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Original Article

A Review Article On: Gastro-Retentive Drug Delivery System (GRDDS)

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ABSTRACT

Controlled release dosage forms have been widely utilized to enhance the effectiveness of various important medications. Nevertheless, the development processes encounter numerous physiological challenges, such as the difficulty in controlling and targeting the system to a specific area within the gastrointestinal tract, along with the highly variable nature of gastric emptying. This variability can result in unpredictable bioavailability and varying times to reach peak plasma concentrations. The aim of this review on gastro retentive drug delivery systems was to gather recent literature, with a particular emphasis on the different gastro retentive strategies that have recently emerged as prominent methodologies in the realm of site-specific orally administered controlled release drug delivery. This encompasses floating systems, swelling and expanding systems, bio/mucoadhesive systems, high-density systems, and various devices designed for delayed gastric emptying. The current review provides a brief overview of the classification, formulation considerations for gastro retentive drug delivery systems (GRDDS), factors influencing gastric retention, advantages, disadvantages, and applications of these systems.

Keywords: GRDDS, various approaches ,suitable drug candidates, evaluation parameters, advantages, disadvantages, strategies, marketed formulations , conclusion

INTRODUCTION

A new method of medication administration is represented by gastro-retentive drug delivery systems (GRDDS). Increasing a drug's duration of residency in the stomach is their main goal in order to guarantee site-specific release in the upper gastrointestinal tract for both local and systemic effects. (3) all the delivery methods to the systemic circulation, oral administration is the most practical and favoured. (1) Regular use of these drugs is necessary for their effectiveness. Additionally, because to the short gastric emptying time of 2.7±1.5 hours (h) and the intestinal transit time of 3.1±0.4 hours, oral, sustained release systems are not appropriate for medicines with low absorption fencing in the upper region of the GIT. (5) The inability of sustained release dosage forms to extend the dosage form's residence duration in the stomach and proximal section of the small intestine is a common issue. Therefore, creating formulations with sustained release that stay at the absorption site for a long time would be advantageous. One potential strategy for attaining the desired and delayed medication delivery profile in the GIT is to regulate the formulation's gastric retention time (GRT). (6) Fast gastrointestinal transit may hinder the full release of a drug in the absorption area, decreasing the effectiveness of the given dose, as most drugs are absorbed in the stomach or the initial section of the small intestine. Floating drug delivery systems present various advantages for medications with low bioavailability due to the limited absorption window in the upper region of the gastrointestinal tract. (9)

GRDDS is utilized for medications that deteriorate in the colonic area. It is also advantageous for:

– Decreasing the required dosage of the drug.
– Keeping a consistent concentration of the drug in the bloodstream.
– Minimizing variations in the therapeutic concentration of the drug. (13)

Dosage forms that stay in the stomach longer than traditional dosage forms benefit greatly from the capacity to extend and regulate the emptying time

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

because the process of gastric emptying is incredibly varied. Constricting the dose form to the appropriate region of the gastrointestinal tract is one of these challenges. (10)

Physiology of Stomach:

The stomach can be separated anatomically into three areas. Body, Antrum, and Fundus (pylorus) The smallest part made of fundus is the main centre for mixing motions and serves as a pump for stomach emptying by driving the movement of the fundus and body, which serves as a reservoir for undigested materials activities. (2) The former, which passes through the stomach and intestine every two to three hours, is stronger while fasting and serves the main purpose of clearing the upper GI tract of everything that remains. This is arranged into cycles of activity and passiveness and is known as the inter digestive myloelectric activity cycle or migrating myloelectric cycle (MMC). (6) There are four phases in each cycle, which lasts 90 to 120 minutes. The amount of the phases is determined by the blood's level of the hormone motilin. The several stages are listed below.

Phase I (basal phase): 40–60 minutes during which there is no contraction;

Phase II (pre-burst phase): Intermittent contraction period (20–40 minutes),

Phase III (burst phase): It is characterised by compatible contractions at maximum frequency that move distally, also known as the housekeeping wave. These movements are powerful and occur for a short period. This wave removes undigested material from the stomach and transfers it to the small intestine (10-20 minutes).

Phase IV: It is the transition period between phases III and I (0-5 minutes). (6)

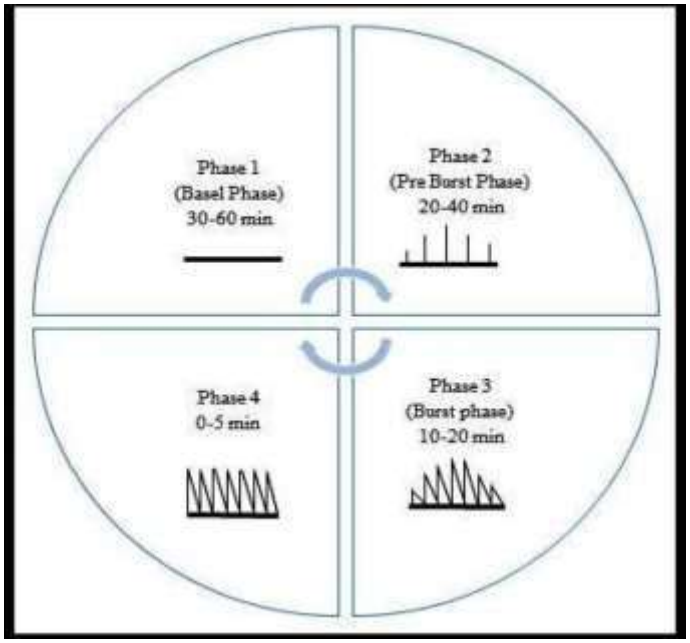


Fig. Motility Pattern in Stomach

Factors Affecting Gastric Retention:

A number of factors affect a dosage form's gastric residence time. The particle size must be between 1 and 2 mm13 in order to pass through the pyloric valve and enter the small intestine. The stomach's pH ranges from 1.5 to 2.0 when fasting and from 2.0 to 6.0 when consuming food. (1) Administering an adequate amount of water orally raises the pH of stomach contents to 6.0-9.0. Basic medications are more likely to dissolve in an eating state than in a fasted state, as the stomach does not have enough time to develop enough acid once liquid is cleared. (1) A meal with high protein, fat, or carbohydrate substance is not important if the calorie content remains constant. However, increasing acidity and caloric value slows gastric emptying time. Gastric emptying is affected by biological factors such as age, BMI, gender, posture, and disease status (e.g. diabetes, Chron's disease). People of old age experience slower stomach

emptying. Females often have a slower stomach emptying rate than males. Stress boosts the pace, while depression decreases it down. (1)

1. Density: There should be less in the dosage form than the stomach contents (1.004g/ml).

2. Dimensions: A dosage form with a diameter more than 7.5 mm has a longer stomach residence period than one with a diameter of 9.9 mm. The dose form's shape. Compared to other devices of the same dimension, the tetra hadron remained in the stomach for an extended period of time.

3. One-unit or multi-unit formulation: the other one exhibits a more consistent release profile and little performance degradation as a result of unit failure. enable a higher margin of safety against dosage form failure than single unit dosage form 12 and permit co-administration of units with distinct release profiles or containing incompatible chemicals. (11)

4. Fed or non-fed state: Periods of intense motor activity that happen every 1.5 to 2 hours are exactly determine gig motility when fasting.

5. Meal type: The stomach's motility pattern can be altered to a fed state by feeding unprocessed polymers or fatty acids, which slows down the rate at which the stomach empty and increases the release of drugs. (11)

6. The calorie Value: A meal that is strong in fat and protein may improve GRT by 4–10.

7. Feed frequency: Because of the small amount of MMC, the GRT can be raised over 400 minutes when continuous meals are given as compared to a single meal.

8. Gender: Regardless of height, weight, or body surface, the mean ambulatory GRT for males (3.4 hours) is lower than that of their age and ethnically diverse female counterparts (4.6 hours).

9. Age: Individuals over 70 have a significantly longer GRT15. (11)

10. The viscosity of the polymer: The drug release and rafting characteristics of GRDDS are significantly affected by the polymer's viscosity and how they interact.

11. Position: An upright position protects rafting forms from gastrointestinal emptying because, independent of size, the rafting form stays above the stomach contents in this position. At this point, the conventional dose form sinks to the bottom portion of the distal stomach, from where it is eliminated through the pylorus via astral peristalsis.

12. Additional aspects / Factors include:

a) the person's health conditions (diabetes, chronic illness, etc.)
b) body mass index
c) physical activity; and
d) the drug's molecular weight and lipophilicity based on its ionisation state.

Approaches For GRDDS:

The following are the several methods developed for creating a dose form that will result in an acceptable gastric retention and release inside the gastric region:

A. Floating drug delivery system (FDDS):

- Another name for floating medication delivery
- systems is low density systems. There are several
- types of floating medication delivery systems:

1. Effervescent system:

- ❖ Volatile liquid containing system
- ❖ Gas generating system:

2. No effervescent system:

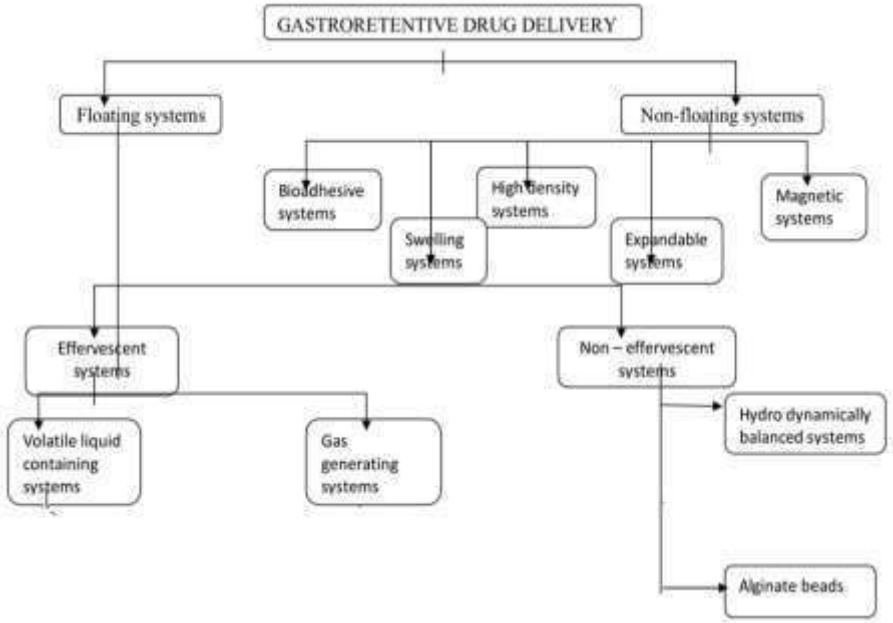
- ❖ Hydro dynamically balanced system
- ❖ Alginate beads

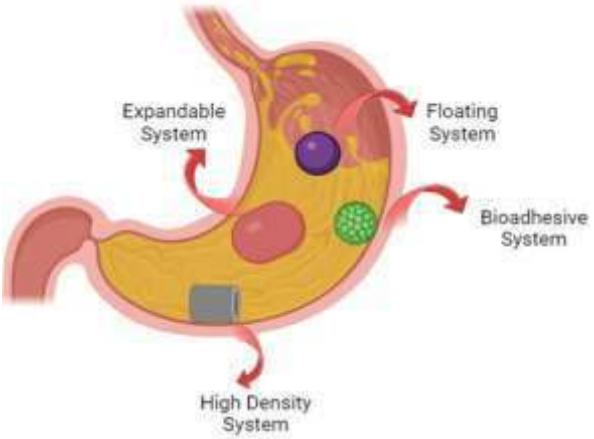
B. Non-floating system:

- Different processes keep these gastro-retentive drug
- delivery systems in the stomach, even if they don't float there.
- Non-floating system is further divided into.

1. High density drug delivery system.
2. Bioadhsive or mucoadhesive system.

3. Magnetic system.
4. Swelling System
5. Expandable System.
6. Raft forming system. (7)





A. floating drug delivery system:

Floating systems, often referred to as dynamically regulated systems, are low-density systems that have sufficient buoyancy to float above the contents of the stomach and remain buoyant there for a prolonged period of time without affecting the gastric emptying rate. As a result, the stomach retention period is prolonged and fluctuations in plasma medication concentration are better managed. Numerous buoyant systems have been made using granules, powders, pills, capsules, laminated films, and hollow microspheres.

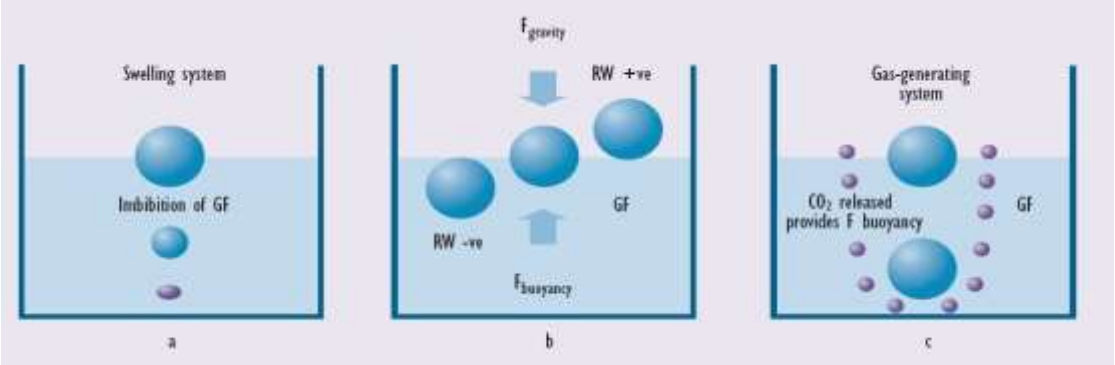
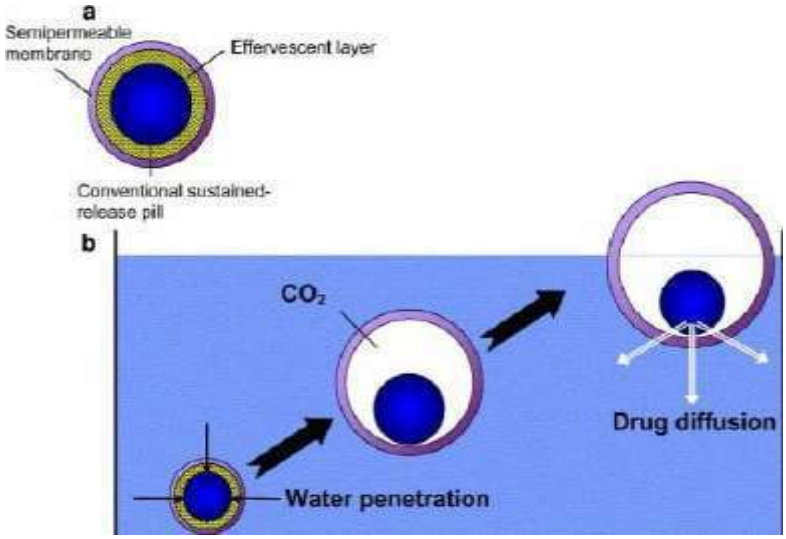


Fig. floating system

1. Effervesent floating system:

Swellable polymers and a range of effervescent-producing chemicals are used to create such systems. When the measurement dosage forms come into contact with the acidic stomach material, they are made to release CO2 and become entangled in swelling hydrocolloids, which is what gives them their light weight. To introduce gas into the floating chamber, a naturally occurring organic solvent that dissolves, like ether or cyclopentane, can volatilise. As an alternative, organic acids and carbonate-bicarbonate salts can respond by floating, producing CO2. These devices have a hollow deformable unit that alternates between an extended and a collapsed configuration before returning to the collapsed position after a predefined period of time, allowing the free release of a thin floatable system from the stomach. The recommended ratio of sodium carbonate to citric acid for optimal gas generation is 1:0.76.



a. Volatile liquid containing system:

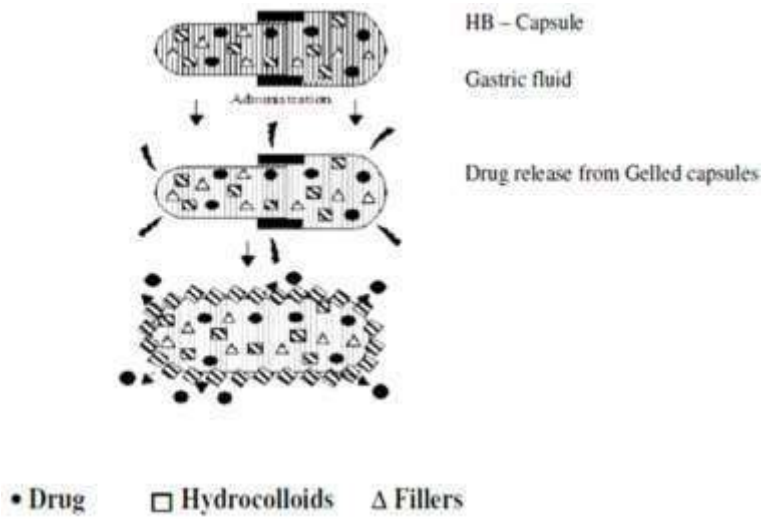
Two chambers make up this type of system, which is separated by a movable, pressure-responsive bladder. The volatile liquid is in the second chamber, while the medication is in the first. A liquid (like ether or cyclopentane) that gasifies at body temperature and causes the stomach chamber to inflate can be used to fill an inflatable chamber and maintain the GRT of a medication delivery system. The device may additionally incorporate a erodible plug made of polyethylene, polyvinyl alcohol, etc.

2. Non-effervescent floating system:

Gel-forming, highly swellable cellulosic hydrocolloids (like sodium carboxymethylcellulose, hydroxypropyl cellulose, hydroxy propyl methyl cellulose [HPMC], and hydroxyethyl cellulose), polysaccharides, or matrix-forming polymers (like polycarbophil, polyacrylates, and polystyrene) are present in high concentrations (20–75% w/w) in tablets or capsules used in non-effervescent systems. These gel formers, polysaccharides, and polymers hydrate and form a colloidal gel barrier when they come into contact with stomach contents. This barrier controls the rate at which fluid enters the device and, consequently, the medication's release.

❖ **Hydrodynamically balanced gel systems:**

The creation of manically balanced systems requires the addition of a high concentration (20–75% w/w) of gel-forming hydrocolloid to the medication, which keeps the medication afloat above the stomach contents. Alginic acid, hydroxypropyl methyl cellulose, ethyl cellulose, and other gel-forming cellulose hydrocolloids may be present in these systems. Additionally, matrix-forming polymers such polyacrylate and polycarbophil are present. These systems create a colloid gel barrier around their surface when they come into touch with stomach juices, causing the hydrocolloid to hydrate.



❖ **Alginate beds:**

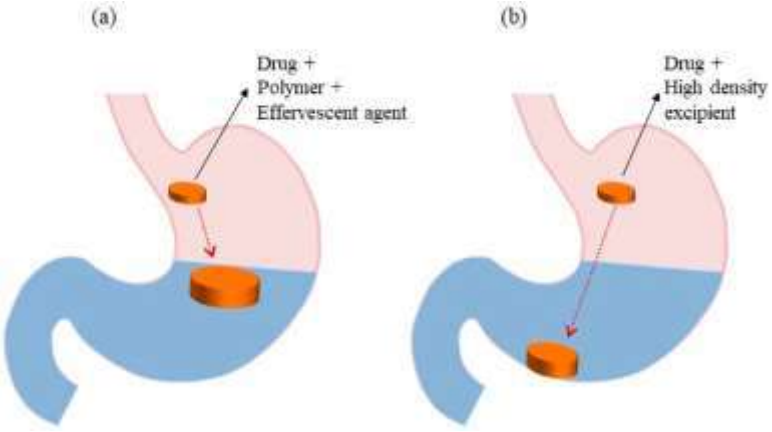
Calcium alginates that have been freeze-dried have been used to create multi-unit floating dosage forms. When sodium alginate solution is dropped into an aqueous calcium chloride solution, spherical beads around 2.5 mm in diameter can be produced. These beads are separated and dried using air. These beads are separated and dried using air. This leads to the creation of an a porous system, which keeps the stomach a float.

B. Non-floating drug delivery systems:

These systems are a type of gastro retentive drug delivery system (GRDDS) designed to remain in the stomach for an extended period without relying on buoyancy. Instead of floating on top of gastric fluids, these systems use other mechanisms to increase their residence time, providing sustained drug release to the upper gastrointestinal tract.

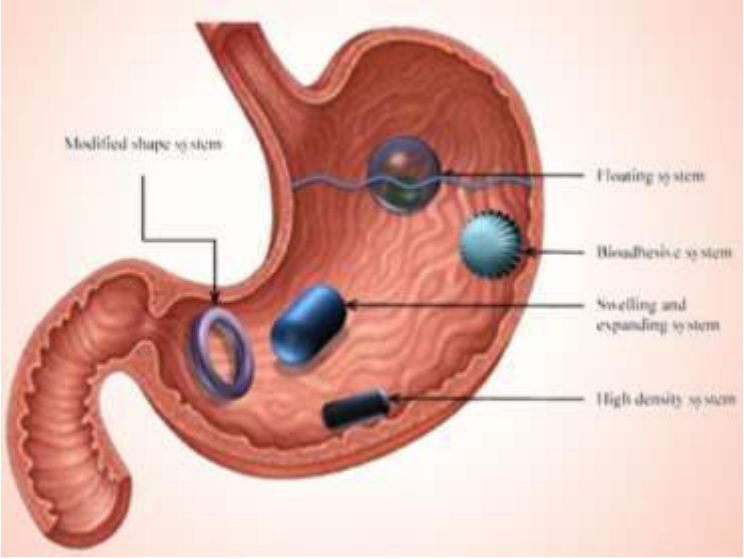
1. High density system:

These systems, which are held in place by the stomach's rugae and can tolerate its peristaltic movements, have a density of about 3 g/cm3. The lower portion of the stomach can hold such systems above a threshold density of 2.4–2.8 g/cm3. The only significant disadvantage of such systems is that they are technically challenging to produce with a high drug content (>50%) and to get the necessary density of 2.4–2.8 g/cm3.



2. Bio-adhesive Systems:

The fundamental basis of these systems is bioadhesive polymers, which attach to mucous and non-mucous membranes, such as the surface of the epithelium and mucin. The term muco-adhesion refers to bio-adhesion that is limited to the mucosa's surface. The most common ligand for accurate bio-adherence is lecithin. Non-specific bio-adhesion is dependent on the system's polymer quality. They are said to have a bio adhesive nature. (9)



The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism. These mechanisms are:

1) The wetting theory: which is based on the ability of bio adhesive polymers to spread and develop intimate contact with the mucous layers.

2) The diffusion theory: which proposes physical entanglement of mucin strands the flexible polymer

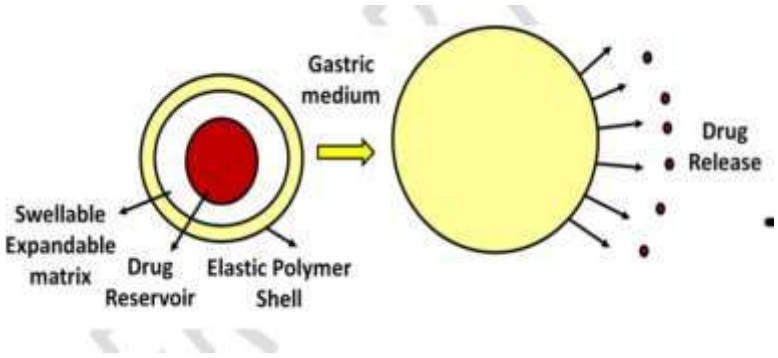
chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.

3) The absorption theory: suggests that bio adhesion due to secondary forces such as Vander Waal forces and hydrogen bonding.

4) The electron theory: which proposes attractive electrostatic forces between the glycoprotein mucin network and the bio adhesive material.

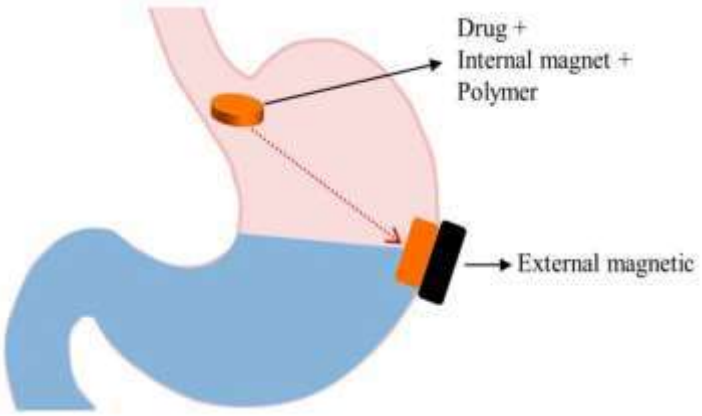
3. Swelling systems: -

These are the dosage forms, which after swallowing, swells to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer period of time. These systems may be named as 'plug type systems. Sustained and controlled drug release may be achieved by selection of polymer of proper molecular weight and swelling of the polymer retards the drug release. on coming in contact with gastric fluid, the polymer imbibes water and swells. (10)



4. Magnetic systems:

The magnetic system incorporates a small internal magnet within the dosage form, which interacts with an external magnet positioned on the abdomen above the stomach. Although this method appears effective, the necessity for precise external magnet placement may affect patient compliance remained in the targeted location for two hours (3)



Evaluation Parameters:

Assessment of Floating System for delivering drugs

1) Powder blend evaluation:

a) Repose Angle
b) Bulk Density
c) Porosity percentage

2) Tablet evaluation:

a) buoyancy properties
b) floating and dissolving behavior in vitro
c) weight fluctuation
d) hardness and friability
e) surface characterisation and particle size analysis (for floating microsphere and beads)
f) Gamma/X-Ray Scintigraphy
g) Research on pharmacokinetics

1) Powder blend evaluation:

a) Repose angle:

"The maximum angle possible between the surface of the pile of powder and the horizontal plane" is the definition of angle of repose. The flow characteristics improve when the angle of repose is reduced. By using a ruler to measure the pile's height (h) and the base's radius (r), one can determine the angle of repose. Tan $\theta = h/r$.... 1

b) Bulk Density:

The overall density of the substance is indicated by its bulk density. It comprises the actual volume of the intraparticle pores and interparticle gaps. The primary cause of bulk is the way the particles are packed.

Bulk density is calculated as follows:

powder weight divided by powder bulk volume...2, When particles are closely packed together, there may be a significant number of gaps between them. As a result, trapping powder enables the particles to travel and eliminate voids to a minimum volume.

2. Evaluation of Floating tablet:

a) Buoyancy properties:

Weight measurements are used to assess the floating behavior. Deionized water and a mock meal are the two distinct media used in the experiment. The findings demonstrated improved floating behavior in larger molecular weight polymers with slower rates of hydration, which was more noticeable in simulated meal medium than in deionized water.

b) floating and dissolving behavior in vitro:

USP dissolution equipment is typically used to conduct dissolution testing on a variety of medications. According to USP 28, "before the blade rotates, the dosage unit is allowed to sink to the bottom of the vessel."

c) Weight fluctuation:

During the compression process, composite samples of tablets typically ten are obtained and weighed.

d) Friability and Hardness:

The "force required to break a tablet in diametric compression test" is the definition of hardness. The Roche Friabilator is the name of the laboratory friability tester.

e) Surface characterization and particle size:

The optical microscopy approach is used to evaluate the size distribution and particle size of beads or microspheres in their dry state.

ADVANTAGES:

1) Optimize dose utilization in a cost-effective manner.
2) Minimize the risk of antibiotic resistance by maintaining constant therapeutic levels.
3) Improve drug release efficiency, especially for medications with short half-lives.
4) Favorably influence pharmacokinetic characteristics.
5) Promote patient compliance by reducing dosing frequency.
6) Remain buoyant in the stomach due to the lower bulk density of gastric fluid, thereby mitigating issues related to GET and GRT.
7) It lowers the frequency of doses, increasing patient compliance
8) Gastric residence duration is extended by buoyancy.

DISADVANTAGES:

1) System drawbacks for gastro-retentive drug administration Unsuitable for medications that are not very soluble in acids.
2) Drugs that are unstable in an acidic environment shouldn't be used. For instance, erythromycin.
3) medications that irritate the stomach or cause lesions when taken slowly. such as aspirin and NSAIDs.
4) medications, including corticosteroids, that selectively absorb in the gut need the stomach to contain more fluids. (2)
5) Drugs that have issues with solubility in stomach fluid are not appropriate. For example, phenytoin cause annoyance to G.I. For instance, NSAIDS. In an acidic environment, they become unstable.

CONCLUSION:

Current methods for improving the bioavailability and regulated delivery of medications with an absorption window include gastroretentive drug delivery systems. The primary gastroretentive drug delivery methods are magnetic, bioadhesive, swelling, floating, and high-density systems. These methods offer the medication in an absorbable form at the areas of best absorption in addition to regulated release. Each of these drug delivery methods has pros and cons of its own. In order to create an effective GRDDS, it is essential to take into consideration.

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