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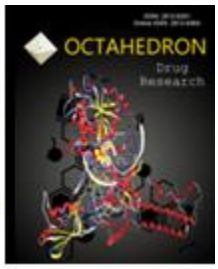

Review Article

Gastroretentive drug delivery systems: A summarized overview.

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ABSTRACT

Gastric emptying is a complicated process, thus the *in vivo* performance of drug delivery systems is unknown. Many physiological obstacles including; short gastric residency time (GRT) and variable gastric emptying time (GET), have reduced the efficacy of oral dosage forms. To combat this fickleness, attempts have been undertaken to increase the dosage form's retention time, resulting in the creation of Gastroretentive Drug Delivery Systems (GRDDS). The GRDDS can stay in the stomach for an extended period of time, increasing the gastric residence duration of medications and improving their bioavailability. These are commonly employed in the treatment of gastrointestinal illnesses and disorders for site-specific drug administration. Also, they enhance the absorption of drugs that are only soluble in the stomach. In this review, we will discuss numerous and different techniques for GRDDS such as floating systems, non-floating systems and their sub-types. A list of recent patents on GRDDS is also included, along with a full description of the assessment parameters.
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Introduction:

1. Conventional oral dosage forms

In the pharmaceutical industry, conventional oral administration is frequently employed to treat disorders. However, traditional delivery has several drawbacks; the most significant one is the lack of site specificity. Some medications can only

be absorbed at a specific location. They demand that the drug be released at a specific location or that the largest amount of drug be delivered to that location. Thus, the pharmaceutical industry is now concentrating on medications that require site specificity [1]. Gastroretentive delivery is a type of site-specific drug delivery that takes place in the stomach or intestine. It is achieved by maintaining the dosage form in the stomach and releasing the drug to a specified spot in the stomach, duodenum, or intestine. Besides, it remains in the stomach for a suitable time interval despite all physiological barriers, releases active moiety in a controlled manner, and is easily metabolized in the body [2, 3]. The fact that not all drugs are absorbed uniformly throughout the GIT, is a significant obstacle in oral controlled drug delivery. Some drugs are only absorbed in one segment of the GIT or are absorbed in different segments of the GIT with varying degrees. An 'absorption window' is a term used to describe such medication prospects. Only the medicine delivered in the region preceding and near to the absorption window is available for absorption in the case of 'narrow absorption window' pharmaceuticals. The released substance is absorbed after crossing the absorption window. With little or no absorption, the released medication goes to waste. This event greatly reduces the amount of time available for drug absorption, thereafter, resulting in lower bioavailability. As a result, various physiological obstacles, such as short gastric residency time (GRT) and variable gastric emptying time (GET), have hindered the efficacy of oral controlled drug delivery [4]. Prolonged GRT improves bioavailability, extends drug release time, lowers drug waste, and increases the solubility of drugs that are less soluble in a high pH environment [4, 5]. This has stimulated interest in the development of several GRDDS that can deliver medications with a "narrow absorption window" and increase bioavailability. Gastroretentive dosage forms are meant to stay in the gastrointestinal region for a long time and release drug molecules, allowing for sustained and prolonged drug input into the upper part of the GIT and providing excellent bioavailability. As a result, they not only extend dosing intervals, but also improve patient compliance beyond that of currently available controlled release dosage forms. This technique is very useful for delivering insoluble and sparingly soluble drugs. Gastroretentive dosage forms greatly improved GIT pharmacotherapy through local drug release, resulting in high drug levels at the gastric mucosa (eradicating Helicobacter pylori from the submucosal tissue of the stomach), allowing for the treatment of gastric and duodenal ulcers, esophagitis, and other gastrointestinal conditions while reducing the risk of gastric carcinoma and the administration of non-systemic, controlled release antacid formulations [3, 4]. Many technological attempts have been made to devise various controlled release GRDDS, such as high density (sinking) systems that are retained in the stomach bottom [6], low density (floating) systems that confers buoyancy in gastric fluid [7], muco-adhesive systems that involves bio-adhesion to stomach mucosa [8], un-foldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach [9], super porous hydrogel systems [10], magnetic systems [4].

2. Anatomical and physiological aspects of gastroretentive dosage forms

Between the esophagus and the small intestine is the stomach, which is an extended part of the digestive tract. The stomach contracts when it is empty, and the mucosa and submucosa are thrust up into folds called rugae. The secretory epithelial cell that covers the stomach and spreads into gastric pits and glands is divided into four categories.

- Alkaline mucus is secreted by mucous cells.
- HCl is secreted by parietal cells.
- Pepsin is secreted by the chief cells.
- Gastrin hormone is secreted by G cells.

The stomach is where gastroretention occurs. The anatomy and physiology of the stomach contain parameters that should be addressed when developing gastroretentive dosage forms. Its volume changes depending on the amount of distension: up to 1500 mL after a meal; when the food has been emptied, it collapses to a resting capacity of 25-50 mL. The stomach is separated into three anatomical regions: fundus, body, and antrum (pylorus). The fundus and body of the proximal part serve as a reservoir for undigested material, whilst the distal part (antrum) is the focal point for

mixing motions and works as a pump for stomach emptying through propulsive action [4, 8] as shown in Figure 1 **Error! Reference source not found.Gastrointestinal motility and emptying of food**

Gastric emptying happens in both fasted and fed states, but the pattern of motility differs significantly between the two. An inter-digestive series of electrical events occurs during a fasting condition, cycling through the stomach and intestine every 2 to 3 hours [4, 9]. Wilson and Washington explain that this is known as the inter-digestive myoelectric cycle or migrating myoelectric cycle (MMC), which is divided into four phases:

• Phase I (Basal phase), also known as the quiescent stage, lasts from 40 to 60 minutes and is characterized by a lack of secretary, electrical, and contractile activity.

• Phase II (Preburst phase) lasts from 40 to 60 minutes and is characterized by intermittent action potential and contractions. The strength and frequency of the attacks gradually increase as the phase advances.

• Phase III (Burst phase) is a 4 to 6 minutes' period of powerful big regular contractions known as 'housekeeper waves,' which sweep out undigested material.

• Phase IV is a 0 to 5 minutes' transition interval between phases III and I of two consecutive cycles.

The pattern of contractions shifts from a fasted to a fed condition once food is consumed. This is referred to as the digestive motility pattern and comprises constant concentrations like phase II of the fasting state. Food particles larger than 1 mm are driven into the pylorus in suspension state because of these contractions. The beginning of MMC is delayed in the fed state, resulting in a slower stomach emptying rate [4, 10].

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in a slowdown of gastric emptying rate [2, 10].

3. Factors controlling gastroretention of dosage forms

3.1. Dosage form densities

GRT is a function of dosage form buoyancy that is affected by dosage form density. Dosage forms with a lower density than the gastric contents can float in the gastric fluids, causing gastroretention, whereas high density systems sink to the bottom of the stomach, causing gastroretention. The dose system may be isolated from the pylorus in either location. Floating property requires a density of less than 1.0 gm/cm^3 [4, 5].

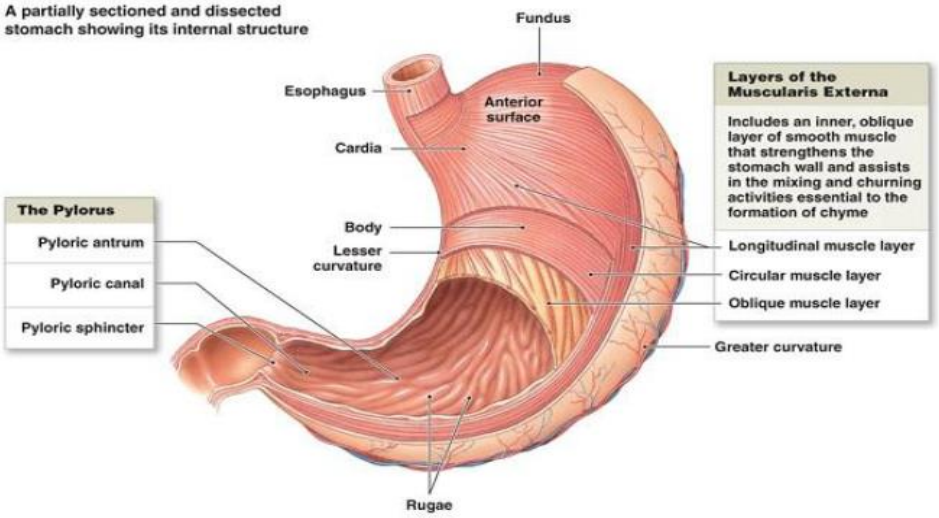

Figure 1. Physiology of stomach

3.2. Shape and size of the dosage form

In constructing indigestible single unit solid dosage forms, the shape and size of the dosage forms are critical. In most circumstances, the larger the dosage form, the higher the GRT, because the larger dosage form would not be able to move through the pyloric antrum into the intestine as rapidly [4]. Dosage forms with a diameter of more than 7.5 mm had a longer stomach residence duration than those with a diameter of 9.9 mm. When compared to other shapes, ring-shaped and tetrahedron-shaped devices with a flexural modulus of 48 and 22.5 kilo-pounds/inch^2 had a better GRT (90 -100% at 24 hours) [4, 11].

3.3. Food intake and its nature

Food intake, viscosity and volume of food, caloric value, and feeding frequency all have an impact on dosage form gastroretention. Food in the GIT usually improves the GRT of the dosage form, which increases medication absorption by allowing the drug to linger at the absorption site for longer. GRT can be enhanced by 4-10 hours with a high-protein, and high-fat meal. An increase in acidity and caloric value decreases GET, which can improve dosage form gastroretention [4, 12]. Due to the lower frequency of MMC, GRT can increase by almost 400 minutes when multiple meals are consumed instead of a single meal.

3.4. Effect of gender, posture and age

Females' stomach emptying rates are typically slower than males. Individuals in an upright, ambulatory, or supine position have no significant differences in mean GRT. Gastric emptying is slower in elderly people (those above the age of 70) [4, 13].

3.5. Disease state

GRT is increased in conditions such as gastric ulcers, diabetes, and hypothyroidism. GRT is lowered due to hyperthyroidism and duodenal ulcers. Diseased states of the individual (e.g. diabetes, gastrointestinal diseases, Chron's disease) can alter gastroretention of oral dosage forms [4]. Drugs acting as anticholinergic agents (e.g. atropine, propantheline), opiates (e.g. codeine), and prokinetic agents (e.g. metoclopramide, cisapride) can alter gastroretention of oral dosage forms [4, 14].

3.6. Electrolytes and osmotic pressure

Water, isotonic solution, and low-concentration solution quickly empty the stomach, whereas a larger electrolyte concentration slows down the rate of gastric emptying [2, 10, 15].

Advantages of GRDDS

- Reduces dosing frequency, which improves patient compliance.
- Because fluctuations in plasma drug concentration are minimized and a desired plasma drug concentration is maintained by continuous drug release, bioavailability improves despite the first pass effect.
- Because of the buoyancy, the time spent in the stomach is extended.
- Enhanced absorption of medications that are only soluble in the stomach.
- Drugs are released in a regulated manner over a long period of time.
- It is possible to administer drugs to the stomach in a site-specific manner.
- Microspheres are superior to single-unit floating dosage forms in that they distribute medicine uniformly and without the risk of dose dumping.
- Because of the continuous release effect, gastrointestinal discomfort is avoided.
- Short half-life medicines can have a better therapeutic effect [2].

6. Disadvantages of GRDDS

- Floating systems have the limitation of requiring a high amount of fluids in the stomach to float and function properly. As a result, with this dosage form, increased water intake is recommended.
- If the floating dose form is not large enough, contractile waves may sweep it away in supine posture (like sleeping). As a result, the patient should avoid taking the floating dose form right before night.
- Pharmaceuticals with low solubility in acidic environments, as well as drugs that irritate the stomach mucosa, cannot be included in GRDDS.
- Bio/muco-adhesives systems have issues with mucus layer turnover, thick mucus layer, and soluble mucus limitations.

- The swellable dosage form must be able to swell quickly before exiting the stomach and acquire a size greater than the pylorus aperture. It must be able to withstand the housekeeper waves of MMC's Phase III. Many factors influence gastric retention, including stomach motility, pH, and the presence of food. Because these variables are never consistent, buoyancy cannot be anticipated.
- The fast turnover rate of stomach mucus is a big barrier for a bio adhesive system. Bio adhesive drug delivery technologies have the potential to bond to the esophagus. Drugs with GIT stability and solubility issues are not appropriate choices for these systems.

7. Potential drug candidates for gastroretentive drug delivery systems

- Drugs with a small absorption window in the GI tract (e.g. L-DOPA, p-aminobenzoic acid, furosemide, riboflavin) [4, 5].
- Drugs that have a local effect in the stomach (e.g. misoprostol, antacids) [4].
- Drugs that are unstable in a colonic or intestinal environment (e.g. captopril, ranitidine HCl, metronidazole) [4, 16].
- Drugs that disrupt the usual microflora in the colon (e.g. antibiotics used for the eradication of Helicobacter pylori, such as tetracycline, clarithromycin, amoxicillin) [4, 17].
- Drugs with a low solubility at high pH levels (e.g. diazepam, chlordiazepoxide, verapamil) [4].

8. Techniques of GRDDS

8.1. Floating Systems

Floating Drug Delivery Systems (FDDS) have a lower bulk density than gastric fluids, allowing them to float in the stomach for longer periods of time without altering the rate of gastric emptying. The medicine is released slowly and at a controlled pace from the system while it is floating on the gastric contents. The residual system in the stomach is emptied once the medicine has been released. As a result, the GRT rises and variations are better controlled [18].

Advantages of FDDS

- These systems are especially useful for medications like riboflavin and furosemide, which are specifically absorbed from the stomach or the proximal section of the small intestine.
- Fluctuations in plasma drug concentration are reduced, and undesirable effects associated with peak concentrations can be avoided. This is particularly important for medications with a limited therapeutic index.
- It has been discovered that the efficacy of medicaments provided using the sustained release principle of floating formulation is unaffected by the site of administration.
- Even at the alkaline pH of the intestine, complete absorption of the medicine from the floating dosage form is expected. The medicine dissolves in gastric juice and then passes through the stomach.
- When there is a lot of activity in the intestines and a short transit time, as in some types of diarrheas, poor absorption is expected. In such cases, it may be preferable to retain the medicine in a floating state in the stomach to elicit a better response.
- Drugs with low bioavailability due to site specific absorption from the upper gastrointestinal tract could be manufactured as floating drug delivery devices, allowing them to be absorbed more effectively. When compared to commercially available LASIX tablets (33.4%) and enteric coated LASIX long product, floating dosage forms could provide a considerable improvement in bioavailability (42.9%) [19].

Disadvantages of FDDS

- The most significant disadvantage of a floating device is that it requires enough stomach fluids to float without sinking. This constraint can be solved by covering the dosage form with bio adhesive polymers that stick to the gastrointestinal mucosa easily.
- Drugs that are readily absorbed throughout the gastrointestinal system and undergo extensive first-pass metabolism are the most suitable candidates.
- Certain medications in the floating system may irritate the mucosal linings of the stomach.
- Gastric emptying in floating systems can happen at any time and is greatly dependent on the size of the system. As a result, patients should not take their dosage before going to bed.
- FDDS must be taken after a meal, although the duration of medication residence and emptying is

affected by the digestive condition, which impacts absorption.

- The dosage form's capacity to float is determined by its hydration condition. To maintain these pills floating *in vivo*, occasional water administration (a tumbler full every 2 hours) is required.
- The capacity of a medicine to float in the stomach is determined by how the individual is positioned.
- Drugs that have problems with solubility or stability in the stomach fluid are not suited for FDDS.
- Certain medications, such as nifedipine, which are rapidly absorbed in the stomach and have successful first-pass metabolism, are not suited because slow gastric emptying can result in reduced systemic bioavailability.
- These systems are represented as a solution, which makes them more prone to stability issues. Chemical (oxidation, hydrolysis, etc.) and microbiological deterioration are the causes of these problems.
- The formulation should always be well stored as improper storage can result in stability issues. This is related to a pH change in the system because of long-term storage or storing at an incorrect temperature.
- The production of gel within the package is induced by the exposure of specific polymers to radiations (e.g. UV, Visible, Electromagnetic, etc.).

8.1.1. Effervescent Floating Systems

A gas-generating agent and volatile liquids are used in effervescent floating systems. This method has been used for both single-unit and multi-unit systems. Effervescent substances such sodium bicarbonate, calcium carbonate, tartaric acid, and citric acid are combined with hydrophilic polymers [18, 20] in the gas-generating floating system. CO_2 is released when this system comes into touch with stomach fluid due to the effervescent agent's reaction with the gastric fluid. The CO_2 gas is trapped in the hydrocolloid matrix, which gives the pill buoyancy and affects medication release qualities [21]. Volatile liquids such as ether and cyclopentane are delivered into an inflatable chamber in volatile liquid systems, where they volatilize at body temperature, allowing the chamber to be inflated in the stomach [22]. In this technology, hydrophilic polymers are frequently utilized to modulate the medication release rate. Single- and double-layer effervescent floating tablets, as well as multiple-unit effervescent floating systems [23, 24], are the two types of effervescent floating systems. Single-layer effervescent tablets are made by mixing the effervescent agent, polymer, medication, and excipients together closely. In bilayer effervescent floating tablets, however, one layer contains the medicine, polymer, and CO_2 gas-generating agent, while the other layer contains an immediate-release drug and excipients without CO_2, as well as the polymer. Sodium bicarbonate in HPMC matrix formulation was employed to increase GRT by increasing the hydration volume of the dosage form and increasing the surface area of drug diffusion in a recent study [24]. Furthermore, increasing the amount of sodium bicarbonate reduced the drug release rate from the matrix, which could be attributed to CO_2 gas bubbles obstructing the diffusion channel [24]. This method was also used to assess the *in vitro* and *in vivo* behavior of ciprofloxacin hydrochloride effervescent floating tablets [25]. Sustained-release pills are used as seeds in multiple-unit effervescent floating systems, which are enclosed by double layers. Sodium bicarbonate, calcium carbonate, and tartaric acid are used as effervescent agents in the inner layer, whereas polymers having swelling capabilities are used in the outer layer [23]. A low-density system may cause issues in the GIT, such as adhering together or being clogged, which can cause stomach irritation. To float and perform properly, this system requires a lot of water in the stomach. As a result, medicines that irritate the stomach mucosa are not appropriate for low-density systems [23, 26-28].

Advantages of Effervescent Floating System

- Increases the drug's oral bioavailability.
- Enhanced biotransformation in the first pass.
- Sustained drug delivery/reduced dosing frequency.
- Reduced drug concentration variations.
- Improved selectivity in receptor activation.
- Body counteractivity is reduced.

- A period spent over a critical concentration (effectiveness).
- Colon activity was reduced to a minimum.
- The selectivity of receptor activation has improved.

Mechanism of Floating Effervescent Tablets

When an effervescent floating dosage form comes into touch with gastric fluid, it swells up, allowing the medicine to slowly release without the tablet disintegrating. The pill creates effervescence by releasing CO_2 gas when it comes into touch with stomach juice. The tablet begins to float once the fluid has penetrated it. As a result, GRT is raised, and variations in plasma drug concentrations are better controlled [29].

Method of Preparation of Floating Effervescent Tablets

A. Direct compression

It is possible to process a medication with an excipient without the use of granulation or other unit processes. Direct compression is a method of tablet manufacturing that is employed when the formulation ingredients can flow uniformly into a die cavity.

B. Wet granulation

The granulating fluid can be used alone or in conjunction with a binder or granulating agent that is dissolved in a solvent. Granules are formed by mixing powders and combining them with the cohesive characteristics of the granulating agent.

C. Dry Granulation

It is a technique that involves compacting powder particles into huge pieces or compacts, which are then broken down into granules, which can then be processed into dosage forms.

8.1.1.1.1. Gas – Generating Systems

8.1.1.1.2. Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS)

These are formulated by intimately mixing the CO2 generating agents and the drug within the matrix tablet. These have a lower bulk density than gastric fluids, so they float around in the stomach for a long time, slowing down the gastric emptying rate. The drug is released from the floating system at a controlled rate, and the residual system is evacuated from the stomach when the drug has been released completely. As a result, the GRT rises, and fluctuations in plasma drug concentration are better managed [30].

8.1.1.1.3. Intra Gastric Bilayer Floating Tablets

These are compressed tablets with two layers, one for immediate release and the other for sustained release [30].

8.1.1.1.4. Multiple Unit type floating pills

These systems are made up of 'seeds' that are surrounded by multiple layers of sustained release pills. Effervescent agents make up the inner layer, while a swellable membrane layer makes up the outer layer. When the system is submerged in dissolving liquid at body temperature, it lowers immediately and subsequently produces inflated pills that float because their density is lower. CO2 generation and trapping inside the system result in a lower density [30].

8.1.1.2. Volatile liquid containing systems

8.1.1.2.1. Intragastric floating systems

These systems float in the stomach thanks to a floating chamber filled with air, vacuum, or innocuous gas, and a drug reservoir encased inside a tiny porous compartment. The top and bottom surfaces of this micro porous compartment have pores, whereas the peripheral walls of the reservoir compartment were entirely sealed to prevent any physical contact of the undissolved medication with the stomach walls as seen in **.** [31].

Inflatable systems

These systems use an inflatable chamber filled with liquid ether, which gasifies at body temperature and inflates in the stomach. A drug reservoir is enclosed in a gelatin capsule inside this inflatable chamber. The capsule dissolves after oral administration, releasing the drug reservoir along with the balloon as indicated in Error! Reference source not found..

Intragastric osmotically controlled systems

A biodegradable capsule contains an osmotic pressure-controlled drug delivery device and an inflatable support. When the inflatable capsule reaches the stomach, it disintegrates and releases the osmotically regulated drug administration as shown in

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8.1.2. Non-Effervescent Floating System

The principle of non-effervescent FDDS

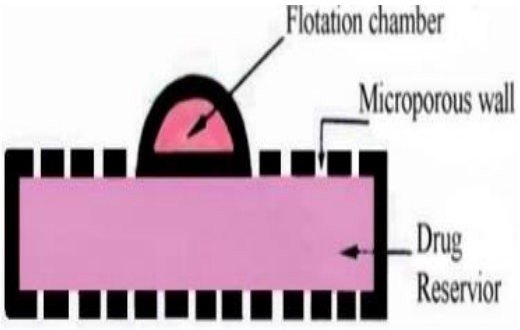

Figure 1. Intragastric floating system.

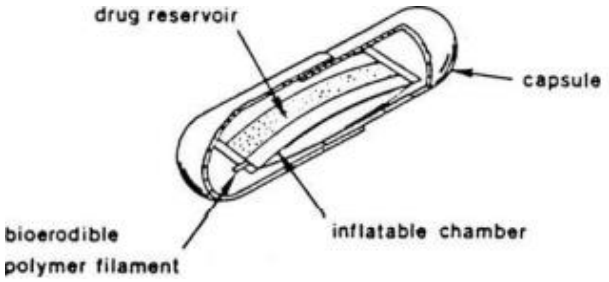

Figure 2. Inflatable system.

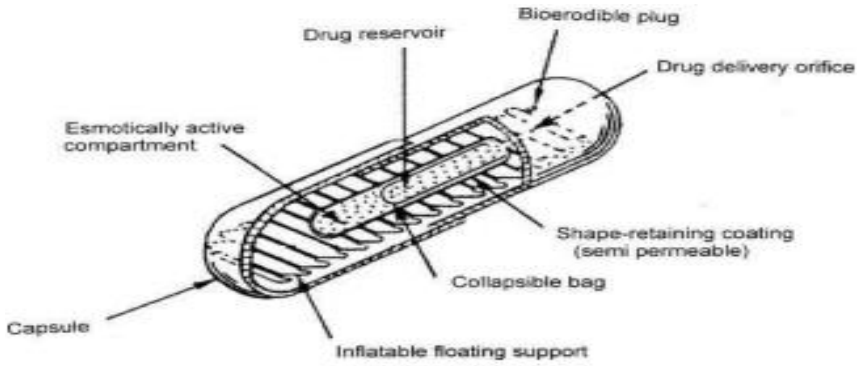

Figure 3. Intragastric osmotically controlled system.

is based on polymer swelling or bio-adhesion to the mucous membrane in the Gastrointestinal system. Gel forming or highly swellable cellulose type hydrocolloids, water - soluble gums, polysaccharides, and fiber forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene, and bio-adhesive polymers such as Chitosan and carbopol are the most used additives in non-effervescent FDDS [32].

8.1.2.1. Colloidal gel barrier system

These systems contain drugs that have gel-forming hydrocolloids in them, allowing them to float in the stomach contents. This prolongs GRT and optimizes the amount of medication in solution at absorption sites for quick absorption. This system contains a high concentration of one or more highly soluble cellulose type hydrocolloids, such as hydroxypropyl cellulose and hydroxyethyl cellulose. When this hydrocolloid comes into touch with gastric juice, it hydrates and creates a colloid gel barrier around its surface, which aids in drug release [33].

8.1.2.2. Microporous Compartment system

A drug reservoir is contained inside a microporous compartment with pores along the top and bottom walls in this technology. The drug reservoir compartment's peripheral walls are entirely sealed. This seal prevents the undissolved medication from coming into direct touch with the stomach surface. In the stomach, the floating chamber containing the delivery system permits it to float above the gastric content enclosed air. Gastric fluid enters through an opening, dissolves the drug, and transports the dissolved drug across the intestine for absorption on a continuous basis [33].

8.1.2.3. Alginate beds

The freeze-dried calcium alginate was utilized to create multi-unit floating dosage forms. Calcium alginate can be precipitated by dropping sodium alginate solution into aqueous calcium chloride solution to make spherical beads with a diameter of around 2.5 mm. The beads are then separated, snap-

frozen in liquid nitrogen, and freeze-dried at -40°C for 24 hours, resulting in a porous system with a floating force of more than 12 h. More than 5.5 hours of residence time was achieved using these floating beads [33].

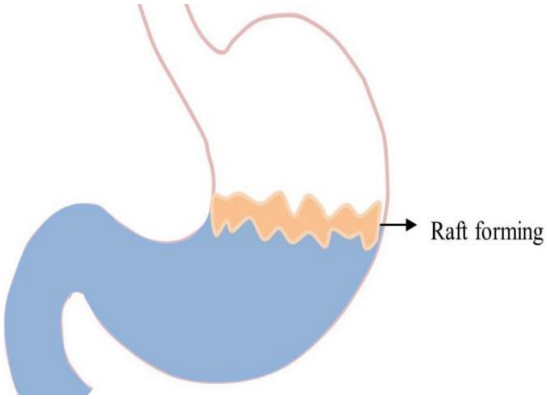

Figure 4. The barrier generated by a raft-forming system.

8.1.2.4. Hollow Microspheres/Microballons

A novel emulsion solvent diffusion method was used to prepare hollow microspheres with drug in their outer polymer shelf. An agitated solution of poly vinyl alcohol (PVA) that was thermally controlled at 40 °C was poured into an ethanol/ dichloromethane solution of the drug and an enteric acrylic polymer. The evaporation of dichloromethane created in the internal cavity of the polymer and drug microsphere generates the gas phase in the dispersed polymer droplet. For more than 12 h, the microballoon floated continuously across the surface of an acidic dissolving fluid containing surfactant [33].

8.1.3. Raft-Forming System

For the administration of drugs for GI infections and diseases, raft forming systems have gained a lot of attention. The production of a viscous cohesive gel in contact with stomach fluids, where each section of the liquid expands to form a continuous layer called a raft, is one of the mechanisms involved in raft formation

. Because of the low bulk density caused by CO_2 production, this raft floats on gastric contents. To make the system less dense and float on the stomach fluids, it mainly contains a gel forming agent and alkaline bicarbonates or carbonates responsible for CO_2 creation [34]. Nabarawi et al. designed a mebeverine hydrochloride-controlled release floating raft system and tested different excipients for their floating characteristic and in vitro controlled-release. When it expands and entraps CO2 bubbles formed by the reaction of carbonates with stomach juice, it creates a thick and cohesive gel [35]. Raft forming polymeric delivery methods include advantages like as ease of administration and reduced administration frequency, greater patient compliance, comfort and enhance therapeutic effectiveness.

Evaluation of Floating System

A. *In Vitro* method:

1) Dissolution study

To evaluate a floating drug delivery system, Gohel et al presented a more applicable *in vitro* dissolving approach (for tablet dosage form). A 100-mL glass beaker was modified by adding a side arm to the bottom of the beaker, allowing it to accommodate 70 mL of 0.1 mole. liter^{-1} HCl dissolution medium and sample collecting. To mimic stomach acid secretion, a burette was set above the beaker and delivered the dissolving medium at a rate of 2 mL/min. The modified dissolution apparatus was compared to USP Dissolution Apparatus 2 in terms of performance (Paddle). The USP dissolving device revealed that the tablet adhered to the shaft of the paddle. With the USP dissolve apparatus, an issue of tablet adherence to the shaft of the paddle was observed. In the proposed dissolve procedure, the tablet did not adhere to the agitating device. In the proposed technique, drug release followed zero-order kinetics. Because an attempt is made to imitate *in vivo* parameters such as stomach volume, gastric emptying, and gastric acid secretion rate, the proposed test may show good *in vitro in vivo* association [37].

B. *In vivo* method:

1) X-Ray method

Nowadays, X-Ray is a relatively common evaluation parameter for floating dosage forms. It aids in the location of dosage forms in the GIT, as well as the prediction and correlation of stomach emptying time and dosage form passage in the GIT. The incorporation of a radio-opaque substance into

a solid dosage form allows it to be viewed using X-rays.

2) Gamma-Scintigraphy

For evaluating gastroretentive formulations in healthy volunteers, gamma-emitting radioisotopes compounded into CR-DFs has become the gold standard. DF is compounded with a small quantity of a stable isotope, such as Sm, during its manufacture. The related ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technology, and the laborious and expensive manufacture of radiopharmaceuticals are the main disadvantages of gamma - scintigraphy.

8.2. Non-floating Systems

8.2.1. Muco-adhesive system

Muco-adhesion is a method of drug delivery that make use of the bio-adhesion of specific polymers, which make them stick to mucous membranes. Bio-adhesion is an interfacial phenomenon in which two surfaces stick together, it's possible that the connection is made between an artificial material and a biological substrate such as the adhesion between a polymer and a biological membrane. When it comes to a polymer linked to a mucosal mucin layer, The word "muco-adhesion" is used to describe the adherence of cells in the mucosa [38].The muco-adhesion extends the formulation's retention time at the absorption site in the GIT, resulting in a longer-lasting release action [39].

Mechanisms of Muco-adhesion:

Muco-adhesion is a phenomenon involving wetting, adsorption, interpenetration of polymer chains [40]. The mechanism of muco-adhesion is as follows;[41]

There are three stages in the process of bio-adhesion as seen in .

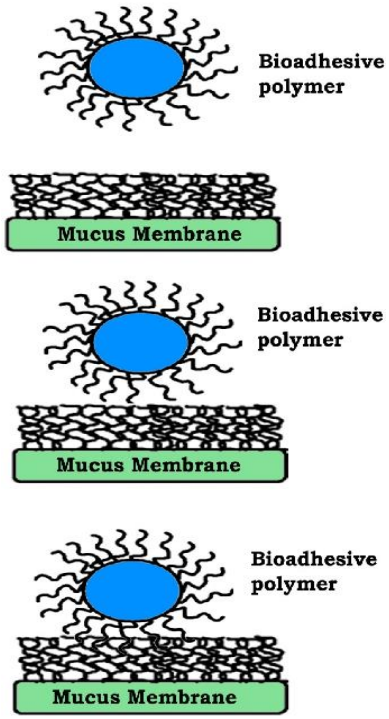

Figure 5. Mechanism of bio-adhesion [42].

stage 1: An intimate contact between a Bio-adhesive and a membrane, resulting from either sufficient wetting of the Bio-adhesive and the membrane or bio adhesive swelling.

Stage 2: is when the bio-adhesive is adsorbed into the tissue's service.

Stage 3: Interpenetration of the polymeric chains.

Theories of muco-adhesion:

There are five general adhesion theories that have been adopted to muco-adhesion research:

I. **The wetting theory**

The wetting theory is generally applied in liquid systems and involves surface and interfacial energy. The ability of a liquid to spread spontaneously over a surface must be considered for the adhesion development. The affinity of a liquid for a surface may be determined using techniques such as contact angle goniometry, which measures the liquid's contact angle with the surface [43].

To obtain favorable conditions for appropriate spreadability, it is suggested and recommended that the contact angle be kept near to or equal zero as illustrated in [44].

II. The adsorption theory

This theory assume that the bio-adhesive connection created between an adhesive substrate and tissue is attributed to weak Van der Waals forces and hydrogen bond formation. It is one of the most largely accepted bio-adhesion theories [46].

III. The electrostatic theory

The development of two electrical layers at the interface and the use of attractive forces to maintain contact between the two layers, as well as the

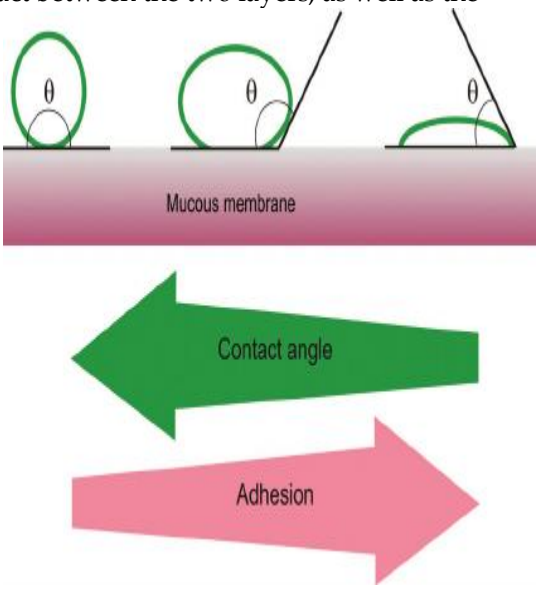

Figure 6. Influence of contact angle between device and mucous membrane on bio-adhesion [45].

transfer of electrons between the mucin and muco-adhesion interface, enhance the formation of an electrical double layer. Attraction forces across this electrical double layer are thought to be responsible for the bio-adhesive force. Because of the electron gradient atmosphere on both sides, the entire migration of electron exchange between the muco-adhesive system and mucus aids in the onset of adhesion [47].

IV. The diffusion theory

The interpenetration of both polymer and mucin chains to a required depth to establish a semi-permanent adhesive connection is explained by diffusion theory. The adhesion force is thought to increase with the degree of penetration of the polymer chains. The diffusion coefficient, the flexibility and composition of the muco-adhesive chains, motility, and contact duration all influence the penetration rate. According to the study, the needed depth of interpenetration to form an effective bio-adhesive bond is between 0.2 and 0.5 m [43].

V. The mechanical theory

According to the mechanical principle, adhesion is caused by the fitting of a liquid adhesive into irregularities on a rough surface after it has set [43].

Factors affecting muco-adhesion [38]

A - Polymer related factors:

1-Molecular weight

The muco-adhesive force rises with polymer molecular weight up to 10000, beyond which it has little impact.

2-Concentration of active polymers

The greater the polymer concentration, the stronger the muco-adhesion in solid dosage forms like tablets. There is an optimal polymer concentration that results in the best muco-adhesion.

3-Flexibility of polymer chain

Interpenetration and expansion need a high level of flexibility.

B- Environment related factors:

1-pH: The charge on the surface of mucus and polymers is affected by pH.

2-Applied strength: It is important to provide a specific strength to place a solid muco-adhesive system.

3-Initial contact duration

As the initial contact duration increases the strength of muco-adhesion increases.

4-Swelling: Swelling is influenced by the concentration of polymers as well as the presence of water.

C-Physiological variables:

1-Mucin turnover

a-The mucin turnover is predicted to reduce the muco-adhesive's residence time on the mucus layers.

b-Mucin turnover produces a larger number of soluble mucin molecules.

2-Diseased state: Mucus has been shown to modify its physicochemical characteristics in diseased states such as the common cold, stomach ulcers, ulcerative colitis, bacterial and fungal infections.

Applied Commercial Muco-adhesive Drug Delivery System

Sucralfate: Aluminum hydroxide (drug) formulated with Sucrose octasulfate (polymer) targeting gastric ulcers [48].

Evaluation of muco-adhesive dosage form

A. Methods determining tensile strength

The most prevalent technique for measuring bio-adhesion test is the tensile strength method, according to a literature review. McCarron et al. and Donnelly have published detailed reports on the use of a commercial instrument, a texture profile analyzer that operates in the laboratory as seen in [49]. The bio-adhesive test mode is used to assess how much force is required to remove bio-adhesive films from excised tissue cultured *in vitro*.

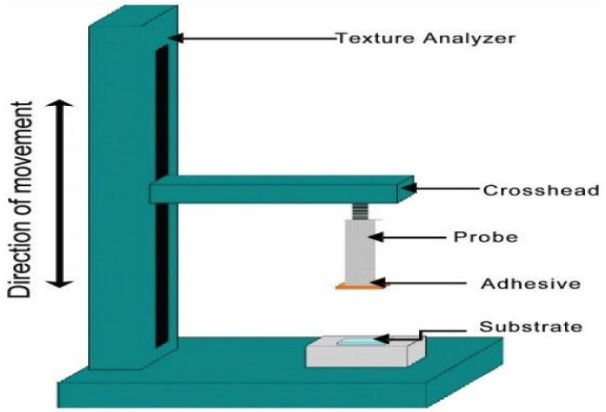

Figure 7. Texture profile analyzer in bio-adhesion test mode.

B. Falling Liquid Film method

Rango Rao and Buri offer a new technique in which the mucous membrane of choice is inserted in a cylindrical tube made of stainless steel that has been longitudinally sliced. This support is positioned in a cylindrical chamber that is kept at 37 ° C, Pumping an isotonic solution.

The fluid is collected in a beaker after passing through the mucous membrane. In the case of particle systems, the amount left on the mucosal membrane can then be quantified using a coulter counter. The non-adhered muco-adhesive in semi-solid media can be measured using high performance liquid chromatography. This method allows for the visualization of the production of a liquid-crystalline mesophase on the mucosal membrane after fluids have flowed over it, as well as examination using polarized light microscopy [50-52].

C. Swelling index

The dosage form can quantify the degree of swelling in terms of percent weight gain. The following formula is used to estimate the swelling index [53, 54].

Swelling Index (S.I.) = $(W_t-W_o) / W_o$

Where, S.I. stands for Swelling Index.

W_t = Tablet weight at time t.

W_o is the weight of the tablet before it is placed in the beaker.

Advantages of muco-adhesive drug delivery system

1) The dosage form is targeted and localized at a certain location at the gastric.
2) Muco-adhesive systems are recognized for ensuring intimate connections between the dosage form and the absorptive mucosa, resulting in substantial drug flow at the absorbing tissue [55].
3) Patient compliance has improved.
4) Enhance plasma level control.
5) The total amount of dosage supplied is being reduced [56].
6) Gastro-retentive dosages reduce medication's concentration and effects fluctuations.
7) The controlled, gradual distribution of medications in gastro-retentive dose forms ensures adequate local action at the affected location, reducing or eliminating systemic drug exposure.
8) The side effects of this site-specific medication administration are reduced [57].

Limitations of muco-adhesive drug delivery system

-For example, a drug like aspirin breaks down into salicylic acid, which can damage the stomach lining and cause ulcers, which can be harmful [57].

- Ibuprofen, for example, can cause severe acidity and ulcers if it adheres to the gastric lining for an extended period [57].

8.2.2. Swelling system

These are the dosage forms that enlarge after being swallowed to the point that they can no longer be swallowed. The pylorus is exited. Therefore, the dose has been reduced. form is kept in the stomach for a longer period a period. These systems might be referred to as 'plug type systems,' since they show a propensity to stay logged at the pyloric If the diameter of the sphincter exceeds the diameter of the sphincter, it is called a sphincter. In their enlarged condition, they measure 12-18mm.The equilibrium between the scope and length of a project. The degree of cross-sectional the

polymeric chains are linked together. a high level the degree of cross-linking reduces edema. the system's capacity to preserve its physical state for an extended amount of time [58]. Controlled and sustained medication release is achieved by selecting a polymer with the appropriate molecular weight and swelling characteristics. can be accomplished When you meet the polymer absorbs water and expands in the stomach fluid. These polymers have a lot of swelling.is caused by the presence of physical and chemical factors. A mixture of hydrophilic polymer (hydroxypropyl methylcellulose), swelling agents, and sustained release tablets is used to create swellable, floating, and sustained release tablets. (Crospovidone, sodium starch glycolate, and sodium starch glycolate) sodium croscarmellose) and an effervescent compound (sodium bicarbonate) (sodium bicarbonate) (sodium bicarbonate. The percentage swelling of formulations is assessed. total length of *in vitro* drug release, floating lag time, total duration of *in vitro* drug release Mean residence time (MRT) and floating in the stomach. The goal was to combine floating and swelling to create gastroretentive drug delivery systems (GRDDSs). For testing floating capacity (floating lag time and duration) and swelling properties, GRDDS tablets made with hydroxyethylcellulose (HEC), chitosan (CS), and sodium bicarbonate (SB) were used. Because it swelled in acidic environments and was biocompatible, CS was chosen. For sustained release profiling, losartan was included into the improved formulations. The results showed that for those formulations including CS and a HEC:CS ratio of 5:5, both the floating lag time and floating duration were ideal, achieving the desired swelling effect and lasting for 24 h. SB increased the floating ability of all HEC:CS ratios but decreased the swelling ability of formulations with a larger proportion of low viscosity grade CS. Sustained Losartan release patterns in those formulations were achieved using all viscosity classes of CS at all tested HEC:CS ratios; however, when employing a lower viscosity grade of CS, it is more changeable at different HEC:CS ratios. Losartan tablets with an optimized GRDDS formulation with an equivalent ratio of HEC to CS and 20 mg SB floated for more than 16 hours and had an adjustable sustained release profile [59].

8.2.3. Expandable system

For the past three decades, expandable gastroretentive dosage forms (GRDFs) have been developed. They were originally designed for veterinary usage, but the design was later changed for improved human medication treatment. Due to swelling or unfolding processes that prolong their gastric retention duration, these GRDFs are easily ingested and attain a much bigger size in the stomach (GRT). Following medication release, the size of the drug is reduced when it is expelled from the stomach. The combination of considerable dimensions with high stiffness of the dose form to withstand peristalsis and mechanical contractility of the stomach improves gastroretentivity. Preclinical and clinical research assessing the GRT of expandable GRDFs yielded positive results. *In vivo* performance of medicines with a narrow absorption window formulated in such systems has improved. These findings represent a significant step forward in the therapeutic use of expandable GRDFs. The current study examines expandable GRDFs as described in literature and patents, as well as the physiological rationale for their development. Relevant imaging methods and pharmacokinetic-pharmacodynamics
characteristics of such delivery systems are also examined using the dog as a preclinical screening model prior to human research [60].

8.2.4. Magnetic system

Because magnetic systems are based on the attraction of two magnets, they are fundamentally distinct from the strategies used by all the other gastroretentive delivery types outlined earlier. These systems are made up of two parts: a small internal magnet in the pharmaceutical dosage form and an external magnet, which is applied under the abdominal region near the stomach

Figure 8 [26]. This allows the dosage form to stay longer time in the stomach and produce prolonged effect.

In 1990, the first magnetic system was developed for use in esophageal cancer targeted therapy. An external magnet was used to route magnetic granules including ultrafine ferrite (-Fe_2O_3) to the esophagus for the first 2 minutes, and

practically the whole amount of granules remained in the region after 2 hours [61]. The primary benefits of magnetic systems include absolute drug targeting for target organs or tissues, increased

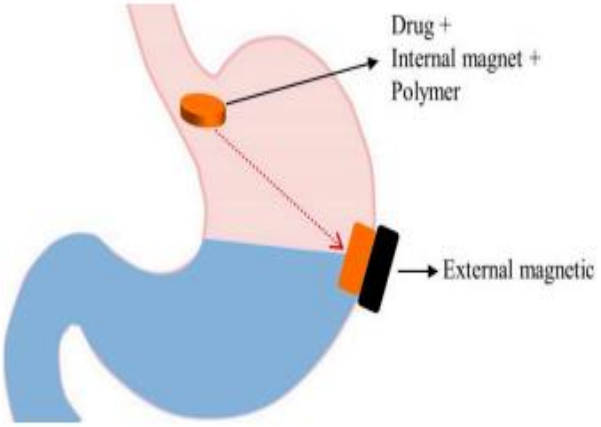

Figure 8. Magnetic system.

absorption as well as bioavailability of encapsulated drugs, and reduced drug concentration at non-target sites. When opposed to other systems, one of the problems of magnetic systems is the need for an external device. It must be carefully applied and precisely positioned in order to facilitate medicine release in the appropriate location while avoiding discomfort for the patient [26].

8.2.5. Nanoparticles system

Nanoparticles are colloidal particles with a size range of 1 to 100 nm that deliver targeted drug delivery [62]. the word 'nano' is derived from the Greek word 'nanos,' which means extremely dwarf. Carbon-based nanoparticles, polymeric nanoparticles, metal nanoparticles, ceramic nanoparticles, semiconductor nanoparticles, lipid-based nanoparticles, and others are different types of nanoparticles based on their shape and physical/chemical properties.

In the field of drug delivery, polymeric drug-loaded nanoparticles have been widely investigated. The physicochemical features of particles, especially their size, play an important role in bio-distribution. The literature's overall message is that little particles have a better chance of achieving their target [63]. Polymeric nanoparticles are a highly investigated issue because to its advantages over other materials and, moreover, due to advancements in polymer science and nanotechnology since polymeric nanoparticles have seen tremendous growth. Polymeric nanoparticles have several advantages, including ease of manufacture, controllable size distribution, and efficient drug retention and protection. Polymeric nanoparticles are polymers derived from natural, synthetic, or semisynthetic sources and can be biodegradable or non-biodegradable [64].

Polymeric nanoparticles can be used to deliver drugs, proteins, or DNA to a specific organ or another therapeutically active chemical can dissolve, adhere, encapsulate, or entrap to the nanoparticles' matrix depending on the technique of synthesis [65]. Nano capsules or Nano spherical polymeric nanoparticles are the most common shapes. Nano capsule polymeric nanoparticles have a therapeutic component contained within a polymeric capsule shell, whereas nanospheres polymeric nanoparticles have a medication or other solid particles embedded in a polymeric matrix [62]. The pictorial representation of nanospheres and nano capsules are as shown in

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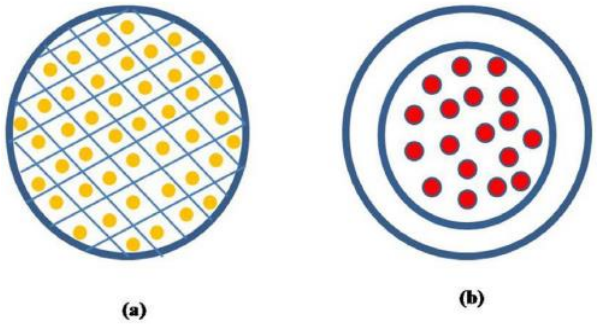

Figure 9. Illustrations of (a) Nano capsules and (b) Nanospheres.

Reaching the target site, which is often far away from the administration site (drug targeting), remaining at the target to deliver the drug, preferably in a time-controlled manner, limiting the drug's adverse effects, and ensuring biocompatibility are all challenges faced by nanoparticle drug delivery systems.

9. Evaluation parameters of gastroretentive dosage forms

A) *In Vitro* Evaluation

1) General tests: Appearance, hardness, friability, drug content, weight variation, and content consistency are among the tests performed.

2) Floating systems

a) Buoyancy Lag Time:

Buoyancy lag is a term that refers to the time it takes for the dosage form to float on top of the dissolution medium after it is placed in the medium is measured. As part of the dissolving test, these parameters can be assessed.

b) Floating Time:

Floating time refers to the amount of time that the dosage form remains afloat on the dissolving media. It is normally carried out in a 37 °C Simulated Gastric Fluid.

c) Specific Gravity / Density

The displacement method, which uses Benzenes as a displacement medium, can be used to calculate density.

3) Swelling systems

Swelling Index

After immersing a swelling dosage form in Simulated Gastric Fluid at 37°C for 30 mi, the dosage form is retrieved at regular intervals and dimensional changes in tablet thickness / diameter are monitored over time.

B) *In Vivo* Evaluation

1) Radiology: The radio-opaque marker barium sulphate is commonly used. Internal bodily systems are examined using X-rays. As a result, $BaSO_4$ is mixed into the dose form, and X-ray images are acquired at various intervals to check for stomach retention.

2) Gastroscopy: Gastroscopy is a technique for visually inspecting the effects of stomach extension.

3) Scintigraphy: Scintigraphy uses emitting elements put into a dosage form to produce images, like X-ray. ^{99}Tc is a common emission substance.

4) Ultrasonography: Ultrasonography is not widely used since it is not detectable in the intestine.

5) Magnetic Marker Monitoring: This approach emits no radiation and so poses no risk. The dose form is magnetically identified by adding iron powder inside, and images can be captured using very sensitive bio-magnetic measurement equipment in this method.

Conclusion

The literature suggests that GRDDS is an effective strategy for maintaining drug release in the stomach environment, hence increasing absorption and bioavailability. All these GRDDS techniques are more convenient and practicable than other drug delivery systems, and each has its own set of benefits and drawbacks. Many research programs are currently underway to produce new formulations employing various polymers or copolymers, as stated in the patents reviewed in this review. GRDDS has systemic, localized, and site-specific effects. GRDDS aids in the treatment of a variety of gastrointestinal disorders while also lowering dose frequency, reducing the risk of contraindications, systemic toxicity, and drug dependence. In the end, GRDDS is a basic and successful drug delivery method.

Declarations of interest:

None.

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