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GASTRO RETENTIVE DOSAGE FORMS: A COMPREHENSIVE REVIEW OF DESIGN STRATEGIES AND THERAPEUTIC BENEFITS

[1*]D. Jeslin, [2]S. Anusri, [2]P. Ashwini, [2]P. Arulselvam, [2]S. Aakash, [2]M. Ajay, [2]V. Harini

[1]Associate Professor, Department of Pharmaceutics, Faculty of Pharmacy, Sree Balaji Medical College and Hospital Campus, Bharath Institute of Higher Educationand Research, Chennai- 600044, Tamilnadu.

[2]Faculty of Pharmacy, Sree Balaji Medical College and Hospital Campus, Bharath Institute of Higher Education and Research, Chennai- 600044, Tamilnadu.

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***Corresponding Author: D. Jeslin**
Associate Professor, Department of Pharmaceutics, Faculty of Pharmacy, Sree Balaji Medical College and Hospital Campus, Bharath Institute of Higher Education and Research, Chennai- 600044, Tamilnadu. **DOI:** https://doi.org/10.5281/zenodo.14252428

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ABSTRACT

GRDDS have emerged as a promising solution for overcoming the challenges associated with conventional oral dosage forms, particularly the issue of unpredictable gastric emptying times andreduced bioavailability of drugs that are preferentially absorbed in the upper gastrointestinal tract.These systems are intended to extend the duration of the drug absorption in the stomach, therebyimproving the bioavailability and subsequent therapeutic efficacy of the medication. The formulation GRDDS type of medication reduce the frequency of dosing by controlling the factors affecting gastric residence time. Hence it bypasses the risk associated with gastric irritation and other side effects associated with conventional form of drugs. This review also elucidate the novel approaches comprises of microsperes, bioadhesives, swellable system to facilitate the retention stomach acids for extended action. It is expected that more pharmaceutical companies will developGRDDS in the future to produce superior benefits, extend patents, and improve results for their marketable formulations.

KEYWORDS: Bioavailability, gastric emptying, controlled release, Buoyancy, Site-specific, Drug candidates.

INTRODUCTION

Since oral administration is convenient and comfortable for patients, it remains popular even with ongoing advancements in drug delivery techniques. Drug delivery systems with controlled release are intended for oral use. These drug delivery systems release themedication in a regulated, predictable, and predetermined manner. Because of problems with stability or absorption, they are not appropriate for medications with low bioavailability. Modern

methods intended to prolong the residence of these medications in the stomach can help improve these issues. Such a delivery system is known as a retentive drug delivery system.[1] Drugs with minimal lower GIT absorption, instability, poor solubility at alkaline pH, short half-lives, and local activity in the upper gut for Helicobacter pylori eradication can be addressed with GRDDS. Effective controlled-release GRDDS have been developed using various formulation techniques,such as expandable, magnetic, raft-forming, bio/mucoadhesive, super porous hydrogel, ion- exchange, low- and high-density systems.[2] High-dose tablets often struggle to maintain buoyancy due to their high bulk density, making non-effervescent techniques unfeasible.

Effervescent floating tablets (EFTs) offer better buoyancy, but a suitable polymer, gas- generating agent, and process variables are necessary for high-quality EFT development. Non- ionic hydrophilic polymers like HPMC, HPC, and PEO are commonly used in controlled-release tablets due to their non-pH sensitivity and safety. Other factors like polymer amount, viscosity grade, molecular weight, and physicochemical properties like tensile strength, porosity, hydration rate, and gel strength can also influence drug release rate and tablet buoyancy.

Therefore, these polymers have the potential to design floating tablets.[3][4]

BASIC HISTOLOGY OF GIT

Understanding the anatomy and functioning of the stomach is crucial to the development of effective gastroretentive dosage forms. Anatomically, the stomach is composed of three parts: the fundus, which is located closest to the esophagus and serves as astorage area for food that has been swallowed; the body; and the antrum as shown in Figure 1 which is the last piece, and connects the body to the small intestine. The antrum assists with stomach emptying and churning.[5]

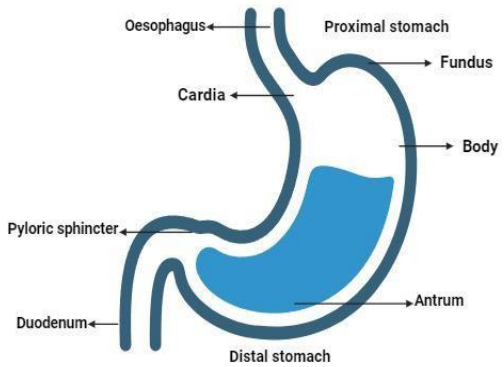

Figure 1: Anatomy of Stomach.

The stomach is a key organ in the digestive system, responsible for the breakdown and digestionof food.

1. **Oesophagus**: The tube that connects the throat (pharynx) with the stomach. It is responsible for transporting swallowed food and liquids to the stomach.
2. **Cardia:** The region of the stomach where the esophagus connects to the stomach. It containsthe lower esophageal sphincter, which prevents the backflow of stomach contents into the esophagus.
3. **Fundus:** The upper part of the stomach, which forms a dome-shaped region above the level ofthe cardia. It stores undigested food and gases released during the process of chemical digestion.
4. **Body:** The central and largest region of the stomach, where the majority of gastric digestion occurs. It secretes gastric juices that aid in the breakdown of food.

5. **Antrum:** The bottom region of the stomach, which combines digestive juices with food to break it up. It is necessary for food digestion to occur.
6. **Pyloric Sphincter:** A smooth muscle found at the junction between the stomach and the duodenum. It controls the passage of partly digested food from the stomach to the duodenum.[6]

The pattern of stomach movement is referred to as the migrating myoelectric complex. While gastric emptying occurs in both fed and fasted states, the rate at which it occurs differs significantly between the two states. In the fasted state, a recurring series of electrical events follow a cyclic pattern throughout the stomach and small intestine every 90-120 minutes. Duringthis phase, the pylorus diameter expanded to approximately 19 mm. However, in the fed state, motor activity is initiated 5-10 minutes after meal consumption and persists until food is completely emptied from the stomach, which can delay the rate of gastric emptying. The phases of migrating myoelectric complex:

Phase I: Typically lasts for 30-60 minutes without any contraction.

Phase II: Lasts for 20-40 minutes and is characterized by intermittent contractions.

Phase III: Lasts for 10-20 minutes and is characterized by short-term, intense contractions.

Phase IV: Serves as a transition period between Phase III and Phase I, lasting for 0 to 5 minutes.[6]

The gastrointestinal (GI) tract is a continuous pathway within the body, featuring the biliary and pancreatic ducts as significant side branches. The GI tract comprises a series of organs that sharea similar structure, appearing as cylinders, spheroids, or intermediate shapes. Its primary functions involve the transportation and digestion of food. The various segments of the GI tract exhibit diverse morphologies and mechanical properties of the muscles. For instance, the esophagus primarily facilitates the swift transport of food from the mouth to the stomach, whereit is stored for a period while undergoing further breakdown into smaller components. The GI sphincters play a crucial role in compartmentalizing the GI tract. Additionally, the gut also playsa vital role in immune functions. Structurally, the wall of the GI tract typically consists of four layers: the mucosa, submucosa, muscle, and serosa. The muscle layer comprises an outer longitudinal layer and an inner circular layer. Within the muscle layer lie the collagen-rich submucosa and mucosa layers. Another thin layer of muscle, known as the muscularis mucosae,exists as well.[7]

FACTORS AFFECTING GASTRIC RETENTION

The gastric retention time of dosage forms is controlled by various factors that affect their effectiveness as a gastroretentive system.

1. **Particle size:** It should be between 1-2 mm in order to move across valves of pylorus andinto the small intestine.[8]
2. **Density**: The dosage form's density affects the gastric retention time (GRT). Because thebuoyancy of the dosage form is directly influenced by its density. If a dosage form possesses a density that is lower than the density of the gastric content, it can float in the gastric fluids and thus remain in the stomach. It is advised that the density of the drugdosage form falls within the range of 1g/cm3 to 2.5g/cm3.[8]
3. **Size**: Dosage forms with a diameter exceeding 7.5mm exhibit longer gastric residence times compared to dosage forms with a diameter of 9.9mm.[8]
4. **Shape of dosage form**: The shape of the dosage form also affects the GRT Round and ring shape show good result.[8][9]
5. **Formulation**: Formulations that consist of multiple units exhibit a more reliable releasepattern and have minimal effect on performance than individual units.[9]

6. **Fed or unfed state**: Typically, when food is present in the gastrointestinal tract (GIT), it prolongs the time that a dosage form stays in the stomach (gastric retention time or GRT). As a result, the absorption of medications is enhanced since they can remain at the absorption site for a longer duration.[10]
7. **Gender, posture, and age:** Male average GRT (3.4 hours) is lower than females' (4.6 hours), independent of body surface area, weight, or height. Individuals over 70 have asignificantly longer GRT.[10]

POTENTIAL DRUG CANDIDATES FOR GASTRO RETENTIVE DRUG DELIVERY

Systems: Various drugs have their greatest therapeutic effect when released from the stomach, especially when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of adverse reactions and provide their therapeutic effects without the need for repeated Doses with a low dose frequency. Sustain It is also helpfulto release stomach contents for therapeutic purposes Agents that are not readily absorbed by thestomach since sustain release prolongs the contact time of the agent in the stomach or the upper part of the small intestine Example. The material passes through the small intestine in as little as1-3 hrs.[11]

1. Drugs acting locally in the stomach, e.g. Antacids and drugs Pylori viz., Misoprostol.
2. Drug that is poorly soluble at alkaline pH e.g. Furosemide.
3. Drugs that are used to degrade or unstable in the colon. E.g. Ranitidine HCl, Metronidazole
4. Drugs unstable in the lower part of GIT, e.g. Captopril.
5. Drugs insoluble in intestinal fluids, e.g., Quinidine, Diazepam.
6. Drugs that disturb normal colonic bacteria, e.g. Amoxicillin trihydrate.
7. Drugs that have a narrow absorption window in the stomach or upper parts of the small intestine g e.g., Riboflavine-5-phosphate, Ofloxacin, Norfloxacin, Domperidone.[12]

ADVANTAGES OF GRDDS

- The medicine that is only soluble in the stomach is absorbed more readily.
- The single-unit floating dosage, like microspheres, releases medications consistently andeliminates the possibility of dose dumping.
- It decreases the frequency of dose, which increases patient compliance. Drugs withshorter half-lives can produce better therapeutic effects.
- The prolonged duration of the stomach retention period is caused by buoyancy.
- The medication is released for a long period of time in a controlled manner.
- It is capable of releasing medications into the stomach at a specific site.
- For drugs like antacids and ferrous salts that are absorbed through the stomach, gastroretentive systems are beneficial.
- The medication prevents stomach discomfort because of its uniform release from a multi-particulate structure, continuous release action, and floatability.[13][14]

LIMITATION OF GRDDS

- There needs to be enough fluid in the stomach for the floating system to function.
- Drugs that irritate the stomach mucosa or have problems with the stability or solubilityof gastrointestinal fluid are not suitable for GRDDS.

- Medications like nifedipine, which is extensively metabolized in the first pass and is widely absorbed throughout the gastrointestinal tract, might not be appropriate for FDDS patients due to the possibility of decreased systemic bioavailability due to delayedstomach emptying.
- Drugs that undergo first-pass metabolism or have distinct sites of absorption were not suitable for (GRDDS).
- Various factors, including pH, the presence of food, and stomach motility, affect gastric retention and can affect buoyancy.[15]

Classification of GRRDS

The two primary categories of GRDDS are floating and non-floating systems. Based on how they float, floating systems are further divided into effervescent and non-effervescent systems and non-floating systems are divided into four groups according to how they perform gastro retention. The overall classification of GRDDS is shown in Figure 2 Classification of GRRDS.

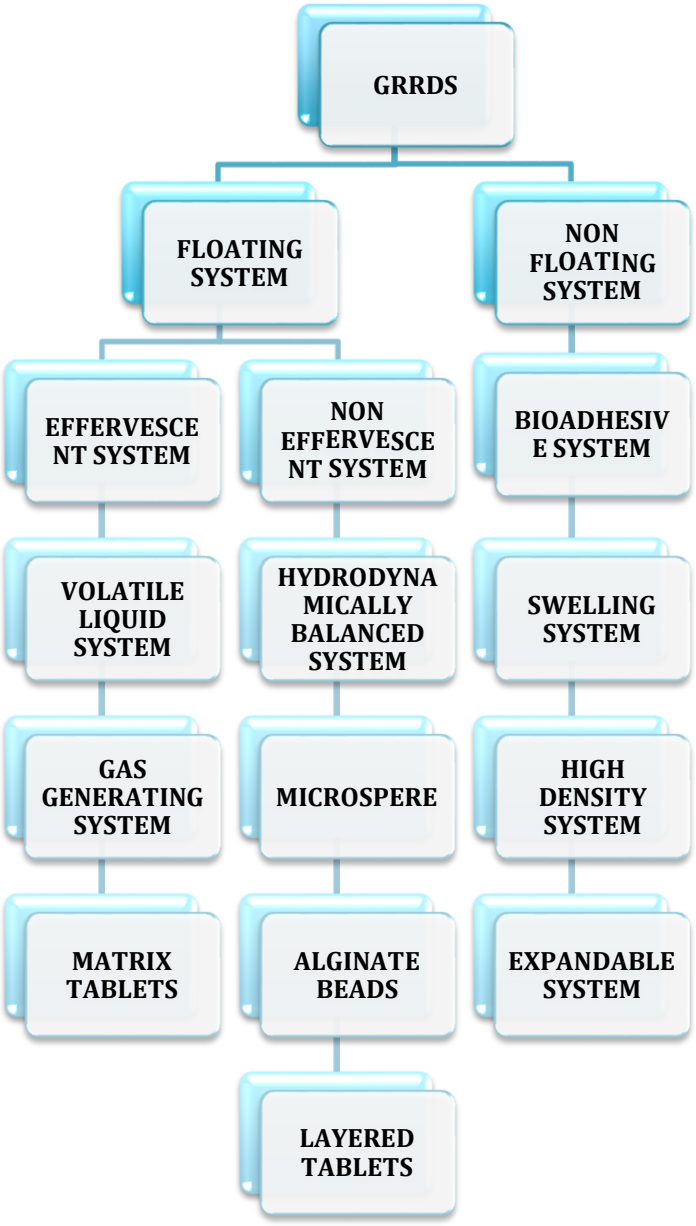

Figure 2: Classification of GRDDS.

APPROACHES OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM

a. floating systems

Hydrodynamically balanced system (HBS) is known as the floating drug delivery system. Because FDDS have a less bulk density than gastric fluids[16], These low-density systems are one of the most effective approaches to achieving gastric retention and obtaining optimum drug bioavailability because they have enough buoyancy to float over the contents of the stomach andremain for a prolonged period of time as shown in the Figure 3 B. For medications that have absorption window in the upper small intestine or stomach, this approach is suitable Because of their lower bulk density than gastric fluids, float in the stomach for an extended duration of timewithout slowing down gastric empty rate. The drug is slowly released from the system at an appropriate rate while it floats over the stomach contents, thereby increasing gastric retention time.[17]

- ***Effervescent system***

Effervescent floating drug delivery systems liberates carbon dioxide (CO2), which lower the density of the system. They also remain float for prolonged period in the stomach andrelease the drug slowly and at the ideal rate. Swellable polymers like chitosan, methylcellulose, guar gum, and HPMC as well as effervescent substances like citric acid and sodium bicarbonate are the major components of an effervescent system.[18]

a) ***Volatile liquid/vacuum type:*** is divided into three types

i. ***Inflatable system***: It comprises a pull-out device with a hollow inside that is filledwith liquids that are volatile and evaporate at body temperature. As a result, the system floats and the chamber expands when these systems are placed into the stomach. The bioerodible polymer filament used in the inflatable chamber is composed of polymers such as polyvinyl alcohol and polyethylene.[19]

ii. ***Intragastric floating system:*** By constantly releasing the drugs for an extended period prior to it reaching its absorption site, intragastric floating (IGF) drug delivery systems can enhance the controlled release of drugs with an absorption window andensure optimal bioavailability.[20]

iii. ***Intragastric osmotically controlled system:*** A biodegradable capsule with inflated floating support congestion and an osmotic pressure-controlled drug delivery devicecan be used to attain osmotic control. Because it has zero-order release, the osmoticpump drug delivery technology is the perfect oral controlled-release formulation.[21]

b) ***Gas-generating system:*** These buoyant delivery systems work by releasing CO2 through the effervescent reaction of bicarbonate salts and citric acid. This Carbon dioxide becomes trapped in the hydrocolloid layer, lower the specific gravity andmaking it to float over time as shown in Figure 3 C.[22]

c) ***Matrix tablets****:* Matrix tablets come in two forms: single-layer and bilayer. A drug and a hydrocolloid gel are used to create single-layer matrix tablets, whereas two layers, one immediate-release, and the sustained-release are present in bilayer matrixtablets.[23][24]

- ***Non effervescent system***

The non-effervescent FDDS works by bioadhesion to the mucosal layer in thegastrointestinal tract or polymer swelling. Gel-forming hydrocolloids, polysaccharides, hydrophilic gums, matrix-forming materials like polycarbonate, polyacrylate, polymethacrylate as well as bioadhesive polymers like Carbopol is themost widely used polymer in non-effervescent FDDS.[25]

a) ***Microballoons****:* Microballoons were synthesized by the solvent evaporation method to extend the gastric residence

time. Alginate, Eudragit S and agar are the commonly used polymers for developing oral drug delivery systems. The degree of buoyancy and drug release from a dosage form relies on the amounts of polymers and the chosen solvent for the formulation.[26][27]

b) ***Alginate beads:*** Adding sodium alginate solution into a calcium chloride aqueous solution, calcium alginate precipitates. The beads undergo drying through air convection and freeze drying, forming a porous system capable of maintaining buoyancy for over 12 hours. These beads enhance GRT by over 5.5 hours.[28][29]

c) ***Microporous compartment system:*** The drug is encapsulated in a microporous compartment with pores on top and bottom walls. The device's peripheral walls werehermetically sealed to prevent contact between the gastric surface and the undissolved drug. The floatation chamber filled with trapped air in the stomach makes the delivery system buoyant in the gastric fluid.[26]

d) ***Super porous hydrogel systems:*** With this method of improving Gastric retention time with super porous hydrogels, the numerous interconnected open pores allow water to be quickly absorbed, causing the hydrogels to swell to equilibrium size in less than a minute. The average pore size of these hydrogels is greater than 100 micrometers. They have a big swelling ratio (100 or above) and are designed to be strong enough to withstand pressure from the contraction of the stomach.[26][30]

e) ***Magnetic system:*** By placing a magnet on the abdomen above the location of the stomach and incorporating a small internal magnet in the dosage form, this strategy aims to prolong gastric retention time. The precise placement of the external magnetfor the magnetic system may affect patient compliance.[26][30]

b. Non-floating system

Excipients with a density higher than stomach fluid, or high-density systems, are frequently employed as shown in Figure 3 A. In 1930, Hoelzel discovered how dosage form density affected gastric peristaltic movements (GRTs), observing that materials with higher densities had slower GRTs than those with lower densities.[31] Theclinical value of high-density pellet formulations is dubious due to the low number of clinical trials on them and the difficulty of creating high-dose pellets. Subsequent investigations must concentrate on animal experiments to examine their practical implications.[22][32]

- ***Mucoadhesive system:*** This method uses bioadhesive polymers, adhere to the stomach's mucosal surface and prolong the gastric retention period as shown in Figure3 D Among the many adhesion mechanisms are:

1. "Wetting theory": The ability of bioadhesive polymers to diffuse and makecontact with mucin layers.
2. "Diffusion theory": The entanglement of mucin with a soluble polymer or its interpenetration into the polymer's structure.
3. According to absorption theory, secondary forces like hydrogen bonding and Vanderwall's forces cause bioadhesion.
4. According to electronic theory, the mucin network and the bioadhesivesubstance are attracted to each other through electrostatic forces.[30]

- ***Swellable system:*** These are the dosage forms that swell after swallowing that the pylorus is unable to release them. Consequently, the drug remains in the stomach for an extended duration of time as shown in Figure 3 E. These systems could be referred to as "plug-type systems" since they have a tendency to remain blocked at the pyloric sphincter if their expanded diameter is more than about 12 to 18 mm.[30]

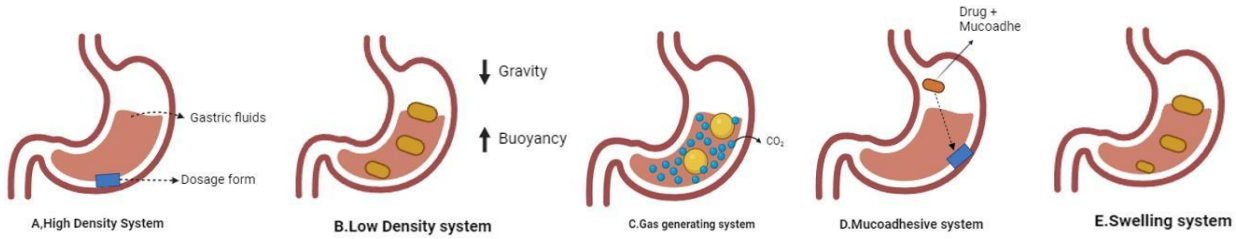

Figure 3: Approaches of GRDDS.

Floating signifies low density and Non-floating signifies high density as explained above High-density system vs. Low-density floating system is shown in **Table 1**.

Table 1: High density vs Low density.

S. No	High-Density System	Low-Density System
1.	Pellets/tablets are denser than stomach fluids, causing them to sink.	Pellets/tablets are less dense than stomach fluids, allowing them to float.
2.	Pellets/tablets should have a minimum density of 150g/ml to ensure sinking.	Pellets/tablets should be less dense than 1 g/ml to ensure floating.
3.	Can use materials like barium sulfate or titanium dioxide as coatings to increase weight and prevent toxic reactions.	Designed with low bulk densities so they float on gastric fluid and release medication slowly over an extended period.
4.	Also called a High-density sinking system.	Also called a hydrodynamically balanced system.

EVALUATION OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM

1) evaluation of powder

a) Angle of repose: The angle of repose refers to "the maximum angle formed between the surface of a powder pile and a horizontal plane." A lower angle of repose indicates improved flow properties. To determine the angle of repose, measure the height (h) of thepile and the radius (r) of its base.[33]

$$\text{Tan } \theta = h/r$$

b) Bulk density: Bulk density refers to the overall density of a material. It includes both the true volume of the interparticle spaces and the intraparticle pores. The arrangement of particles is the primary determinant of bulk density.

$$\text{Bulk density} = \text{Weight of the powder} / \text{Bulk volume of powder}^{[33]}$$

c) Percentage porosity: The total porosity expression for the calculation remained the sameregardless of whether the powder was porous or nonporous. Porosity provides information on hardness, disintegration, and total porosity.

$$\text{Percentage Porosity} = (\text{Volume of Voids} / \text{Total Volume}) \times 100\%^{[33]}$$

2) Evaluation of floating tablets

i. Buoyancy lag time: The amount of time it takes for gastroretentive formulations to move to the surface of the dissolution medium was assessed using a USP dissolutionapparatus, which was filled with 0.1 N HCl solution at a temperature of 37°C. The floating lag time, which is the time required for various dosage forms to float, was measured.[33-35]

ii. Floating time: In this test, the buoyancy of the dosage form was measured, which utilized a specific dissolution apparatus based on the type of dosage form. The dissolution medium was filled with 900 mL and was maintained at a temperature of 37°C. The duration or floating time of the drug was observed and recorded based on visual

assessment.[35]

iii. ***Specific density:*** By the displacement method, The density of the floating tablet was determined,which utilized benzene as the displacing medium. To measure the tablet density,a pycnometer was employed.[35][36]

iv. ***Swelling index:*** Tablets were individually weighed (W0) and placed in dissolution medium. The temperature was kept at 37°C, and periodically, the samples were removed using a basket. The swollen weight (Wt) of each tablet was then measured atpredetermined time intervals.[35][37]

$$\text{Percentage Swelling Index} = (Wt - W0)/\ W0 \times 100$$

Where W0 is the initial weight ofthe tablet and Wt is the weight of the tablet at time t.

v. ***Weight variation:*** As per USP, 20 tablets are individually weighed and their average weight was determined; each tablet's weight is then compared with the calculated average. No more than two tablets can exceed or deviate from the USP limit by morethan twice that limit.[35][33][38][39]

vi. ***Hardness and friability:*** The force needed to break a tablet during a diametric compression test determines its hardness. Hardness is also referred to as the tabletcrushing strength. Monsanto tester and Pfizer tester are used to test hardness. The Roche Friabilator is commonly used friability tester. 0.5 to 1.0 % weight loss in conventional compressed tablets is acceptable.[40]

vii. ***In vitro dissolution tests:*** The Drug release was examined using a paddle-type USP-II dissolution apparatus. The study is to dissolve the substance at a constant temperature of approximately 37.5°C in a suitable solvent. 5 ml samples were taken at time interval while maintaining the volume of the dissolution medium with equal volumes of fresh media. The sample's concentration was determined spectrophotometrically after appropriate dilution based on its calibration curve.[35]

2) Evaluation of microsphere and beads

Particle size analysis, surface characterization: The particle size and distribution of microspheres are measured using optical microscopy in dry state. “Scanning electron microscope” (SEM) is used for external and cross-sectional morphology analysis (surfacecharacterization).[34]

3) In vivo assessment

Gamma scintigraphy*:* This method locates dosage forms within the gastrointestinal tract to predict and correlate gastric emptying time and the dosage form's passage in the GIT. X-rays can visualize solid dosage forms containing radio-opaque materials. γ-emitting radionuclides enable indirect external observation using γ-cameras or scintiscanners.[34]

APPLICATIONS AND ADVANTAGES OF GRRDS

Sustained drug delivery: GRDDS systems have a bulk density of less than 1, they are able to float on the stomach contents for an extended amount of time.

Site-specific drug administration: This administration method is particularly helpful for medications taken to treat H. Pylori infections since it absorbs from the stomach or the firstportion of the small intestine.

The fluctuations of drug concentrations reduced: Which is a crucial characteristic for medications with a limited therapeutic index. Drug impact fluctuations are reduced, and concentration-dependent side effects linked to peak concentration can be avoided.

Enhancement of absorption: This is crucial when it comes to medications that are absorbed from the top portion of the gastrointestinal tract, and by creating these kinds of medications.[41]

CONCLUSION

Gastro retentive drug delivery systems (GRDDS) have emerged as a promising approach to address the challenges associated with conventional oral dosage forms, particularly the issue of unpredictable gastric emptying times and reduced bio-availability of drugs that are preferentially absorbed in the upper gastrointestinal tract. These systems are designed to prolong the residence time of the drug in the stomach, thereby improving the absorption and subsequent therapeutic efficacy of the medication. As a result, it is anticipated that more pharmaceutical companies will step forward in the future to develop gastro-retentivedrug delivery technology to produce superior benefits, extend patents, and improve results for their marketable formulations.

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