as phenytoin.
- Drugs that irritate or produce stomach sores on gradual release, for example erythromycin. Example: Aspirin, NSAIDs.
- Drugs that selectively absorb in the colon, such as corticosteroids.
- Drugs that are equally well absorbed through the GIT. For Example, Isosorbide, Dinitrate, and Nifidipine.
- Floating drug delivery systems need a lot of fluid in the stomach to function properly[6].

❖ **The Anatomy of the stomach**



GRDDSs are a cutting-edge strategy in this field (gastro retentive drug delivery system). GRDDs are dosage forms that can be retained in the stomach. By constantly releasing the drug for a lengthy time before it reaches its absorption site, GRDDSs can enhance the controlled delivery of medications with an absorption window[7]. In order to achieve therapeutic benefits from drugs that are absorbed from the proximal part of the GIT (gastro intestinal tract), are less soluble in alkaline pH, are degraded by it, or come into contact with at the lower part of the GIT, it may be desirable to prolong the gastric retention of the drugs. GRDDS are advantageous for such medications by enhancing their Bioavailability, Therapeutic effectiveness and Potential dose reduction[8].

Long-term maintenance of therapeutic levels at a consistent level, reducing therapeutic level fluctuation

Lower drug wastage

Increases the solubility of medications that are less soluble in environments with high pH levels (e.g. weakly basic drug like Domperidone, Papaverine).

1. Important Elements Impacting GRDDS Efficacy

The effectiveness of gastroretentive dose forms is influenced by a number of factors. These elements primarily fall into three categories: pharmacological, physiological, and patient-related.

❖ Pharmaceutical Factors

Understanding the impact of excipients and polymers on distinct GRDDS types is crucial for the successful design of GRDDS[9]. For instance, high mucoadhesion strength polymers like carbopol and hydroxypropyl methylcellulose (HPMC) may be necessary in the mucoadhesive system for the successful design of the mucoadhesive dosage form. Similarly, polymers with significant swelling capabilities are preferred for the expandable system. Additionally, the dosage form may be impacted by the molecular weight, viscosity, and physiochemical characteristics of polymers. Added ingredients in formulations like gas-generating agents in an effervescent for superporous hydrogels, it could be necessary to use crospovidone, sodium croscarmellose excipients with high swelling, and floating tablets.

Additionally, the dosage unit's size and shape are crucial Tetrahedron-shaped dosage forms and ring-shaped dosage forms had longer GRTs than other shapes. According to Garg and Sharma[10,11]. The GRT of the dose form typically depends proportionately on the size. Because the dose form is greater than the pyloric sphincter's diameter (mean, 12.8 7 mm), an increase in size could prohibit it from passing through the pyloric antrum in the gut[12]. For low- and high-density systems, the dosage form's density is also a crucial consideration. The dose forms in low-density systems should have a density that is lower than the gastric fluid's (1.004 g/cm3)[13,14]. The GRT of the low-density system can be increased by increasing the floating capacity, although this impact is lessened in the presence of food. Additionally, the dosage form's floating force reduces over time, which may be a result of the hydrodynamic equilibrium[15]. Contrarily, in high-density systems, the dosage form's density should be higher than that of the gastric fluid in order to allow it to sink to the stomach's floor and obstruct gastric emptying. The GRT is improved by a dosage form density increase of more than 2.500 g/cm3. [16]

❖ Factors Physiological

According to several studies, a number of extrinsic factors, such as the type of food, caloric content, frequency of consumption, posture, sleep, and physical activity, might influence the GRTs of medications in the stomach[**Error! Reference source not found.**,**Error! Reference source not found.**,**Error! Reference source not found.**,**Error! Reference source not found.**]. Gastrointestinal motility in fasting circumstances is represented by the MMC, which takes place every 90–120 minutes[**Error! Reference source not found.**]. Motor action clears the stomach of any remaining undigested matter during this time. The unit's GRT is

extremely brief if the timing of formulation administration and the MMC are the same. Though the MMC is halted and no housekeeper waves are produced when there is food in the stomach, this results in a longer GRT[**Error! Reference source not found.**,**Error! Reference source not found.**]. Similar to how caloric density affects food intake[**Error! Reference source not found.**], stomach emptying rate is likewise influenced by the food's caloric content and the type of calories it contains the GRT generally increases dramatically when caloric density rises while being mostly unaffected by the type of calories consumed[**Error! Reference source not found.**]. High food viscosity may also cause the GRT to rise[**Error! Reference source not found.**]. Additionally, posture has an impact on the GRT, and floating versus non-floating dose forms have differing effects. The floating system spends a lot of time in the gastric fluid when it is upright, which may gradually raise the GRT[**Error! Reference source not found.**]. However, under comparable circumstances, the non-floating system remains in the lower portion of the stomach, and peristaltic contractions cause the gastric emptying rate to occur more quickly. On the other hand, when lying down, the non-floating The floating system spends a lot of time in the gastric fluid when it is upright, which may gradually raise the GRT[**Error! Reference source not found.**]. However, under comparable circumstances, the non-floating system remains in the lower portion of the stomach, and peristaltic contractions cause the gastric emptying rate to occur more quickly. In contrast, the non-floating system has a longer GRT than the floating system while the patient is supine.[**Error! Reference source not found.**,**Error! Reference source not found.**,**Error! Reference source not found.**,**Error! Reference source not found.**]

Patient-Related Factors,

GRDDS may be impacted by patient-related variables as gender, age, sickness, and emotional state. [32] Gender was found to influence intraluminal pH and stomach emptying time in a recent study [33] . Females exhibited slower stomach emptying times than males, according to the authors' research. The longer GRT in females than in males could be attributed to hormonal effects. According to a different study, men secrete more stomach acid than women do. The patient's age also has an impact on the GRT [34]. Patients who are older have longer GRTs than patients who are younger. The GRT of the dose form may also be impacted by the nature of a patient's disease [35]. For instance, people with Parkinson's disease typically experience constipation along with a prolonged GRT. Similar to this, stomach emptying is reduced by 30–50% in diabetes people. GRDDS may also be impacted by a patient's emotional state. According to a study, depression patients' gastric emptying rates were found to be lower, whilst anxiety patients' rates were shown to be higher. [36,37,38]

❖ Numerous methods for gastrointestinal medication delivery

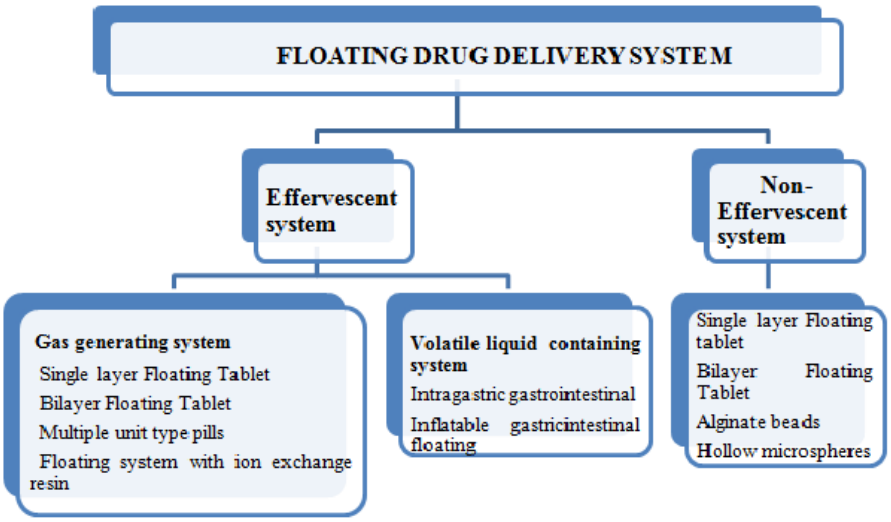
To increase the retention of oral dose forms in the stomach, various strategies have been tried. Some dosage forms are single-component formed, while others are multi-component formulated. In general, GRDDS can be divided into following systems,

• Floating device

• Non-floating apparatus

❖ Floating Drug Delivery System (FDDS)

The floating system is designed to float in and over the gastric content, extending the period that the gastric contents are retained in the stomach (GRT). It is a low density method that releases the medicine gradually without interfering with gastric emptying since its bulk density is lower than that of gastric fluids rate at a high rate for a long time. The delivery mechanism is discharged when the medicine leaves the stomach. [39]

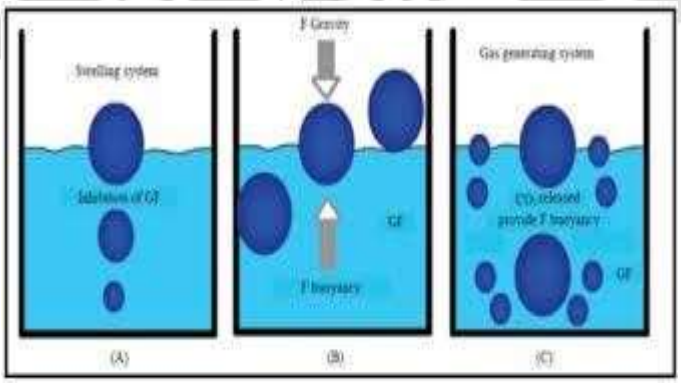


❖ Mechanism of Floating delivery system

Low density systems that have enough buoyancy to float above the contents of the stomach and stay there for a long time are called floating systems. The medicine is delivered slowly at the desired pace as the system floats over the contents of the stomach, lengthening the gastro-retention period and minimizing volatility. To maintain the dosage form consistently buoyant on the surface of the meal, however, a minimal amount of floating force (F) is also necessary in addition to the minimal stomach content necessary to allow the appropriate attainment of the buoyancy retention principle. A unique apparatus for calculating the resultant weight has been described in the literature to measure the floating force kinetics. The device works by continually measuring the force, F, needed to keep the submerged object in place (as a function of time). If F is on the upper positive side, as seen in fig., the item floats more effectively. This device aids in FDDS optimization with regard to the stability and longevity of the floating forces generated in order to avoid the negative effects of unforeseen intragastric buoyancy capability variations.

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. [40]



1. **Effervescent systems**

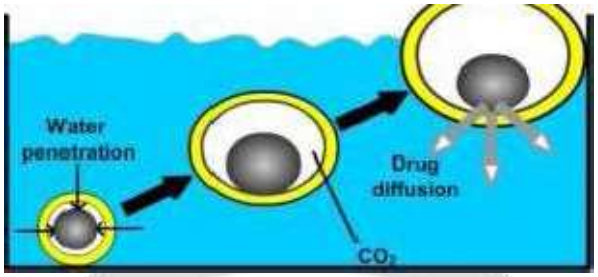
These systems are of the matrix variety. prepared with the use of several effervescent chemicals and swellable polymers, including methylcellulose and chitosan.

Ex: citric acid, tartaric acid, sodium bicarbonate. These are designed in such a way that when they come into touch with gastric contents, CO2 is released and captured in swelling hydrocolloid, giving the dosage form buoyancy. The delivery system's design was based on swellable tablet method with three layers that is asymmetric.

These systems can also be categorised as follows

A). Gas generating systems
B). Volatile liquid/ vacuum system [41]

A). Gas Generating Systems



These buoyant delivery systems use effervescent interactions between citric/tartaric acid and carbonate/bicarbonate salts to generate CO2, which is then trapped in the jellified hydrocolloid layer of the systems, reducing its specific gravity and causing it to float above stomach content. [42]

a) Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS)

These are created by thoroughly combining the medication and CO2 generators in the matrix tablet. These float around in the stomach longer than gastric fluids because they have a lower bulk density, which slows down the rate at which the stomach empties. After a desired amount of medicine has been released completely from the floating system, any remaining substance is evacuated from the stomach. As a result, the GRT rises, and the volatility in plasma drug concentration is better managed. [43]

b) Bilayer Floating Tablets

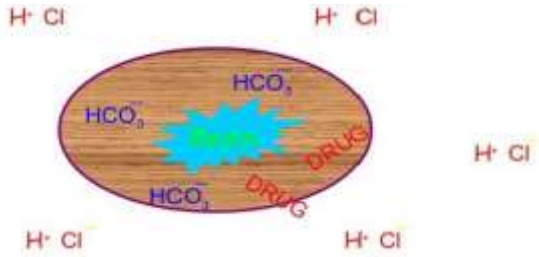
These are likewise compressed tablets with two layers, namely
1.an immediate release layer
2.sustained release layer, as shown in Fig.

c) Multiple Unit Type Floating Pills

These systems are made up of two layers surrounding sustained release capsules that act as "seeds." Effervescent agents make up the inner layer while swallable membrane layers make up the outer layer. The system lowers instantly when submerged in dissolving liquid at body temperature, then generates enlarged pills that resemble balloons and float because they have a reduced density. The system's carbon dioxide generation and trapping are to blame for the decreased density. [44]

d) Ion exchange resin

Ion exchange resins, a multiple unit kind of oral floating dose system, have been developed to extend the period before a dosage form is completely emptied from the stomach. The system is made up of hydrophobic polymer-coated drug resin complex beads that are loaded with bicarbonates ions. The mechanism is constructed in such a way that chloride ions are swapped with bicarbonate and drug ions when the beads reach the stomach. The polymeric coated resins that are formed capture the generated CO2, which makes the beads float. [45]



B). volatile liquid containing system

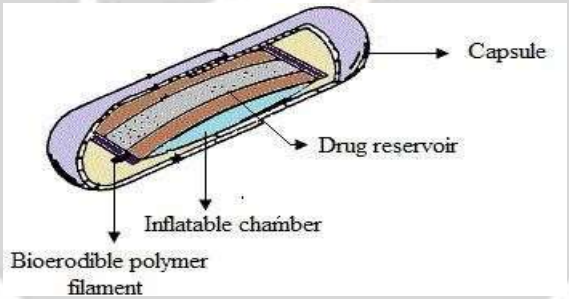
These have an inflatable chamber with a liquid within, such as ether or cyclopentane, which gasifies at body temperature to induce the chamber in the stomach to inflate. These systems consist of a hollow deformable unit and are osmotically controlled floating devices. The system consists of two chambers, the first of which holds the medicine and the second of which holds the volatile system.

They are categorised as,

A. An intragastric floating gastrointestinal drug delivery system

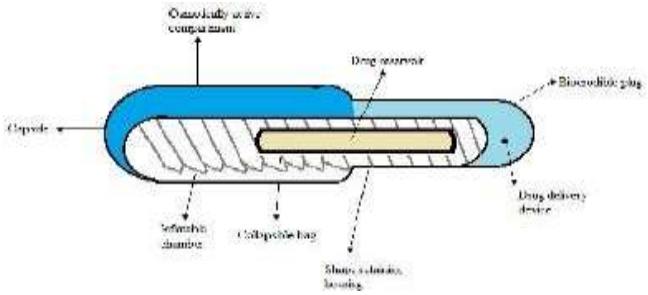
Has a flotation chamber that is vacuum-filled or filled with a harmless gas, and a microporous compartment that houses the drug reservoir.

B. Gastrointestinal medication delivery apparatus that inflates:



The stomach is inflated by these devices' inflatable chambers, which contain liquid ether and gasifiers that operate at body temperature. The bio-erodible polymer filament used in inflatable chambers, such as copolymers of polyvinyl alcohol and polyethylene, progressively dissolves in gastric fluid before causing the inflated chamber to release gas and collapse.

C. Osmotically regulated intragastric medication delivery system



It is made up of an inflatable floating capsule and a drug delivery system regulated by osmotic pressure. The osmotically regulated drug delivery system, which consists of two parts: a drug reservoir compartment and an osmotically active compartment, is released when the inflatable capsule ruptures in the stomach.

1. <u>Non Effervescent System</u>

Hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polystyrene, and polymethacrylate are employed in this type of floating gastro retentive drug delivery system. These are additionally categorised as follows:

a). Hydrodynamically balanced system (HBS),

which mixes medications with hydrocolloids that form gels, was created for the first time by Sheath and Tossounian in 1975. These systems have a high concentration (20–75%w/w) of one or more hydrocolloids of the cellulose type that produce gels and are highly swellable, as well as polysaccharides and matrix-forming polymers. The hydrocolloids in the system hydrate and create a colloidal gel barrier on the surface of stomach fluid when they come into contact with it. This gel barrier regulates how quickly fluids enter the device and release the medicine as a result. [46]

b. compartment system with microporous surfaces

Based on enclosing a drug reservoir inside a small-scale porous compartment with perforations along the top and bottom walls. To avoid any direct contact of the gastric mucosal surface with the undissolved drug, the periphery of the drug reservoir compartment is entirely sealed. [47]

c. Microspheres that float

Because of the center hollow space inside the microsphere, hollow microspheres are thought to be the most promising buoyant system. A unique emulsion solvent Diffusion approach was used to create hollow microspheres that are loaded with medication in their exterior polymer shelves. [48]

d. Alginate floating beads

Freeze-calcium alginate has been used to create multi-unit floating dose forms. By adding sodium alginate solution to aqueous calcium chloride solution, spherical beads with a diameter of around 2.5 mm can be created. causing calcium alginate to precipitate After being separated, the beads are quickly frozen in liquid nitrogen and then freeze-dried at 400°C for 24 hours, creating a porous structure that can sustain a floating force for more than 12 hours. The prolonged residence length of these floating beads was greater than 5.5 hours. [49]

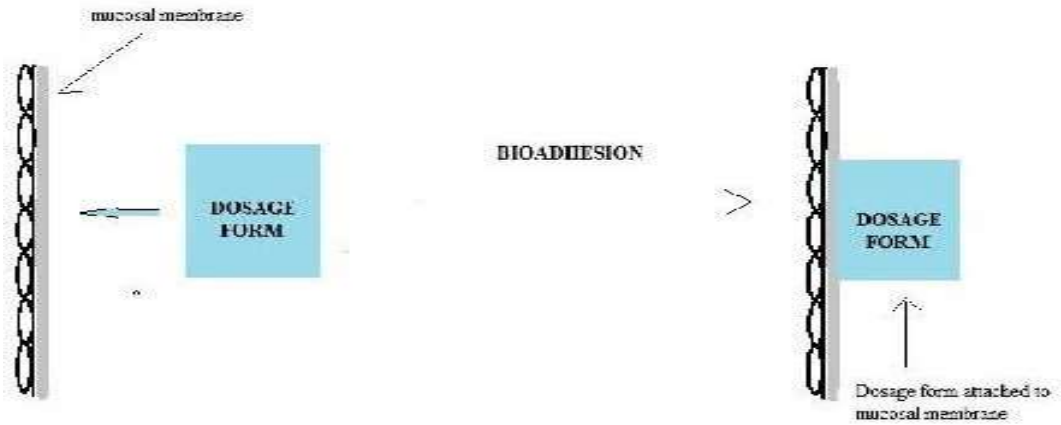
e. Raft-forming system

On contact with stomach fluid, a gel-forming solution swells and produces a viscous cohesive gel that contains trapped CO2 bubbles. This has received a lot of attention for the delivery of antacids and drug delivery for gastro infection and disorders. which creates a raft layer on top of the gastric fluid, releasing the medicine gradually into the stomach. (Frequently used to treat gastroesophageal reflux disease).

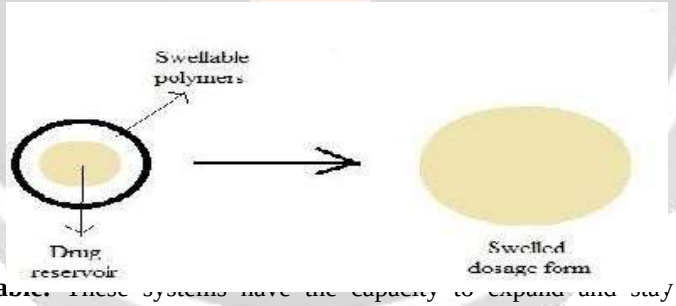
❖ **<u>Non-floating system Drug Delivery System</u>**

Despite not floating in the stomach, these gastro retentive drug delivery devices are kept there by several mechanisms.

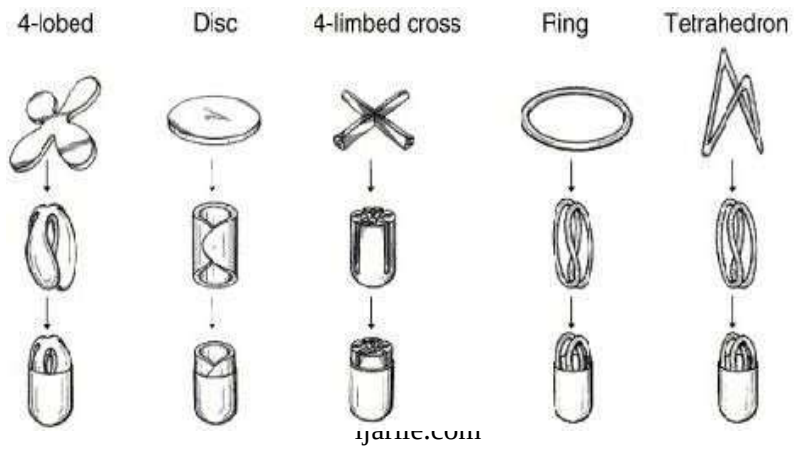
Bioadhesive systems: These kinds of systems stick to the stomach's mucosa, its biological membrane, and keep close contact with it for an extended period of time. As a result, they remain in the stomach for their prolonged release. Bio adhesive polymers are used in the formulation of these systems.



Swelling System: The inclusion of swellable polymers causes these non-floating gastro retentive drug delivery systems to swell when they enter the stomach, preventing them from passing through the pyloric sphincter and causing retention in the stomach.



Systems that are expandable: These systems have the capacity to expand and stay in the stomach for prolonged periods of time. These are often made in the shape of folded, compressed capsules that hold the dosage. The dose form grows and the capsule shell breaks down in the stomach environment, making it impossible for it to pass through. Drug distribution that is maintained and under control can be accomplished by employing the right polymer. [49]



❖ **In-Vitro assessment of GRDDS**

To guarantee the in vivo performance with regard to floating lag time and floating duration, as well as the choice of the proper formulation composition, in vitro assessments of GRDDS are necessary. The standard evaluation procedures for tablet dosage forms include testing for general tableting characteristics, such as hardness, friability, general appearance, drug content, uniformity of content, weight variation, and in vitro drug release. Deionized water and simulated gastric fluid have been employed in the literature for the evaluation of floating behavior such as floating lag time and the duration of floating for any GRDDS. These two media are used to look for potential variations in the dosage forms' buoyancy properties. In order to ensure drug release and floating mechanism, the polymeric dosage forms are further evaluated for swelling property and rate of swelling for at least 8 hours. The size of the swelled tablet or the weight gain after collecting them at the conclusion of the trial are measured to achieve this. The test media for in vitro drug release tests is simulated stomach fluid. Samples are taken out of the dissolve baskets after a predetermined amount of time and properly diluted before being examined for drug content. The surface morphology of the dosage form is visualized under a microscope using various magnification strengths, ideally scanning electron microscopy (SEM). Other further tests, such as drug loading, particle size analysis, and drug entrapment efficiency, are carried out for the gastro-retentive beads and microspheres in order to optimize formulation composition and associated processing parameters. In these kinds of in vitro evaluation tests, spectrophotometers, optical microscopes, and particle size analyzers are frequently employed. [50]

❖ **The use of in vivo gastric retention in pharmacokinetic studies**

To demonstrate the in vivo efficacy of any GRDDS, a well-designed in vivo study using suitable animal models or healthy human volunteers is necessary. According to Turner et al., handling smaller animals like mice, rats, guinea pigs, or rabbits to verify stomach retention and conduct a bioavailability study is challenging, particularly for a large-sized tablet dose form. Because of this, the majority of the literature on the development of GRDDS has demonstrated in vitro characterization studies, such as dissolution studies, estimations of floating lag time and floating duration, and in vivo gastric retention in relatively larger animals, such as dogs or human subjects. It was expected that the GRDDS would provide better therapeutic efficacy than the standard dosage form due to its extended in vivo stomach retention. This is when sophisticated visualization techniques come in handy. One such well-liked and elegant method to provide accurate assessment of human gastro-retentivity is gamma scintigraphy. The dose form contains a little amount of a radioisotope with a brief half-life. The formulation is exposed to a neutron source, which can cause it to generate the distinctive gamma rays, which can then be photographed and processed by a computer to create an image. Diclofenac sodium was created as hollow calcium pectinate beads by Badve et al. for its chronopharmacological activity. The spheres that made up the floating beads had a bulk density of less than 1 g/ml and a porosity of 34%. They were structurally hollow. Gamma scintigraphy was used in an in vivo investigation on rabbits that revealed gastro-retention of beads for up to 5 hours. Floating tablets and microspheres containing adaptable therapeutic compounds such ascaridole, calcium-disodium edentate, and repaglinide have been successfully retained in vivo in many other recent findings. An additional method for demonstrating in vivo gastro-retention of a GRDDS is magnetic resonance imaging (MRI). This method, which combines magnetic fields and radio waves to view the entire anatomical structure as well as the position of the ingested dose form, is comparably safe. For the purpose of visualization, substances having super paramagnetic properties such as ferrous oxide are added. Using this method, Steingoetter et al. were able to examine the intra-gastric tablet position and residence time in human volunteers and describe the in vivo gastric retention of gadolinium chelates (Gd-DOTA) floating tablets containing Fe3O4 as a superparamagnetic agent. A radio-opaque substance is combined with the GRDDS in radiology or X-ray, another alternative approach. The examination of gastro-retentiveness, the disintegration rate of dose forms, and their esophageal transit have all been documented using this technique. However, this method has a safety concern because frequent X-ray exposure might be harmful to your health. Despite this, the method has the benefit of being used effectively on volunteers who are humans, dogs, and rabbits. Gastroscopy is another frequently used method for diagnosing and keeping an eye on the GIT. By employing this method, the dosage form is located via fiber optics or a video system. Because this approach is less convenient, it is occasionally used on people under very light anaesthesia to measure the stomach retention of any dosage form. However, according to Dhiman et al., total anaesthesia is necessary in the case of dogs. [51]

❖ Floating Drug Delivery System Evaluation

1) A Powder Blend's Evaluation

a) Angle of repose
b) Bulk Density
c) Percentage Purity

2) Evaluation of Tablets

a) Buoyancy capabilities
b) *In vitro* floating and dissolution behaviour
c) Weight Variation
d) Hardness & Friability
e) Particle size analysis, surface characterization (for floating microsphere & beads)
f) X-Ray/Gamma Scintigraphy
g) Pharmacokinetic studies

1) A Powder blend's Evaluation

a) Angle of Repose

The definition of angle of repose is "the greatest angle between the surface of the powder pile and the horizontal plane." The flow qualities are better when the angle of repose is lower. Measuring the height will allow you to calculate the angle of repose.

Tan θ = h/r

h= height

r= radius

b). Bulk Density

Bulk density refers to the material's overall density. It takes into account the actual volume of pore sizes and interparticle gaps. Bulk is mostly caused by particle packing. The term "bulk density" means.

Bulk density = Weight of the powder / Bulk volume of powder

When particles are tightly packed, it's likely that there will be a lot of gaps between them. Powder trapping enables the particles to move and reduce the voids to a minimum volume as a result. The bulk volume is the amount of space that the powder takes up in this situation. The bulk density is obtained by substituting this volume for a specified weight of powder in the equation.

c) Percentage porosity

The total porosity expression for the computation is the same whether the powder is porous or not. Information about hardness, disintegration, total porosity, etc. is provided by porosity.

%porosity, Є = void volume x100Bulk volume
% porosity, Є = *(bulk* volumetuer *volume)* x100True density

2) Evaluation of floating tablets

a) Evaluation of the FDDS's buoyancy capabilities

The generated weight measurements are used to analyse the floating behaviour. Deionized water and a simulated meal are the two media used for the experiment. The findings demonstrated that, in comparison to deionized water, higher molecular weight polymers with a slower rate of hydration had increased floating behaviour.

b) In-Vitro floating and Dissolving behaviour

Typically, different medications are subjected to the dissolve testing utilising USP dissolution equipment. The dose unit must reach the bottom of the vessel before the blade can begin to rotate, according to USP 28. The dose units that would otherwise float may have a little, loose piece of nonreactive material attached with no more than a few turns of a wire helix. Standard USP or BP methodologies, however, have not been demonstrated to be accurate predictors of floating dosage form performance in vitro. Theophylline is a sparingly soluble in water swellable floating system that Pillay et al attached a helical wire sinker to, and they found that the swelling of the system was restricted by the wire helix and the drug release was slowed down. A technique was created to get around this restriction, and it was found to increase drug release when the floating drug delivery system was entirely immersed beneath a ring or mesh assembly. It was also demonstrated that the procedure was more consistent and reliable.

When the suggested approach was used with the highly water soluble medication diltiazem in a swellable floating device, no appreciable difference in the drug release was noticed. Thus, it was determined that the medication's solubility in water, surface exposure, and unrestricted swelling were all necessary for the drug to be released from swellable floating systems.

c) Weight variation

Throughout the compression procedure, composite samples of tablets (typically ten) are typically collected and weighed. However, dividing the composite weight by 10 yields an average weight that has an issue with averaged value. The United States Pharmacopeia (USP) establishes limitations for the permitted fluctuations in the weights of individual tablets stated as a percentage of the average weight of the sample in order to assist relieve this issue. By measuring 20 pills individually, figuring out their average weight, and then comparing those weights to the average, the USP offers the weight variation test. If no more than two tablets fall outside the percentage restriction and no tablet deviates by more than twice the percentage limit, the tablets pass the USP test.

d) Hardness & Friability

The "force necessary to break a tablet in diametric compression test" is the definition of hardness. Therefore, hardness is also known as tablet crushing strength. The Monsanto tester, the strong Cobb tester, the Pfizer tester, and other tools are used to measure hardness. The Roche Friabilator is the name of the lab friability tester. This comprises of a mechanism that uses a plastic chamber that rotates at 25 rpm and drops the tablet to a distance of six inches with each revolution to submit several tablets to the combined effects of abrasion and shock. The friabilator is typically operated for 100 revolutions with a pre-weighed tablet sample inside. Conventionally compressed tablets are generally regarded as appropriate if they lose between 0.5 and 1.0% of their weight. The majority of effervescent tablets lose weight due to excessive friability, which is why these types of tablets may need special stack packing.

e) Particle size analysis, surface characterization (for floating microspheres and beads)

The optical microscopy approach is used to determine the particle size and size distribution of beads or microspheres in the dry state. Using a scanning electron microscope, the exterior and cross-sectional morphology (surface characterization) is carried out (SEM).

f) X-Ray/ gamma scintigraphy

X-Ray/Gamma Nowadays, scintigraphy is a relatively common evaluation criterion for floating dosage forms. Locating the dose form in the digestive system aids in predicting and correlating the passage of the dosage form through the GIT and the time it takes for the stomach to empty. Here, it may be seen by X-rays thanks to the incorporation of a radio opaque substance into a solid dose form. Similar to this, adding a radionuclide that emits gamma radiation to a formulation enables indirect external observation with a gamma camera or scinti scanner. In the case of "- scintigraphy," the radionuclide's "-rays" are concentrated on a camera, which aids in tracking the location of the dose form in the GIT.

g) Pharmacokinetic studies

The in vivo research include pharmacokinetic studies, which have been the subject of numerous publications. Sawicki investigated the pharmacokinetics of verapamil using floating pellets packed with the medicine and compared them to traditional verapamil tablets at a similar dose (40 mg). Comparatively greater t-max and AUC (0- ∞) values were achieved for floating pellets than for traditional verapamil tablets (3.75 h and 364.65ng/ml/1h, respectively). (t-max of 1.21 hours and AUC of 224.22 mg/ml/1 hour**).** [52]

❖ Future obstacles for GRDDS

One of the factors influencing the bioavailability of oral drug delivery systems is the duration of the dosage forms' retention in the GIT. GRDDS is a condition that primarily affects the stomach. As a result, maintaining the delivery system in the stomach or upper part of the small intestine for a long time until all the medications have been released at a predetermined rate is the key issue in constructing a GRDDS. Gastric emptying time is a very varied process. It primarily relies on the dosage type as well as whether the stomach is fed or fasting, among many other variables. In a fed state, the stomach retention period is prolonged; in a fasted state, it is shortened. The type of food, caloric amount, gender, and age, along with other physiological barriers, significantly affect how quickly the stomach empties. High-fat meals considerably delay stomach emptying due to their high caloric content. Fatty acid salts or indigestible polymers can also change how the stomach moves when it is fed, which can slow down how quickly the stomach empties. According to Mojaverian et al., patients' GRT varies according to their age and gender. For any GRDDS, the pylorus limitation is crucial to stomach retention. The pylorus is roughly 2 to 3 mm in diameter during digestion and 12.8 to 7.0 mm in diameter during the inter-digestive phase. Therefore, for any particle to enter the duodenum through the pylorus, its diameter must be less than 5 mm. Another thing to take into account in this situation is how the pylorus of an animal (such a dog or a rabbit) differs from a human's in terms of size and peristaltic movement. In vivo efficacy results must therefore be carefully drawn. Other variables that affect stomach residence time and are linked to the effectiveness of the dosage form include body mass index, disease severity, and the size and shape of the dosage form. However, compared to a single-unit GRDDS, it has been claimed that occasionally multiple-unit GRDDS exhibits an enhanced and predictable drug release. A single unit gastro-retentive dosage form (GRDF) may finally leave the stomach before the dosage form becomes functional due to a combination of the lag period and the gastric emptying process. Thus, in order to create an ideal GRDDS, it is necessary to resolve issues with the gastric emptying rate of the stomach as well as maintain a suitable drug release rate for a long time before the medication is metabolised in the body. [53]

❖ CONCLUSION:

The nature of a patient's illness may also have an effect on the GRT of the dose form. As an illustration, patients with Parkinson's disease frequently have constipation and a prolonged GRT. Similar to this, stomach emptying is 30–50% less in patients with diabetes. The emotional condition of a patient may also have an effect on GRDDS. In a study, it was discovered that people with depression had lower stomach emptying rates than patients with anxiety.

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