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A recent update on gastro retentive drug delivery systems

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Abstract

Gastro retentive drug delivery systems (GRDDS) have garnered significant attention in recent years due to their potential to enhance therapeutic efficacy and patient compliance by prolonging gastric residence time and optimizing drug release kinetics. This review provides a comprehensive overview of the latest advancements in GRDDS, focusing on formulation strategies, design principles, and evaluation methodologies. Various approaches such as floating systems, mucoadhesive systems, expandable systems, and magnetic systems are discussed in detail, highlighting their mechanisms of action and applications in targeted drug delivery. Furthermore, recent innovations in materials science and formulation technologies have enabled the development of novel GRDDS with improved biocompatibility, stability, and controlled release profiles. The review also addresses challenges associated with GRDDS, including physiological variability, drug stability, and regulatory considerations, and proposes potential strategies to overcome these obstacles. Additionally, the clinical relevance of GRDDS in the treatment of various gastrointestinal disorders and their future prospects in personalized medicine and targeted therapy are explored. Overall, this review aims to provide valuable insights into the current state-of-the-art in GRDDS research and its implications for the advancement of drug delivery science.

Keywords: Gastro retentive drug delivery system (GRDDS); Bio-adhesive; Mucoadhesive; Floating drug delivery system.

1. Introduction

The most practical and recommended method of delivering any medication to the systemic circulation is oral administration. Recently, the pharmaceutical industry has become more interested in oral controlled release drug delivery to gain increased therapeutic advantages, such as ease of dose administration, patient compliance, and flexibility in composition. Medications with short half-lives and easy absorption from the gastrointestinal tract (GIT) are rapidly removed from the systemic circulation. These medications must be dosed often in order to produce the desired therapeutic effect. In an effort to get around this restriction, oral sustained-controlled release formulations have been developed. These formulations release the medication gradually into the gastrointestinal tract (GIT) and keep an effective concentration of the medication in the systemic circulation for an extended period of time. Following oral ingestion, this kind of medication distribution.

A longer stomach residence time by the drug administration is desirable to design an oral controlled release dosage form that is site-specific. Extended stomach retention raises the length of drug release, decreases drug waste, and enhances the solubility of drugs that are less soluble in high pH environments. Additionally, extended gastric retention time (GRT) in the stomach may be beneficial for local action in the upper portion of the small intestine, such as the management of peptic ulcers. By extending the stomach residence duration, Gastro retentive medication delivery aims to target the upper gastrointestinal tract (GIT) for local or systemic effects by site-specific drug release. The gastric retention time (GRT) of medications can be greatly extended by using gastro retentive dose forms, which can stay in the

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stomach area for extended periods of time. A number of gastro retentive drug delivery strategies have been developed over the past few decades, such as: Super porous hydrogel systems, Magnetic systems, Mucoadhesive systems that cause bio-adhesion to the stomach mucosa, High density (sinking) systems that are retained in the stomach bottom, Low density (floating) systems that cause buoyancy in gastric fluid, and Unfoldable, Extendible, or Swellable systems that limit the amount of dosage forms that can be emptied through the pyloric sphincter of the stomach, among others. The purpose of gastro retentive dosage forms (GRDFs) is to release their active components in the stomach over an extended period of time, allowing the medication to be absorbed into the upper gastrointestinal (GI) tract continuously.

Why there is need of GRDDS? Certain medications absorbed via the gastrointestinal tract (typically with short half-lives) are rapidly eliminated from the circulatory system, necessitating regular administration. To deal with this issue, novel gastro retentive medication delivery systems are being implemented. They have an efficient plasma drug concentration, which reduces the need for frequent doses. Another advantage of this approach is that it eliminates variability in plasma drug concentrations by administering the medication in a regulated and consistent manner.

2. Stomach

The stomach is located just underneath the diaphragm in the top left section of the abdominal cavity. Its volume changes according on the degree of distension, which can reach 1500 ml after a meal. After the food has emptied, it collapses to a resting capacity of 25–50 ml (Waugh & Grant, 2001). The fundus, body, and antrum (sometimes known as the pylorus) comprise the three anatomical sections of the stomach. The fundus and body parts of the proximal stomach function as a storage for the materials that are consumed, while the antrum, located in the distal area, is the main location of mixing movements and functions as a pump to facilitate gastric emptying.

2.1. Structure and Function of stomach

Human anatomy divides the gastrointestinal tract into three main sections: the fundus, the neck, and the antrum (pylorus) (figure 1). The body stores undigested food in the proximal part, known as the fundus. By acting as a propeller, the antrum acts as a stomach emptying pump and supplies the primary mixing location. In addition to hydrochloric acid, the stomach produces endogenous factor in its parietal cells. The following absorption of vitamin B_{12} (cobalamin) into the small intestine is made possible by the intrinsic factor that develops at this stage of digestion in stomach. Given the vital function that vitamin B_{12} plays in the formation of red blood cells and brain processes, the development of the intrinsic factor is essential. Dehydration-setting water, some medications, such as aspirin, amino acids, ethanol, caffeine, and certain water-soluble.

2.2. Physiology of stomach

The stomach is divided into three parts anatomically:

- Body,
- Antrum pylorus,
- Fundus.

The antrum is the main site for mixing motions and functions as a pump for stomach emptying via thrusting activities, while the proximal portion, composed of the fundus and body, serves as a reservoir for undigested material. Both while eating and when fasting, gastric emptying takes place. Nonetheless, the motility patterns in the two states differ. An electrical sequence of inter-digestional events occurs while fasting; these events occur in the stomach and intestine every two to three hours. This is known as the migrating myloelectric cycle (MMC), or inter-intestinal myloelectric cycle (fig.3), and it may be further split into the following four phases:

- Phase I (basal phase)
- Phase II (pre-burst phase)
- Phase III (burst phase)
- Phase IV
  - Stage I (basal stage): It endures from 40-60 min with uncommon compressions.
  - Stage II (pre-burst stage): Final from 40-60minwith discontinuous potential and compressions.
  - Stage III (burst stage): Final for 4-6 min. in this strongly and standard withdrawal happen for brief periods. Due to these withdrawals the un-digestive nourishment is cleared from stomach to digestive system. These are known as house guardian waves.
  - Stage IV: It keeps going for 0-5 min and happens between stages III and I for two continuous cycles.

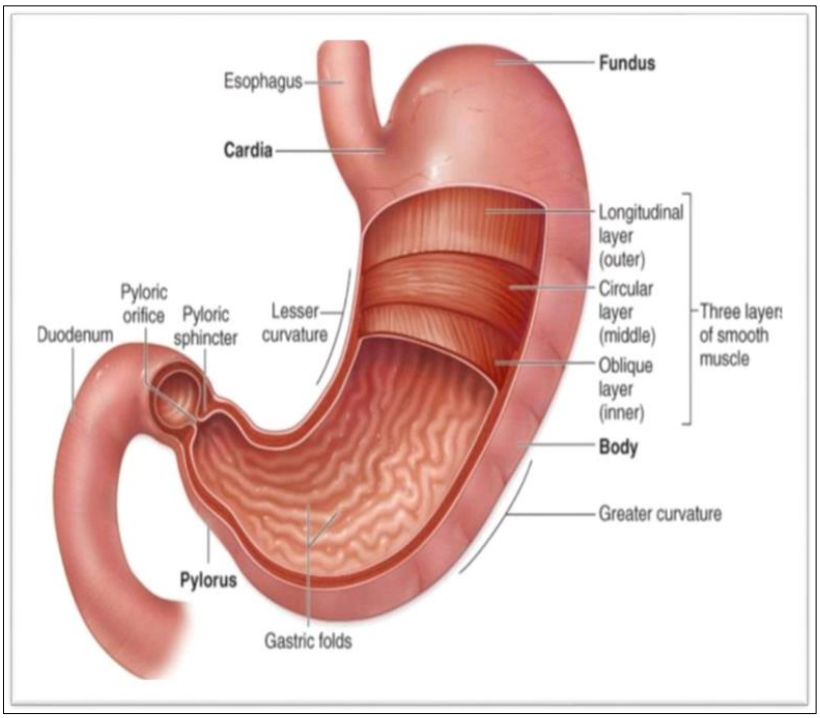

Figure 1 Physiology of stomach

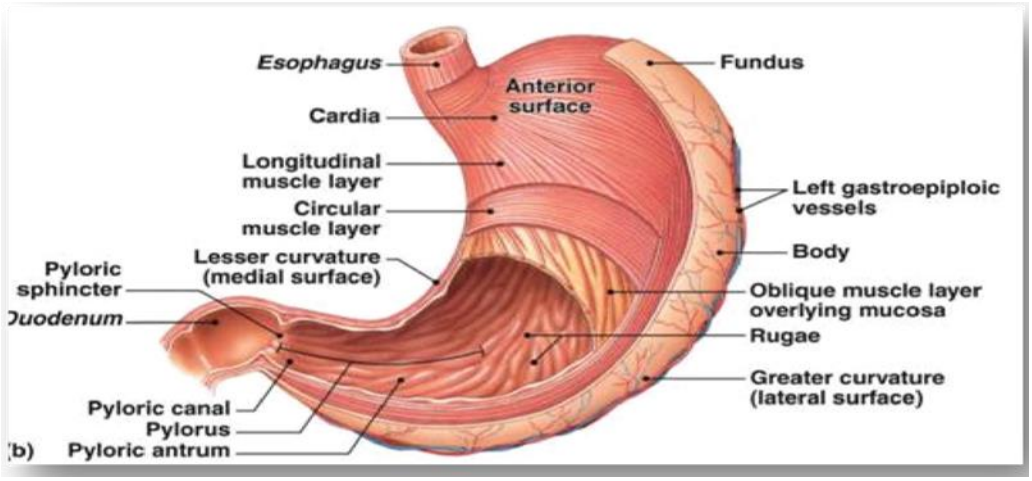

Figure 2 Physiology of stomach[64]

After the ingestion of a blended dinner, the design of withdrawals changes from fasted to that of nourished state. Usually moreover known as stomach related motility design and comprises persistent compressions as in stage 2 of fasted state. These withdrawals result in reducing the measure of nourishment particles (to less than 1 mm), which are moved towards the pylorus in a suspension from. During the encouraged state onset of MMC is delayed coming about in slowdown of gastric purging rate.

2.3. Advantages of gastro-retentive drug delivery systems

2.3.1. Enhanced bioavailability

When riboflavin CR-GRDF is administered instead of non-GRDF CR polymeric formulations, the bioavailability of the former is markedly increased. The rate of medication absorption is influenced by a number of interrelated mechanisms that are involved in both drug absorption and transit through the gastrointestinal system[11].

2.3.2. Enhanced first-pass biotransformation

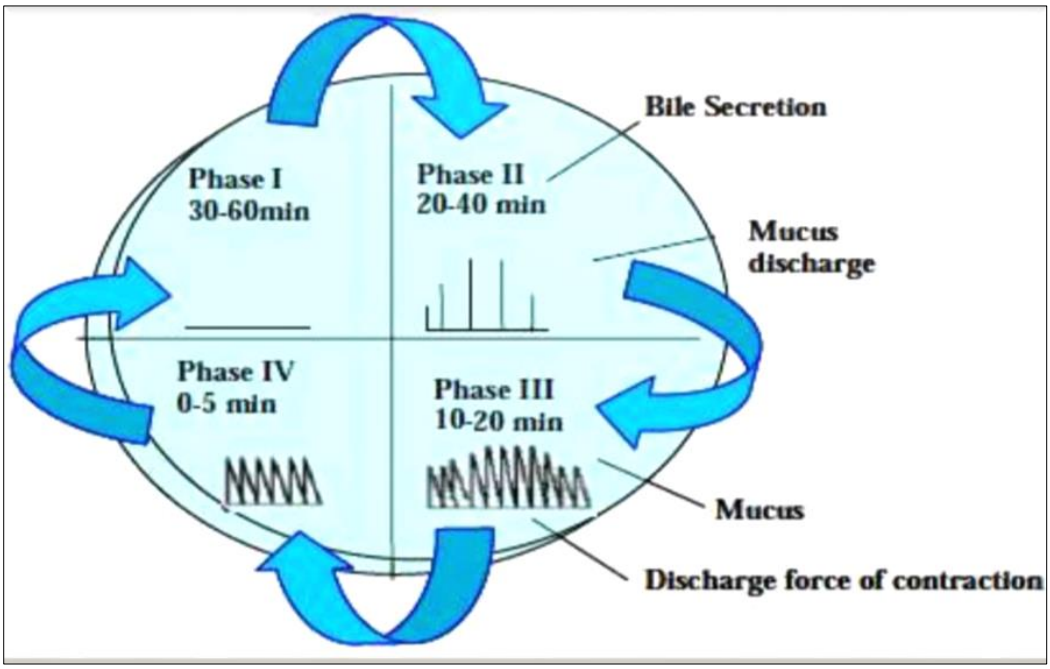

Figure 3 Phases of Gastric motility and gastric emptying rate[65]

Pre-systemic metabolism of a compound can be significantly increased by presenting it to metabolic enzymes (cytochrome P450, specifically CYP3A4) in a sustained manner, similar to how active transporters with limited capacity can improve efficacy[5].

2.3.3. Sustained drug delivery/reduced frequency of dosing:

Sustained and slow input from CR-GRDF can result in flip-flop pharmacokinetics, allowing for decreased dose frequency for medicines with short biological half-lives. This characteristic leads to enhanced patient compliance and therapeutic outcomes.

2.3.4. Targeted therapy for local ailments in the upper GIT:

Long-term medication delivery from GRDF to the stomach may benefit local treatment in the stomach. Also included is the small intestine. This route of administration allows for therapeutic drug concentrations to be achieved locally while minimizing systemic amounts due to absorption and distribution.

2.3.5. Reduced fluctuations of drug concentrations:

Continuous CR-GRDF delivery leads to narrower blood drug concentrations compared to instant release dose formulations. This minimizes oscillations in medication effects and prevents concentration-dependent adverse effects at peak concentrations. This aspect is especially important for medicines with a limited therapeutic index[25].

2.3.6. Minimization of fluctuations in drug concentration:

It enables selective pharmacological effects by activating distinct types of receptors at varying doses.

2.3.7. Reduced counter-activity of the body:

The human body's rebound activity is frequently triggered by the pharmaceutical reaction that interferes with natural physiological processes. This reduces the amount of pharmacological action. It has been demonstrated that allowing the medicine to enter the body gradually reduces counteractivity and increases pharmacological efficiency.

2.3.8. Extended time over critical (effective) concentration:

For certain drugs that have non-concentration dependent pharmacodynamics, such as etalactam anti-microbials, the clinical reaction isn't related with peak concentration, but or maybe with the term of time over a basic restorative

concentration. The maintained mode of organization enables extension of the time over a basic concentration and hence upgrades the pharmacological impacts and moves forward the clinical results.

2.3.9. Minimizing adverse activity at the colon:

Retaining the medicine in the GRDF in the stomach reduces its exposure to the colon. As a result, the drug's negative effects in the colon can be avoided. The GRDF formulation for beta-lactam antibiotics, which are exclusively absorbed from the small intestine, is based on this pharmacodynamic characteristic, as their presence in the colon might lead to microorganism resistance.

2.3.10. Site specific drug delivery:

It makes sense to use a floating dose form, particularly for medications with restricted upper small intestine absorption sites. In addition to providing enough local therapeutic levels, the drug's regulated, gradual release to the stomach also reduces its systemic exposure. This lessens adverse effects on blood circulation that the medication causes. Additionally, the frequency of dose may be decreased by the extended stomach availability provided by a site-directed administration system.

2.4. Disadvantage of GRDDS

- Unsuitable for drugs with limited acid solubility. E.g. Phenytoin.
- Unsuitable for drugs that are unstable in acidic environment. E.g. Erythromycin.
- Drugs that irritate or causes gastric lesions on slow release. E.g. Aspirin & NSAID's.
- Drugs that absorb selectively in colon. E.g. Corticosteroid.
- Drugs that absorb equally well through GIT. E.g. Isosorbide dinitrate, Nifedipine.
- Floating drug delivery systems require high fluid level in stomach to float and work effectively.

2.5. Factors affecting GRDDS

2.5.1. Density of dosage form

Density of dosage form should be in range of $1g/cm^3$ to $2.5g/cm^3$. Dosage form with lower density in the gastric content can float to the surface while high density sink to the bottom of the stomach. Suitable density required for floating property is less than 1.0 gm/ cm^3.

2.5.2. Shape and size of dosage form

Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units. In most cases, the larger the dosage form the greater will be the gastric retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm. Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes.

2.5.3. Fed or unfed state

Gastric retention time is less during fasting condition due to rise in gastric motility.

2.5.4. Nature of meal

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

2.5.5. Caloric content

GRT can increased by 4-10 hours with a meal that is high in protein and fat.

2.5.6. Frequency of meal

Feeding increase over 400 min when successive meals given are compared with the single meal due to low frequency of MMC.

2.5.7. Effect of gender, posture and age

Generally females have slower gastric emptying rates than male. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down.

2.5.8. Disease states

Gastric ulcer, diabetes, hypothyroidism increase GRT. Hyperthyroidism, duodenal ulcers decrease GRT. Concomitant drug administration Anticholinergic like atropine and propantheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.

2.5.9. Posture

GRT can vary between supine and upright ambulatory states of the patient; the floating and non-floating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions and the floating units remained away from the pylorus. However, in supine position, the floating units are emptied faster than non-floating units of similar size.

2.5.10. Volume of GI fluid

The resting volume of the stomach is 25 to 50 ml. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder of warmer fluids.

2.6. Approaches for gastro retentive drug delivery system

Figure 4 Approaches for GRDDS

3. Floating drug delivery system

The lower density of these systems (1.004 g/cm^3) when compared to gastric fluids, allowed them to stay buoyant in the stomach for Extended periods of time, facilitating the drug's gradual release and raising GRT. There are two types of floating systems: effervescent and non-effervescent. Drugs are combined with gel-forming polymers or highly swellable cellulose derivatives to create non effervescent systems. While hydrophilic polymers are combined with effervescent agents including calcium carbonate, sodium bicarbonate, tartaric acid, and citric acid. Consequently, upon interaction with stomach fluid, CO_2 is released and ensnared in a hydrocolloid matrix, impacting the release of drugs.

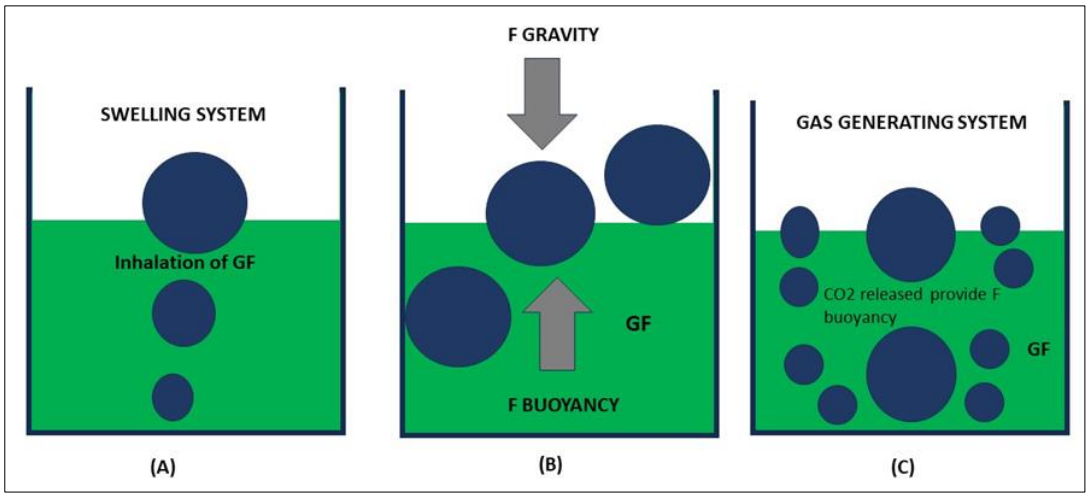

Figure 5 Floating drug delivery system

4. Effervescent systems

These systems are matrix-type. developed with the aid of many effervescent substances as well as swellable polymers including methylcellulose and chitosan. Example: citric acid, tartaric acid, and sodium bicarbonate. These are designed in a way that releases CO_2 upon contact with stomach contents, encapsulating it in a swelled hydrocolloid to provide the dose form buoyancy. The swellable asymmetric triple layer tablet technique served as the foundation for the delivery system's design.

4.1. Volatile liquid systems

The GRT of a drug delivery system can be maintained by utilizing an inflatable chamber filled with a liquid (such as ether or cyclopentane) that gasifies at body temperature, causing the chamber to inflate in the stomach; alternatively, the device can include a bio-erodible plug composed of poly vinyl alcohol, polyethylene, etc. that gradually dissolves, causing the inflatable chamber to release gas and collapse after a predetermined amount of time, allowing the inflatable systems to discharge spontaneously from the stomach. These have an inflatable chamber that holds a liquid, such as ether. These systems are further classified as follows:

4.1.1. Intra gastric floating gastrointestinal drug delivery system

This approach consists of a micro porosity compartment with a pharmaceutical reservoir inside and a flotation chamber filled with either an inert, harmless gas or vacuum.

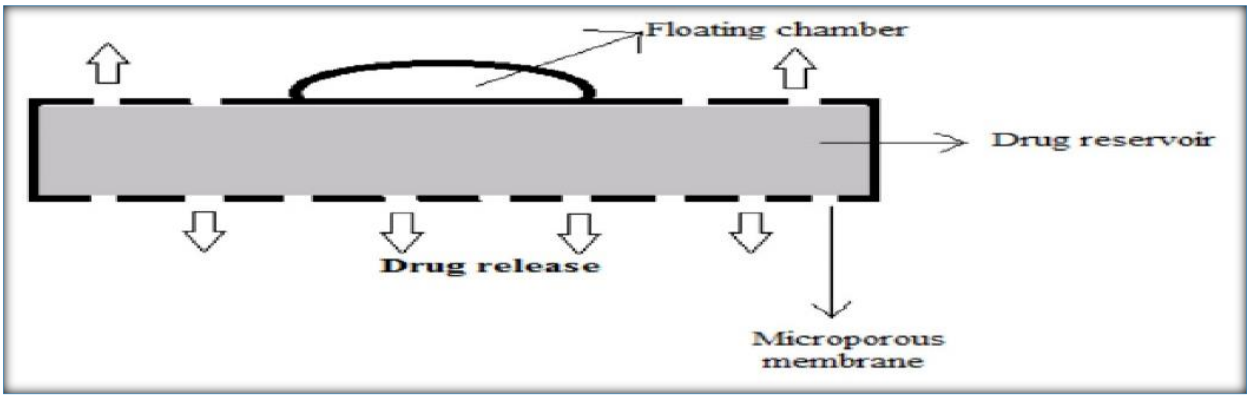

Figure 6 Intra gastric floating gastrointestinal drug delivery system[38]

4.1.2. Inflatable gastrointestinal drug delivery system

An inflatable chamber filled with liquid ether gasifiers to inflate the stomach at body temperature. A bio erodible polymer filament, such as a copolymer of polyvinyl alcohol and polyethylene, is included in the inflatable chamber. As this filament progressively dissolves in stomach fluid, the inflated chamber collapses and releases gas.

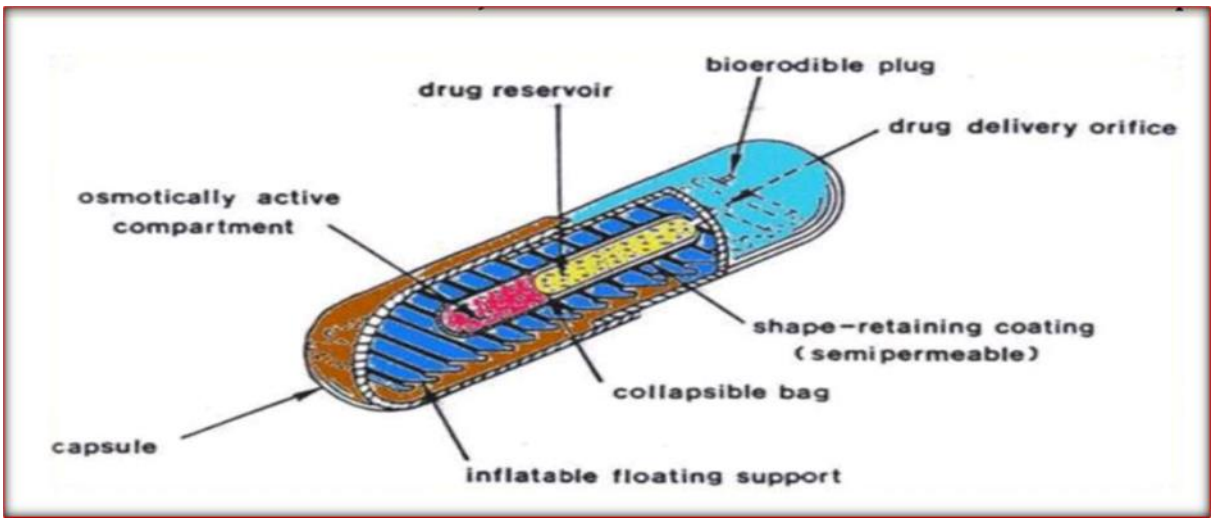

Figure 7 Inflatable gastrointestinal drug delivery system[46]

4.1.3. Intra-gastric osmotically controlled drug delivery system

It consists of a drug delivery system controlled by osmotic pressure and an inflated floating capsule. The osmotically controlled drug delivery system, consisting of an osmotically active compartment and a drug reservoir compartment, is released when the inflated capsule breaks down in the stomach. Using this technique, extremely porous hydrogels are a prime illustration. When the dosage form comes into touch with stomach fluid, it swells to many times its original volume. The larger size of the dose form causes the gastric contraction to slide over the surface of the system, forcing the dosage form back into the stomach after it has been pushed to the pylorus.

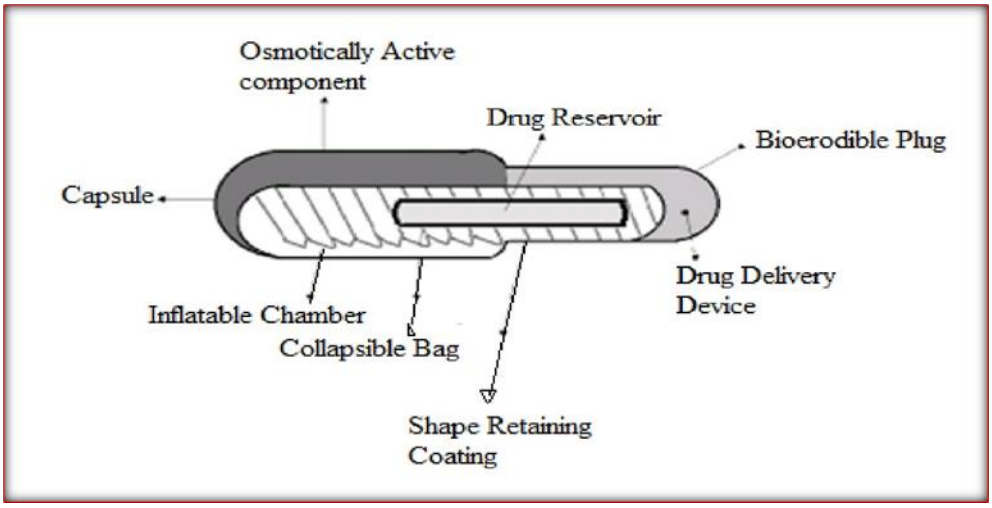

Figure 8 Intra-gastric osmotically controlled drug delivery system[66]

4.2. Matrix tablet systems

It can be made as a single layer matrix surface by adding bicarbonates to the hydrocolloid gel agent in the matrix, or as a dual layer matrix combined with the gas-generating matrix as a separate layer. The second layer is the medication. A triple layer matrix tablet is possible. But currently, there is just one layer that produces gas, and the other two layers are medication layers.

4.3. Gas generating systems

The main procedure in this system is the reaction between sodium bicarbonate, citric acid, and tartaric acid, which produces CO_2 gas. The gas generated causes the system's density to decrease, causing it to float on the stomach juices. Citric/tartaric acid and salts release CO_2, which becomes trapped in the system's jellified hydrocolloid layer, lowering its specific gravity and causing it to float over chime 24. A sustain release tablet that is encased in two layers makes up the mechanism that operates. The inner layer is an effervescent layer made up of tartaric acid and sodium bicarbonate. PVA shellac is present in the swellable membrane layer that makes up the outer layer. (Fig. 9& 10: Gas Generating Effervescent drug delivery system).

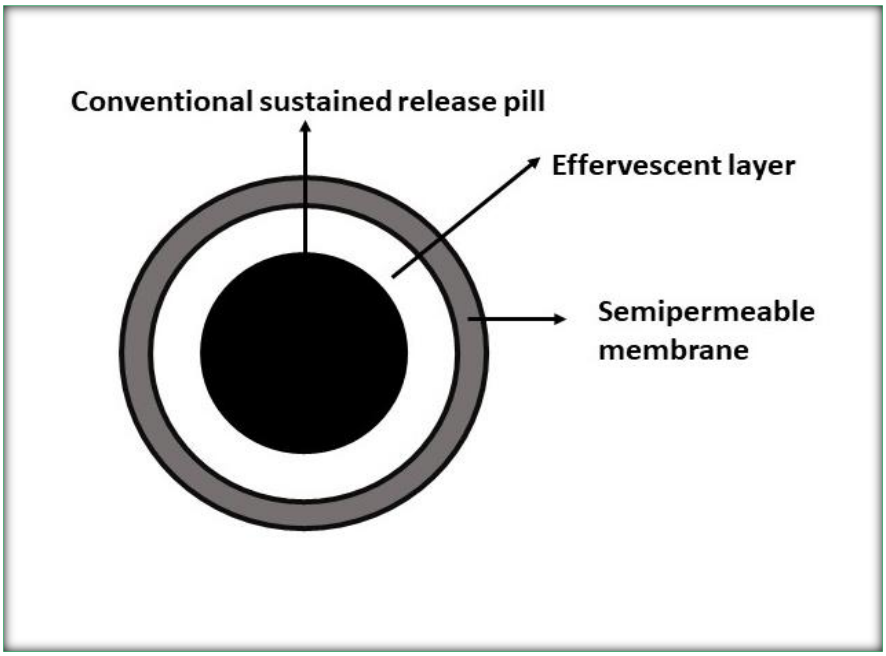

Figure 9 Gas generating system

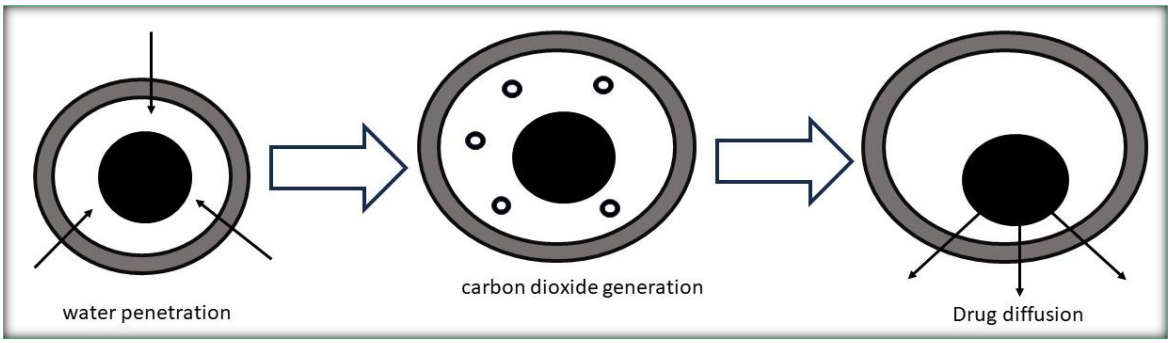

Figure 10 Drug release from effervescent (gas generating) systems

5. Non-effervescent systems

Non-effervescent FDDS is often made from gel-forming or highly swellable cellulose hydrocolloids, polysaccharides, or matrix-forming polymers such as polyacrylate, polycarbonate, polystyrene, and polymethacrylate. In one technique, drugs are intimately mixed with a gel-forming hydrocolloid, which comes into contact with stomach fluid after oral administration and maintains a relative shape integrity and a bulk density less than unity inside the gastrointestinal environment. The inflated polymer traps air, which gives these dose forms buoyancy. The most frequent excipients utilized in these systems include HPMC polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide, and polycarbonate.

5.1. Micro balloons/ microsphere

To increase the GRT of the dosage form, micro balloons or hollow microspheres with medications in their other polymer displays were made using a straightforward solvent evaporation or solvent diffusion technique. Polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar, low methoxylated pectin, and other polymers are frequently utilized to create these systems. Polymer amount, plasticizer polymer ratio, and formulation solvent all affect buoyancy and medication release from dosage forms. For more than 12 hours, these tiny balloons floated nonstop on the surface of an acidic dissolving medium containing surfactant. Because hollow microspheres combine the benefits of superior floating and multiple-unit systems, they are now regarded as one of the most promising buoyant systems.

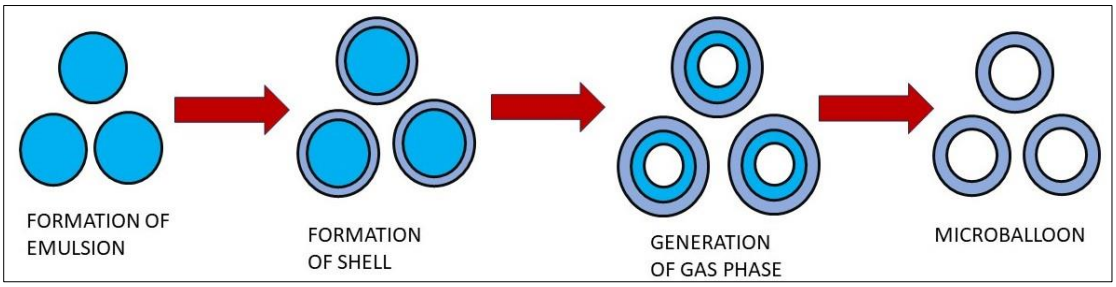

Figure 11 Micro balloons/ microsphere

5.2. Alginate beads

Multi-unit floating dose forms have been developed with freeze dried calcium alginate. Dropping sodium alginate solution into an aqueous calcium chloride solution causes calcium alginate to precipitate, resulting in spherical beads with a diameter of around 2.5 mm. The beads are separated, snap-frozen in liquid nitrogen, then freeze-dried at -40ºC for 24 hours. This creates a porous structure that can retain a floating force for more than 12 hours. These floating beads have a longer residence duration of almost 5.5 hours.

5.3. Hydrodynamically balanced systems or colloidal gel barrier system:

These systems incorporate drugs with gel-forming hydrocolloids that are designed to remain buoyant in the stomach contents. This prolongs GRT and increases the quantity of medication that reaches its absorption sites in solution form, which leads to faster absorption. These are single-dose formulations that comprise one or more gel-forming hydrophilic polymers. HPMC (hydroxy propyl methyl cellulose), hydroxypropyl. The polymer is combined with medications and

often delivered in an HB-capsule. When the capsule shell comes into touch with water, it dissolves and expands to produce a gelatinous barrier that keeps the dose form buoyant in gastric juice for an extended length of time. Because constant erosion of the surface permits water access to the inner layers, surface hydration and buoyancy are maintained in dose form. The use of fatty excipients results in low-density formulations, which reduce erosion. Madopar LP® is based. Hydro dynamically balanced intragastric delivery are explain in figure 12.

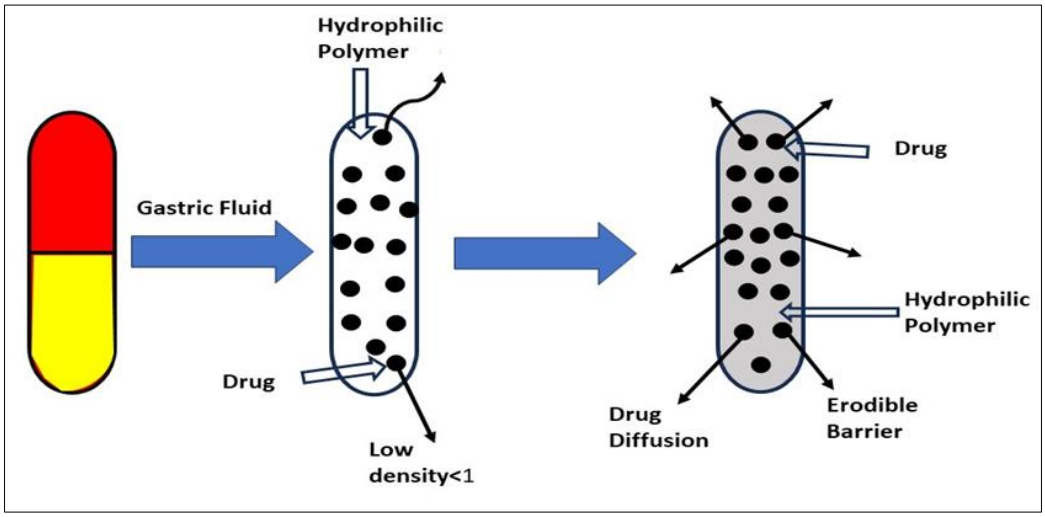

Figure 12 Hydrodynamically balanced intragastric delivery system (HBS)

5.4. Layered tablets

Non-effervescent floating dosage forms include single-layer and bilayer floating tablets. Single-layer formulations combine medication with hydrocolloid to make a gel. When the medication enters the stomach fluid, it begins to swell and can retain a bulk density of less than unity. However, bilayer-floating tablets have two layers. The first layer provides a quick release, which removes the original dosage from the system. On the other hand, the other layer supports released traditional tablets.

6. RAFT forming system

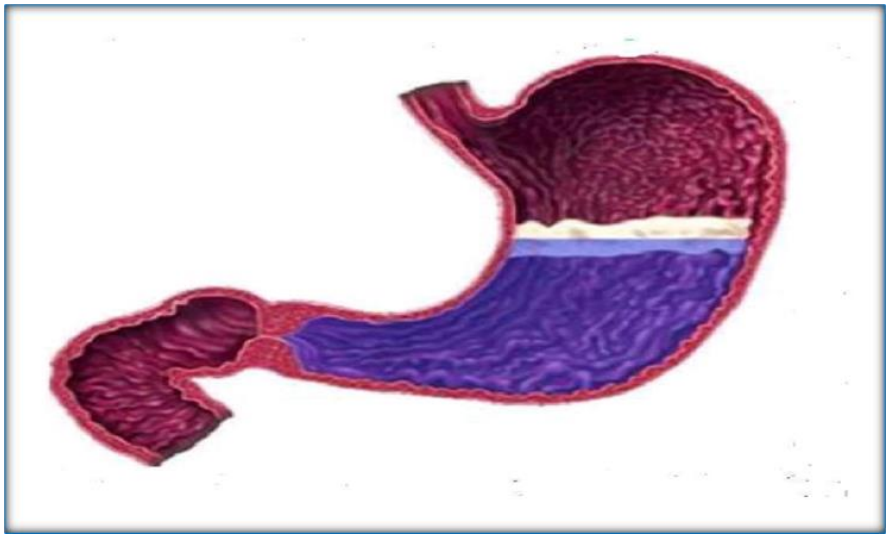

Figure 13 Raft forming system[67]

Raft forming systems have generated a lot of interest in the treatment of gastrointestinal infections and diseases through medication delivery. When viscous cohesive gel comes into touch with stomach fluids, a continuous layer known as a raft is formed when each piece of the liquid expands. This is one of the mechanisms underlying the development of rafts. Because CO_2 production results in a low bulk density, this raft floats on stomach juices. In order to make the system less

thick and allow it to float on the stomach juices, the elements of the system often contain a gel-forming agent and alkaline bicarbonates or carbonates that cause CO_2 to form. A floating antacid raft formation technique was described by Jorgen et al. Sodium bicarbonate, acid neutralizer, and gel forming agent (such as sodium alginate) combine to form a foaming sodium alginate gel (raft) that floats on gastric fluids and acts as a barrier between the stomach and the esophagus to stop the reflux of gastric contents, such as gastric acid, into the esophagus.

7. Non-floating drug delivery system

7.1.1. High density (sinking) drug delivery systems

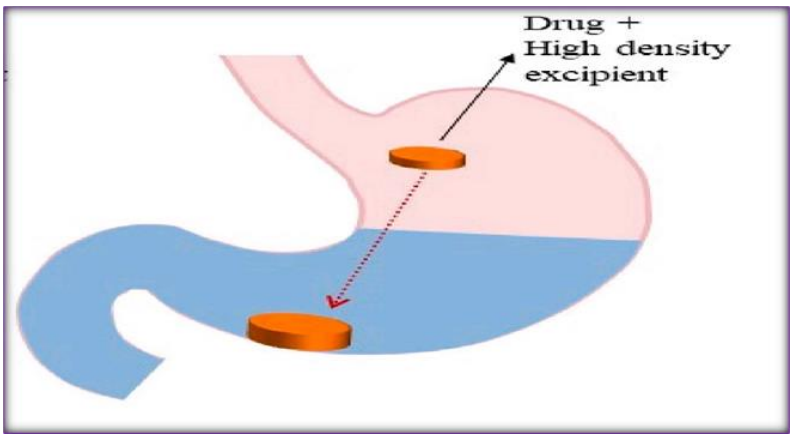

Figure 14 GRDDS based on high density systems[43]

Pellets that are small enough to be held in the folds of the stomach body close to the pyloric area have been maintained with the use of sedimentation. Closely packed, dense pellets (approximate $3g/cm^3$) also have a tendency to resist the stomach wall's peristaltic motions. The average GI transit time with pellets can be extended from 5.8 to 25 hours; this is dependent more on the density of the pellets than on their diameter. Excipients such iron powder, zinc oxide, barium sulfate, and titanium dioxide are frequently utilized. Density may be increased by these materials by up to $1.52.4g/cm^3$.

8. Bio-adhesive/Mucoadhesive system

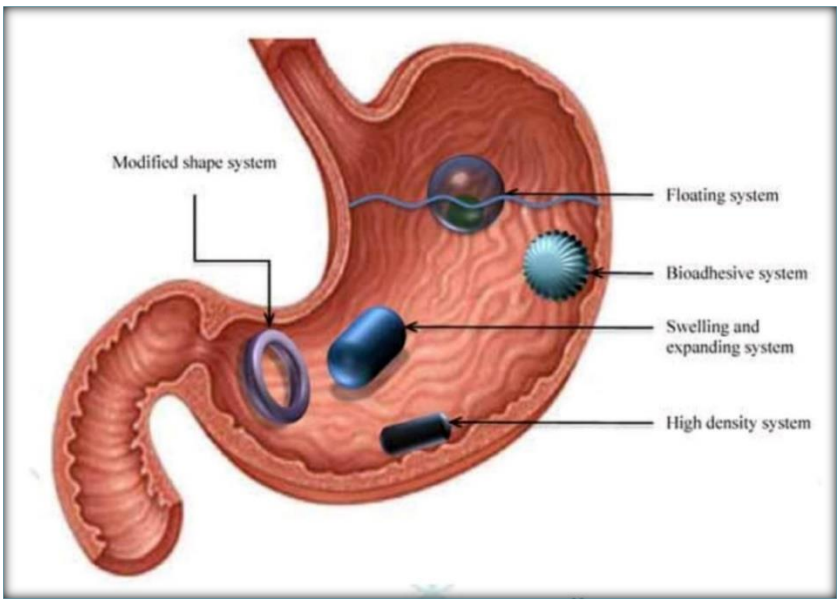

Figure 15 Bio-adhesive/Mucoadhesive systems[68]

Muco-adhesive or bio adhesive formulations were first created to manage medication distribution of various sorts and to raise GRT. Park and Robinson initially described the mucoadhesive system in 1984. By maintaining a rigid, long-term

contact between the drug delivery device and the absorption site, mucosal adhesive improves the efficacy of medication administration. The most recent technique, created 35 years ago, involves using mucoadhesive systems to extend the stomach's residence period. The process known as mucosal adhesion is what makes synthetic or natural polymers stick to mucosal tissues. The active pharmaceutical ingredient (API) is combined with polymers that have unique surface characteristics to create mucoadhesive drug delivery systems. Mucoadhesive polymers attach themselves to the surface of mucosal tissues due to their high affinity to these tissues. To accomplish both chemical and physical retention of gastric retention, Muco-adhesion is a potential strategy to combine with the previously described procedure. Muco-adhesion is a helpful tactic for drug delivery applications such as tablets, patches, micro/nanoparticles, gels, liposomes, nano suspensions, and colloidal dispersions.

8.1. Mechanism of muco-adhesion

An interfacial phenomena known as muco-adhesion occurs when two materials are drawn together by interfacial attraction. The mucin layer of the mucosal tissue or a manufactured substance like a mucoadhesive polymer might be the two components. The term "mucoadhesive" refers to an artificial material that has the ability to interact with mucous membranes, stay on them, or keep them together for extended periods of time. The next two steps are often identified throughout the bonding procedure.

8.1.1. Contact stage

Tight wetting takes place between the mucous adhesion and mucosa at this point when the mucoadhesive substance comes into contact with the mucosa. The mucus found in the mucosa facilitates this wetting of the muco-adhesives.

8.1.2. Consolidation stage

The mucoadhesive substance attaches to the mucous membrane by various physical and chemical attractive factors, resulting in mucous membrane adhesion that lasts for a long time. This stage is referred to as the consolidation or merge phase. The mucous membrane adhesion process completes after these two phases.

Adhesion is based on the fact that multiple mechanisms allow a dose form to adhere to the mucosal surface. The mechanisms involved are as follows:

- The wetting theory, which relies on the bio-adhesive polymers' capacity to diffuse and form close contact with the mucosal layers.
- The notion of diffusion suggests that mucin physically entangles with flexible polymer chains or interpenetrates into the porous structure of the polymer substrate.
- The absorption hypothesis postulates that secondary forces like hydrogen bonds and Vander Waal forces are responsible for bio adhesion.
- The electron theory, which suggests that the bio-adhesive substance and the glycoprotein mucin network are attracted to each other by electrostatic forces.

9. Swelling/ Expanding Systems

These dose forms grow to a size that obstructs their transit through the pylorus after swallowing. The dose form is therefore kept in the stomach for an extended amount of time. Because of their propensity to stay trapped in the pyloric sphincter, these systems are also referred to as plug type systems. Even when fed, these polymeric matrices stay in the stomach cavity for a few hours. Choosing a polymer with the right molecular weight and swelling characteristics can result in sustained and regulated medication release.

10. Expandable System

The hydrophilic polymer network's physical-chemical crosslinking is the cause of these polymers' extensive swelling. The physical integrity of the dosage form is preserved by these cross-links, which stop the polymer from dissolving. The degree to which the polymeric chains are cross-linked determines how much swelling occurs and for how long. A high degree of crosslinking slows the system's capacity to expand and keeps its structural integrity for a longer period of time.

On the other hand, a low degree of cross-linking causes a large amount of swelling, which is quickly followed by the polymer dissolving. The ideal level of cross-linking is necessary to keep swelling and disintegration in check. Eventually, the swelling system will break into smaller pieces when the membrane ruptures due to constant expansion, or it will

lose its integrity due to a lack of mechanical strength brought on by abrasion or erosion. The expandable GRDFs are usually based on three configurations:

A small, folded configuration that permits sufficient oral intake.

The stomach's expanded shape, which is attained during swelling and inhibits the pyloric sphincter's action.

A smaller version that is obtained in the stomach after the GRDF releases its active component and allows evacuation, meaning that retention is no longer necessary. The expansion can be achieved by

i) Swelling system
ii) Unfolding system

11. Magnetic systems

The basic concept behind this method of improving the GRT is that a small internal magnet is included in the dose form, and a magnet is applied to the abdomen above the stomach location. The magnetic system appears to function, however patient compliance may be compromised by the need for exact positioning of the external magnet. The use of bio adhesive granules containing ultra-fine ferrite in rabbits is a technical method. For the first two minutes, they used an external magnet to direct them to the esophagus, and after two hours, nearly all of the granules remained in the area.

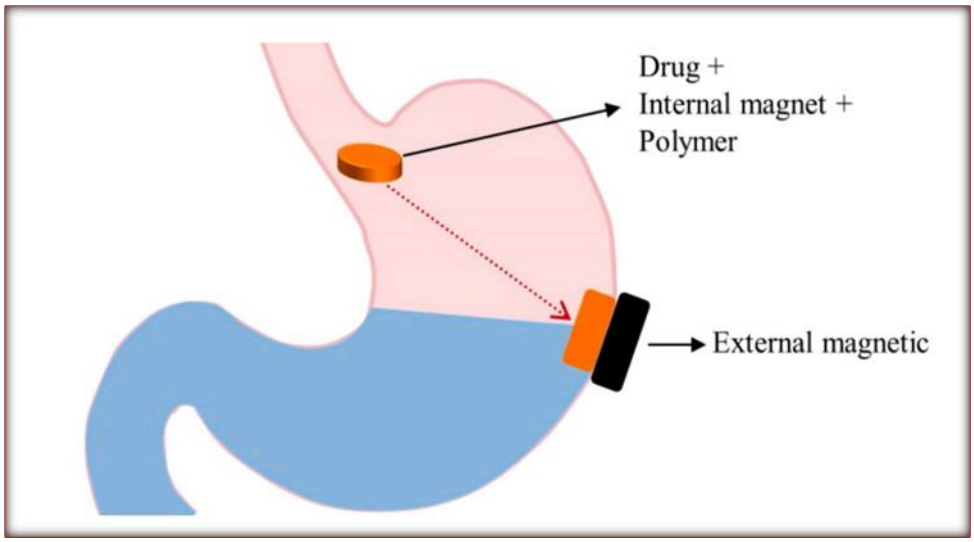

Figure 16 GRDDS based on magnetic systems[43]

Table 1 Commonly used drugs in formulation of GRDDS[18,70,71]

S.No.	Formulation	Drug
1	Tablet	Acetaminophen, Acetylsalicyclic acid, Amoxicillin trihydrate, Atenolol, Ampicillin, Captopril, Cephalexin, Ciprofloxacin, Cinnarazine, Cholrpheniramine maleate, Dilitiazem, Florouracil, Furosemide, Isosorbide mononitrate, Isosorbide dinitrate, Losartan, Metformin hydrochloride, Nimodipine, P-Aminobenzoic acid (PABA), Pentaoxyfillin, Prednisolone, Piretanide, Riboflabin- 5'phosphate, Sotalol, Theophyllin, Verapamil HCl, Ziduvudine
2	Capsule	Chlordizepoxide HCl, Celiprolol HCl, Diazepam, Furosemide, L-Dopa and Benserazide, Misoprostal, Nicardipine, Pepstatin, Propranol, Urodeoxycholic acid
3	Films	Albendazole, Cinnarizine, P-Aminobenzoic acid (PABA), Piretanide, Prednisolone, Quinidine gluconate

4	Microspheres	Aspirin, Cholestyramine, Dipyridamol, Flurbiprofen, Griseofulvin, Ibuprofen, Ketoprofen, Nicardipine, Nifedipine, Orlistat, P-nitro aniline, Piroxicam, Rosiglitazone maleate, Terfenadine, Theophylline, Tranilast, Verapamil, amoxicillin
5	Powders	Several basic drugs-Riboflavin, Sotalol, Theophylline.
6	Granules	Cinnarizine, Diclofenac sodium, Diltiazem, Fluorourocil, Indomethacin, Isosorbide dinitrate, Prednisolone, Ranitidine HCl
7	Beads	Beta-cyclodextrin, Curcumin, Diltiazem HCl, Loratidine, Ranitidine HCl

12. Evaluation

12.1. Floating lag time

It is calculated to evaluate how long it takes the dosage form to float on top of the dissolving media following its placement in the medium. The dissolving test may include measurements of these factors.

12.2. Floating time

An imaging method is used in conjunction with γ-scintigraphy and X-rays to assess stomach retention and dosage form placement throughout the GIT in-vivo. A tiny amount of solid isotope is mixed under the supervision of the dose bureaucracy in γ-scintigraphy. When a γ-emitting radionuclide is present in a system, it becomes possible to utilize a γ-digicam or scinti scanner indirectly. Barium sulfate is used as an assessment medium for x-rays. The GIT makes it easier to identify a dose form that one is able to predict and associate with the duration of the stomach emptying and the dosage shape's passage. In addition, in vivo assessment of GRDDS may be safeguarded by research using gastroscopy and ultrasound. Using a fiberoptic and video device, gastroscopy combines many techniques from oral endoscopy. For the purpose of evaluating GRDDS, ultrasonography is not mechanized. Performing the investigation in an appropriate animal model can also yield an in vivo plasma profile.

12.3. Swelling studies

For an extensible, highly porous hydrogel system. The weighted dosage form is added to the swelling medium (0.01N HCl) to carry out the test. The weight, diameter, and length of the swelled samples are then assessed at pre-established time periods.

12.4. Viscosity and rheology

For systems that produce rafts-forming and mucoadhesion, The viscosity of the polymer influences the dosage form's consistency when it comes into contact with stomach fluid; texture analyzers and Brookfield/Ostwald's viscometer are often used tools for this.

12.5. Particle size, ion exchange capacity, moisture content

For the system of ion-exchange resin, A sieve shaker, laser diffraction, and a Coulter counter analyser have all been used in particle size measurement. The functional group that is accessible for cross-linking determines the ion exchange capacity. Karl Fischer can be used to test the moisture content.

12.6. Gel strength

It is preferred to have a high gel strength for improved mechanical integrity.

12.7. Drug – Excipient interaction study:

High performance liquid chromatography, differential scanning calorimetry, and FT-IR spectroscopy may all be used to study it.

12.8. Specific Gravity / Density

Benzenes displacement medium can be used in the displacement technique to measure density.

12.9. Water uptake study

The dosage form is submerged in simulated Gastric fluid at 37 ^{0}C, and dimensional changes, including thickness and diameter, are monitored at regular intervals. Following the allotted time, the swollen tablets are weighed, and the percentage weight increase associated with water intake is calculated using the formula WU= (W_t-W_o) X 100/Wo. where W_t and Wo stand for the tablet's weight at time t and beginning, respectively. Hardness, friability, weight fluctuation, and other factors that are relevant to traditional immediate release tablets are also assessed for the tablets. In addition to the tests mentioned above, the following tests are also crucial for multiple unit dose form Spheres such as microspheres:

- Morphological and dimensional analysis:- Morphological and dimensional analysis is carried out using optical and scanning electron microscopy.
- Percentage yield of microsphere.
- Entrapment efficiency: The drug is removed using an appropriate technique, and its concentration is determined by analysis.

12.10. Stability study

In addition to the tests mentioned above, the following tests are also crucial for multiple unit dose form Based on the proportion of medicine released and buoyancy, the optimal formulation for the manufactured floating micro balloons was chosen. For ninety days, the chosen mixture was kept in glass containers with borosilicate screw caps, and it was held at three different temperatures: 27±2°C, 40±2°C, and 5-8°C in the refrigerator. Drug entrapment (drug content) was tested for in the samples on a regular basis.

12.11. In vitro buoyancy studies

Floating lag time refers to the time it takes for the tablet to appear on the surface of the medium. Total floating time refers to the amount of time that the dosage form remains on the surface of the medium. Tablets were put in a 100 mL flask containing a pH 1.2 buffer solution. The time required for a tablet to rise and float on the liquid's surface, as well as the duration of floating, was recorded.

12.12. Pharmacokinetic studies

Pharmacokinetic investigations include AUC (Area under Curve), C max, and duration to reach maximum. A radiograph is taken before administering the floating tablet to check the absence of radio-opaque substances. The presence of a radio-opaque substance allows for X-ray visualization of the dose form. The formulation is consumed by natural swallowing, followed by 50 mL of water. Gastric radiography was performed every 30 minutes for 5 hours with an X-ray equipment. A computer was used to determine plasma concentrations of γ-emitting radionucleides (T_{max}). Statistical analyses were carried out using a Student t test with a p-value of 0.05 as the cutoff.

12.13. In-vitro Dissolution Tests

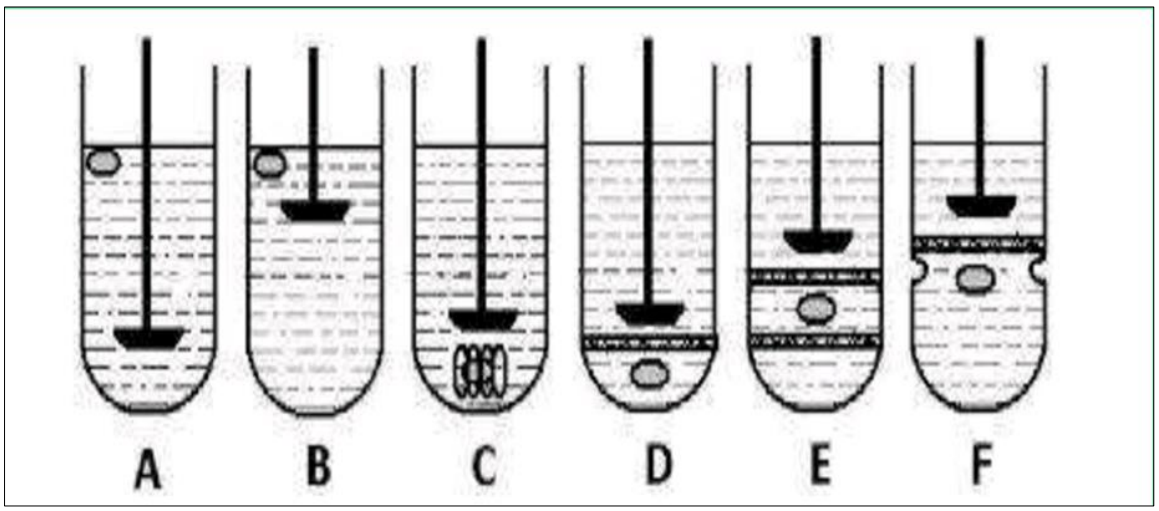

Figure 17 In-vitro dissolution tests[69]

In-vitro dissolving tests are often done using a USP equipment with a paddle, and GRDDS is put routinely as with other common tablets. However, when the vessel is big and the paddles are near the bottom, the floating dose form tends to float on the surface due to reduced paddle force. Failure to rotate the floating dose form might lead to inaccurate and inconsistent results. Reproducible outcomes have been achieved by various dissolution assembly transformations. They are depicted in the following figure 17.

12.14. Site-Specific Drug Delivery

These systems are especially useful for medications that are only absorbed from the stomach or the proximal section of the small intestine, such as riboflavin. Furosemide is absorbed mostly by the stomach, followed by the duodenum. It has been claimed that a monolithic floating dosage form with a longer stomach residence time was created, increasing bioavailability. The AUC attained with the floating pills was about 1.8 times that of traditional furosemide tablets. A bilayer floating capsule was designed for local delivery of misoprostol, a synthetic analogue of prostaglandin E1 utilized as a protectant against stomach ulcers produced by the ingestion of NSAIDs.

12.15. Absorption Enhancement

Drugs with low bioavailability at the site of specific absorption from the upper part of the gastrointestinal tract are potential candidates for formulation as floating drug delivery systems. In some cases, the bioavailability of floating dosage forms could be increased (42.9%) when compared to commercially available LASIX tablets (33.4%).

13. Conclusion

Gastric retention drug delivery systems offer potential advantages in terms of improved bioavailability and controlled drug delivery. The gastric retention drug delivery system has shown the potential to increase the retention of drug in the stomach. Increased understanding of the impact of GIT physiology on drug delivery will ensure the development of more and more drug delivery systems to optimize drug delivery by molecular means There are different levels of drug absorption according to region .The development of more gastro-retentive drug delivery methods will be made possible by the advancement of delivery technology, which will optimize the administration of molecules with long first pass metabolism, limited bioavailability, and an absorption window. Our analysis of the literature led us to the conclusion that gastro-retentive drug delivery offers a number of potential benefits for drugs with low bioavailability because it limits the absorption of these drugs to the upper gastrointestinal tract and allows for efficient delivery, which maximizes absorption and improves absolute bioavailability. A gastro-retentive medication delivery device maximizes the patient's benefit.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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