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SAGA OF GASTRORETENTIVE DRUG DELIVERY SYSTEM: EMERGING CONCEPTS, RECENT ADVANCES AND TECHNOLOGICAL PROGRESS

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Keywords:

Drug delivery system, Floating dosage form, Gastric retention, Oral controlled release, Formulation, Applications

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ABSTRACT: Oral controlled release and site-specific drug delivery systems have gained interest in the pharmaceutical industry to improve the treatment of certain critical medications. To overcome physiological barriers, such as short stomach resident lengths and variable gastric emptying periods, the idea of a novel drug delivery mechanism evolved. To improve the bioavailability of drugs with narrow therapeutic windows, delay the onset of drug elimination from the body, and increase patient compliance, one of these novel approaches is the gastroretentive drug delivery system (GRDDS), which is implanted in the upper part of the gastrointestinal tract. This investigation discusses the GRDDS, factors associated with the GRDDS, the advantages and disadvantages of the GRDDS, alternative approaches to the GRDDS, and different polymers used for gastroprotection. A great deal of work is being put into developing several GRDDS types at the moment. Because of this, pharmacotherapies of all types stand to benefit from their growing prominence shortly.

INTRODUCTION: Taking drugs via mouth is the most common and popular option when getting them into the body's bloodstream. The pharmaceutical industry has recently placed a greater emphasis on oral controlled-release drug delivery as a method of gaining improved therapeutic advantages such as ease of dose administration, patient compliance, and formulation versatility. Toxins swiftly eliminated from the body's bloodstream include those that have a short half-life and are well absorbed by the GIT. Such medications need frequent dosing for optimal therapeutic effects.

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To get around this problem, scientists are working on oral sustained-controlled-release formulations, which will release the medicine gradually into the GIT while keeping an effective level of the drug in the body's bloodstream for an extended time. After oral administration, this method would remain in the stomach and slowly release the medicine, ensuring that it reaches the intestines and liver, where it may be absorbed **Fig. 1**.

Incomplete drug release from the dosage form in the absorption zone (stomach or upper portion of small intestine) may occur due to the short gastric retention time (GRT) and unexpected short gastric emptying time (GET) of these drug delivery methods [1-3]. The FDA is interested in developing a site-specific, orally administered, controlled-release dosage form and would want to achieve it by extending the amount of time the medicine spends in the stomach. Prolonged stomach retention improves bioavailability, delays medication release,

reduces drug waste, and raises solubility for less soluble pharmaceuticals in a high pH environment. Peptic ulcer treatment and other forms of local action in the upper small intestine may benefit from GRT left in the stomach for an extended period of time.

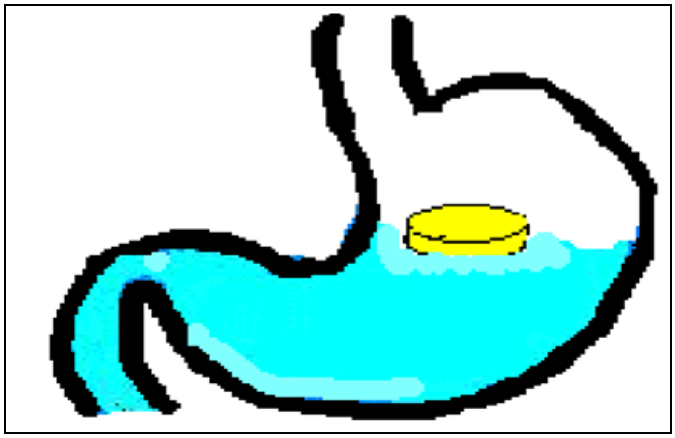


FIG. 1: GASTRORENTIVE DRUG DELIVERY SYSTEM

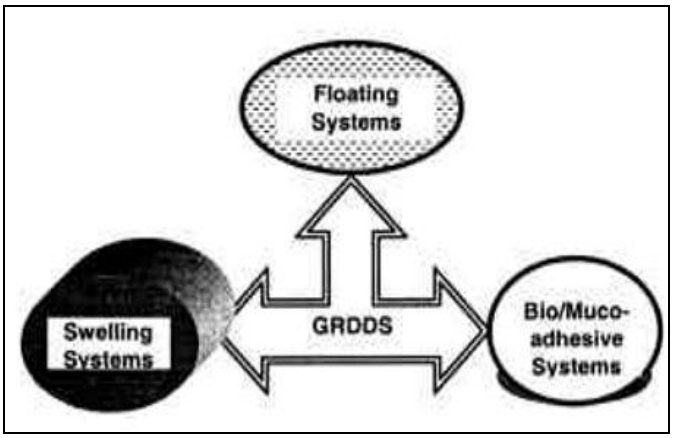


FIG. 2: CLASSIFICATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

Site-specific drug release in the upper GIT for local or systemic effects is made possible by the use of a gastroretentive drug delivery system (GRDDS). Because gastroretentive dosage forms have the potential to remain in the stomach for an extended period, GRTs of many medications may be significantly prolonged. Over the past few decades, researchers have developed a number of different GRDDS strategies, including sinking systems with a high density that are retained in the stomach's lining, floating systems with a low density that float in gastric fluid, mucoadhesive systems with a bioadhesive surface that adhere to the stomach lining and unfoldable, extendible, or swellable systems that slow stomach emptying **Fig. 2**. The current research examines many gastroretentive strategies that have recently emerged as cutting-edge approaches in the field of site-specific orally administered controlled release medication delivery systems.

Anatomy of the Gastrointestinal Tract: The GIT can be divided into three main regions, namely:

- Stomach
- Small intestine - Duodenum, Jejunum and Ileum
- Large intestine

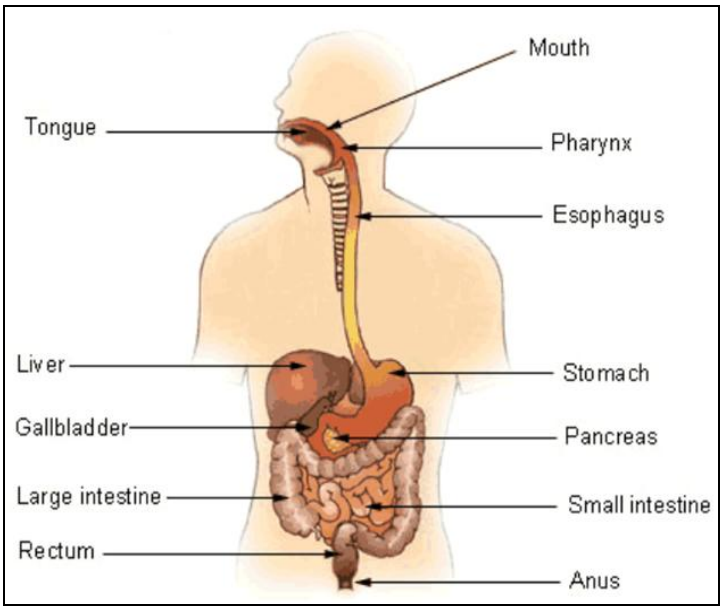


FIG. 3: GENERAL GASTROINTESTINAL TRACT

Secretion, motility, digestion, absorption, and excretion are just few of the physiological activities that take place in the gastrointestinal tract (GIT). This muscular tube extends from the mouth to the anus and is responsible for absorbing nutrients and getting rid of waste. The stomach is an anatomical extension of the gastrointestinal tract (GIT) in the form of a J. It is divided into four sections the cardia, fundus, body, and antrum **Fig. 3**.

The stomach's main job is to hold food while it mixes with gastric secretions, and then to release its contents (chyme) into the small intestine at a controlled rate that's optimal for digestion and absorption through the pyloric sphincter. An empty stomach can hold around 50 ml, whereas a full stomach may hold up to 1 liter. The GIT wall tissues are organized similarly from the stomach to the large intestine, with the serosa, longitudinal muscle, intermuscular plane, circular muscle, submucosa, muscularis mucosae, lamina propria, and epithelium lining the outside. In addition to longitudinal and circular muscle, the stomach also has a "muscular layer" known as the "oblique muscle layer," which begins in the upper stomach and extends distally through the fundus and upper gastric body. A variety of smooth muscle layers are responsible for the GIT's motor functions, including gastric emptying and intestinal transit [4].

Mucus: Structure, Function and Composition: Specialized goblet cells secrete a thick, sticky substance known as mucus. All organs that come into contact with the outside environment are lined with goblet cells, glandular columnar epithelial cells. Mucus is determined to have several roles in these areas, such as lubrication for item passage, epithelial layer hydration maintenance, barrier function against infections and noxious chemicals, and permeable gel layer that enables gases and nutrients to move to and from the underlying epithelium [5] **Fig. 4**.

As a great water-based lubricant, mucus has many technical applications in the natural world. The glycoprotein mucin has a molecular weight of 2-14×10^6 g/mol, making up most of the mucus. Water accounts for the remaining 5-9%. This viscous brew also contains proteins, lipids, and mucopolysaccharides, but at much lower concentrations (less than 1%).

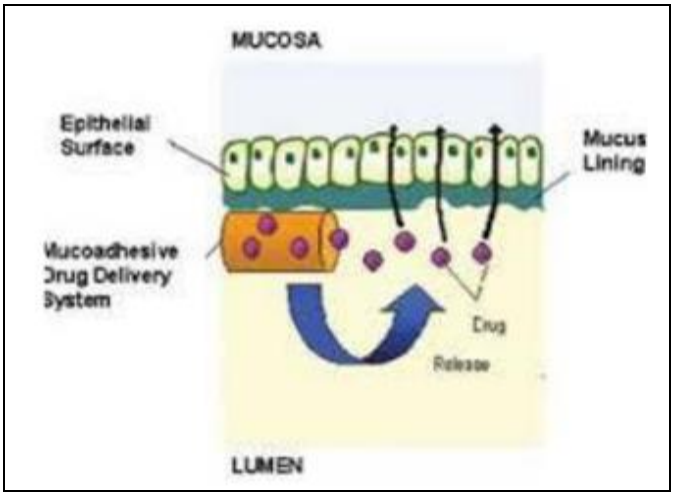


FIG. 4: MUCOADHESION ON THE EPITHELIAL SURFACE

Mucin glycoproteins form a complex web of macromolecules held together by weak interactions. This molecular interaction is crucial to the structural integrity of mucus, and as a result, mucus exhibits unique rheological properties.

At neutral pH, mucin acts as an anionic polyelectrolyte because of the sulfate and sialic acid groups on its glycoprotein molecules (sialic acid has a pKa of 2.6). Non-mucin components of mucus include secretory immunoglobulin A, lysozyme, lactoferrin, lipids, polysaccharides, and many ionic species. It is believed that the bacteriostatic action of mucus is partly due to these non-mucin components.

Basic Stomach Physiology: Anatomically, the stomach is divided into 3 regions:

- Fundus
- Body
- Antrum pylorus

The proximal fundus and body store undigested food, whereas the antrum is where digestion takes place and where the stomach is emptied by pushing motions **Fig. 5**. Conditions of fasting and feeding both lead to stomach emptying. However, the movement pattern in the two jurisdictions is distinct. During fasting, the stomach and intestine undergo a periodic electrical cycle every 2–3 hours [6]. The interdigestive myloelectric cycle (MMC), also known as the migrating MMC, is split into four stages:

1. Phase-I (basal phase)
2. Phase-II (pre-burst phase)
3. Phase-III (burst phase)
4. Phase-IV

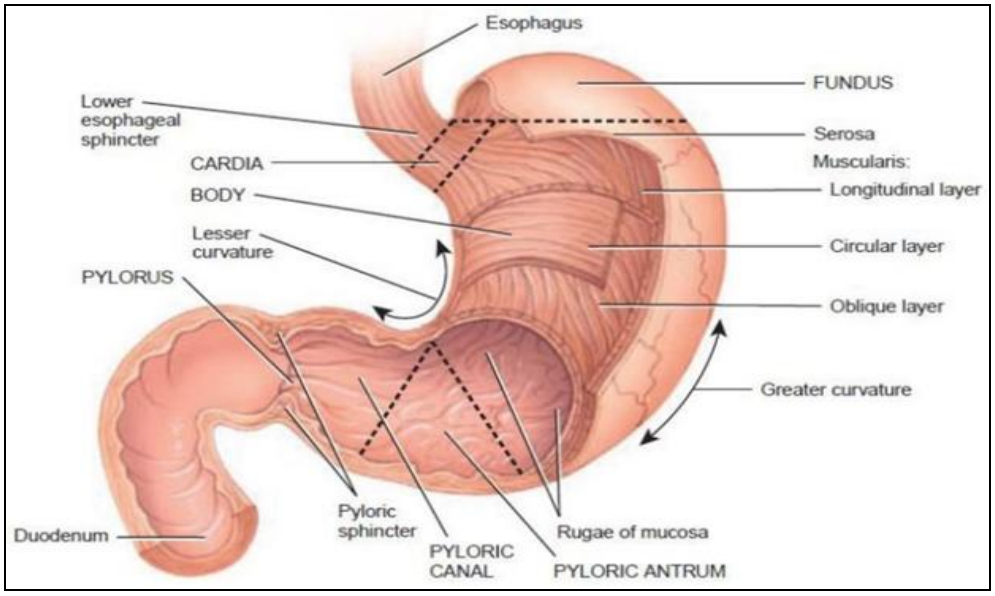


FIG. 5: ANTERIOR VIEW OF REGIONS OF THE STOMACH

After eating a balanced meal, your contraction pattern will shift from the fasting state to the fed one. Consisting of continuous contractions like those in Phase-2 of the fasting state, this pattern is also known as the digestive motility pattern **Fig. 6**. These contractions break down food into smaller pieces (less than 1 mm) and force them into the pylorus in a suspension. In the fed condition, the stomach empties slower because MMC begins later. Scintigraphic investigations measuring gastric emptying rate have shown that oral controlled-release dosage forms are vulnerable to issues such as short stomach residency time and variable gastric emptying rate.

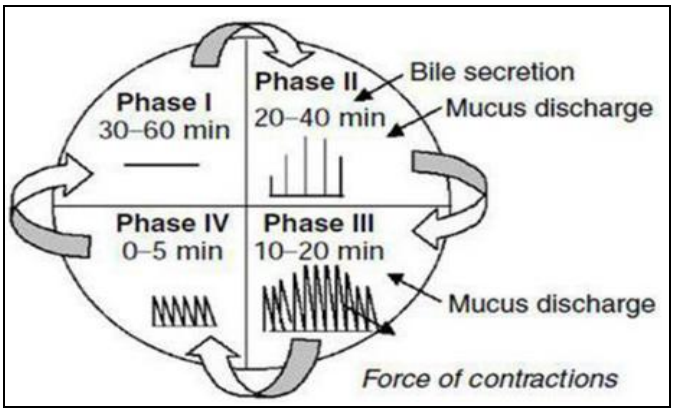


FIG. 6: GASTROINTESTINAL MOTILITY PATTERNS

Factors Controlling Gastric Retention of Dosage Forms: When designing gastroretentive dose forms, it is important to consider the stomach's unique anatomy and physiology. In order to enter the small intestine, particles must be between 1 and 2 millimeters in size, since the pyloric valve would block anything larger than this. The GRT of oral dosage forms is affected by many factors, including the density, size, and shape of the dosage form; the type, amount and frequency of food consumed; the individual's posture; the individual's gender, age, sex, amount of sleep, body mass index, and level of physical activity; and the individual's disease state (such as chronic disease, diabetes, *etc*). (e.g. metoclopramide, cisapride, *etc*.) [7, 8]. The drug's molecular weight and lipophilicity in relation to its ionization state are other essential factors to consider:

Density of Dosage Forms: A dosage form's density influences the pace at which it is emptied from the stomach and where it ultimately is positioned. When ingested, dosage forms having a higher density than the gastric contents may sink to the bottom of the stomach, while those with a lower density may float to the top.

In either case, the dosing mechanism may be kept separate from the pylorus. A density of less than 1 g/cm3 is necessary for flotation.

Viscosity of Polymer: GRDDS's drug release and rafting properties significantly affect the polymer's viscosity and interaction. The rafting qualities of low-viscosity polymers (such HPMC K100LV) were superior to those of high-viscosity polymers, making them ideal candidates for GRDDS (e.g., HPMC K4M). When the viscosity of the polymer rose, the release rate also decreased.

Shape and size of the Dosage Form: The shape and size of the dose units are essential for creating solid dosage forms that cannot be digested. The mean stomach residence times of non-floating dose forms are very variable and are mostly determined by the unit size, which may vary from large to medium to small. The general rule is that the GRT should be at least as long as the longest dose form. This is because the larger size of the dose form slows down the drug's transit via the pyloric antrum and into the small intestine. The stomach residence time of dosage forms with a diameter of more than 7.5 mm is higher than that of forms with a diameter of 9.9 mm. The devices in ring and tetrahedron shapes remain in the stomach longer than in other shapes.

Food Intake and its Nature: Gastric retention of a dosage form is affected by factors such as the amount of food consumed, the meal's viscosity and volume, its caloric content and how often the person eats. With or without food in the GIT, the GRT of the dose form will change. The GRT of a dosage form is often increased by the presence of food in the GIT, allowing the drug to linger at the absorption site for longer. Higher doses may be retained in the stomach due to increased acidity and caloric content, increasing the drug's effectiveness.

Fed or Unfed State: Under fasting conditions, the GRT of the unit is predicted to be very brief because of periods of intense motor activity or migrating MMC that occur every 1.5 to 2 hours. Since the MMC empties the stomach of undigested materials, the GRT for the dosage form should be very short if the formulation's administration time is similar to that of the MMC. In contrast, GRT is much longer in the fed condition due to the delayed MMC.

Effect of Gender and Age: Women often have slower gastric emptying rates than men. There is little difference in the average GRT of persons while they are sitting, standing, or lying down. Elderly people have a markedly reduced pace of stomach emptying.

Posture: No matter how large, the rafting form is safe from postprandial emptying if it maintains an upright position and remains above the stomach contents. After settling on the distal stomach's floor, conventional dosage forms are expelled by the pylorus by the stomach's astral peristaltic movements. On the other hand, rafting dosage forms are vulnerable to premature and erratic emptying in the supine position. Only large dosage forms (both standard and rafting) have prolonged retention when positioned between the lower and greater curvature of the stomach. Since these units move distally by peristaltic action, their ground reaction times (GRTs) are much lower than those of upright people.

Gastroretentive Dosage Form: The gastric residence time of a medicine is increased in gastroretentive dose forms, which may linger in the stomach for many hours. After oral administration, this dosage form remains in the stomach and gradually releases the drug, allowing for continuous dosing throughout the upper gastrointestinal tract. Medicines that are less soluble in a high pH environment are more bioavailable, less wasteful, and more soluble after being retained longer in the stomach.

Other Factors:

- Diseased states of the individual (chronic disease, diabetes, *etc*.)
- Body mass index
- Physical activity
- Molecular weight and lipophilicity of the drug depend on its ionization state.

Requirements for Gastric Retention: When the dose form complies with the following criteria, successful stomach retention is achievable **Fig. 7**.

1. The dose form has to be robust enough to withstand the stomach's constant contractions and churning movement, often known as peristaltic waves.

2. To be effective as a gastric retention tool, it must prevent the stomach from emptying prematurely.

3. Remove the gadget from the stomach with ease if its purpose has been met [9].

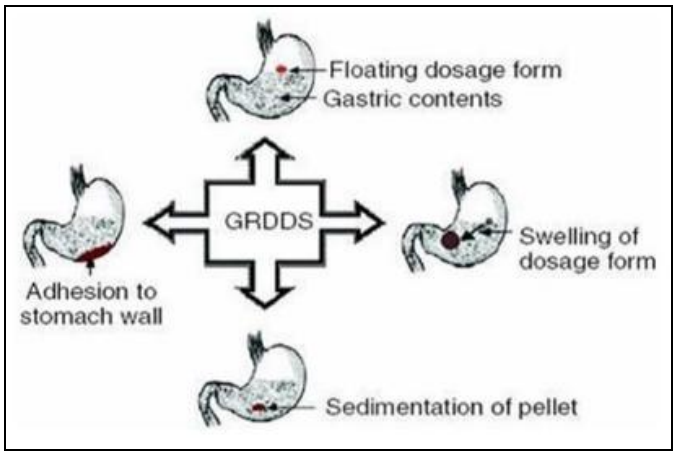


FIG. 7: TECHNIQUES OF GRDDS

Potential Drug Candidates for Gastroretentive Drug Delivery Systems: Medications have a limited scope of action in the stomach, such as misoprostol and antacids. L-dopa, para-aminobenzoic acid (PABA), furosemide (Furosemide window), riboflavin (Ribo Window), and other drugs have a narrow GIT absorption window. Captopril, ranitidine HCl, and metronidazole are drugs that break down in the colon and intestines. Drugs that interfere with healthy gut microorganisms, such as antibiotics used to treat Helicobacter pylori (H. pylori). Diazepam, chlordiazepoxide, and verapamil HCl are just a few examples of drugs that aren't very soluble at higher pH levels [10].

Drugs that are Unsuitable for Gastroretentive Drug Delivery Systems: Phenytoin, among other drugs, is hardly acid-soluble. Erythromycin and other antibiotics are examples of drugs that are unstable in the stomach. Drugs like 5-aminosalicylic acid and corticosteroids are intended for selective colonic release [11].

Methods Used For Gastric Retention: By enclosing the particles to reduce their size. Utilizing hydrocolloids (such as hydrophilic gums, gelatin, alginates, cellulose derivatives, and other gel-forming substances). Enteric materials with a low density are employed. Examples include methacrylic polymer and cellulose acetate phthalate. The gel network produces carbon dioxide gas and traps it [12].

Recent Combinational Approaches for Gastroretention: Currently following combination approaches used in GRDDS Fig. 8:

1. Swellable and floating.

2. Bioadhesive and floating.

3. Bioadhesion and swelling.

4. Bioadhesion and High density.

5. Floating pulsatile system [13].

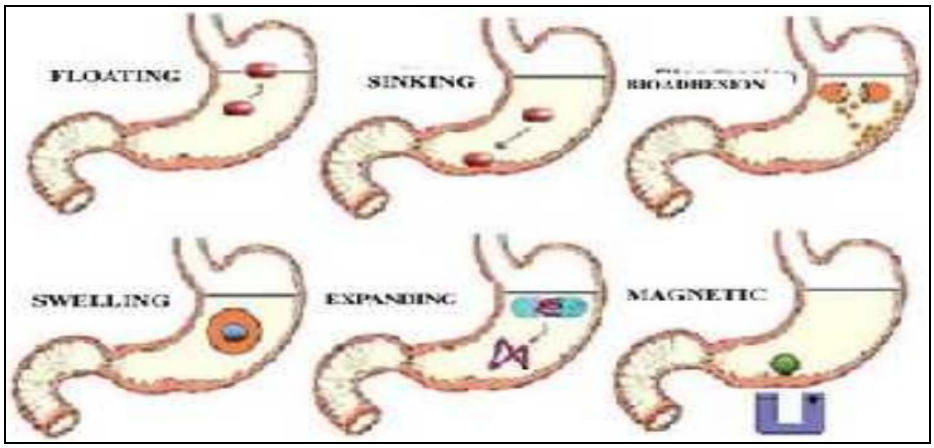


FIG. 8: APPROACHES OF GASTRO RETENTION

Methods for Preparing Floating Dosage Form: The following methods may be used to make floating dose forms:

1. To create a gel, hydrocolloids such hydrophilic gums, gelatin, alginates, cellulose derivatives, and so on is used.

2. Low-density enteric chemicals such methacrylic polymer and cellulose acetate phthalate.
3. To reduce particle size and enclose it in a capsule.
4. Carbon dioxide gas is created and trapped in the gel's porous structure.
5. Acrylic polymer hollow microballoons are used to transport the medicament into the capsules.
6. The inclusion of an inflatable chamber filled with a liquid, such as a solvent, which gasifies at body temperature causing the chambers to expand in the stomach [14].

The factors which govern the effectiveness of active medicaments in HBS are:

1. The dose of an active pharmaceutical ingredient needed for therapeutic benefit.
2. Density in Mass
3. Characteristics that make it either hydrophilic or hydrophobic
4. Gastric fluid stability.

Technological Developments in FDDS: Davis's 1968 proposal of a method to prevent gagging and choking while eating medicinal tablets is when the concept of FDDS first appeared in the literature. Tablets having a density of less than 1.0 g/ml, which would float on the water's surface, were presented as a potential solution to the issue by the author. Since, then, several strategies have been tested to create the perfect floating delivery system. There are a wide variety of floatable formulations, including hollow microspheres (HM) ('microballoons'), granules, powders, capsules, tablets (pills), and laminated films. Several single-unit floating systems, such as the HBS and floating tablets, have been reported in the literature **Fig. 9**. These methods are unreliable and difficult to replicate when it comes to increasing the stomach dwell time after oral administration because of their chance ('all-or-nothing') emptying mechanism. However, multiple-unit dosage forms seem to be preferable due to the reduced danger of dose-dumping and reduced inter-subject variability in absorption they provide [15].

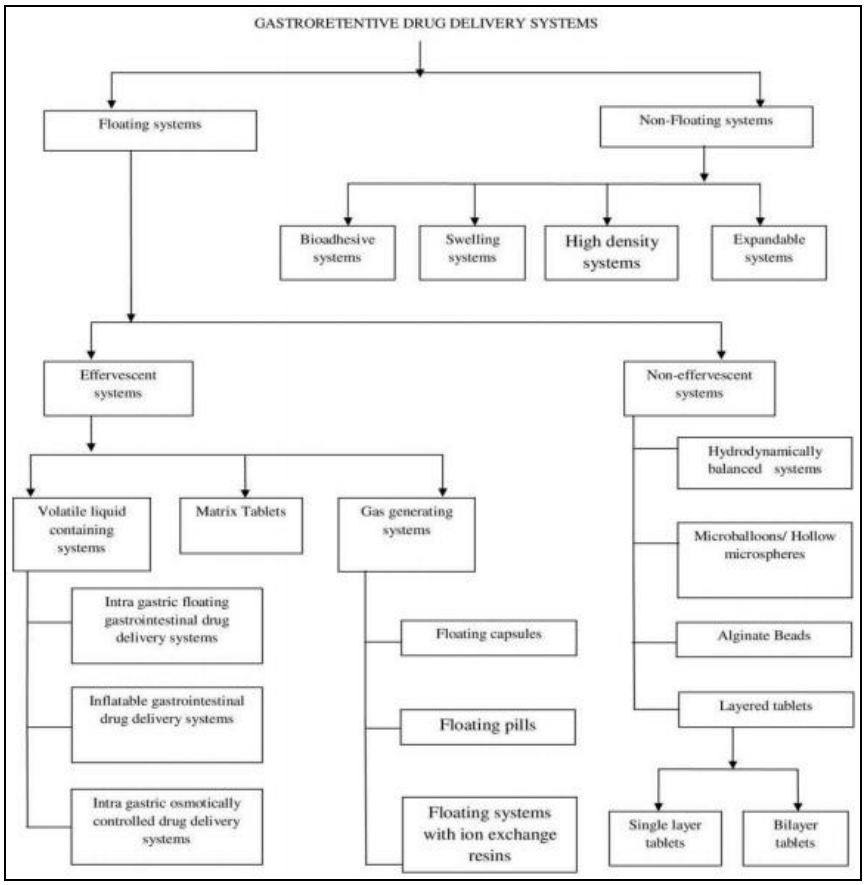


FIG. 9: VARIOUS TYPES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Approaches to Achieve Gastric Retention:

High Density (Sinking) System or Non-Floating Drug Delivery System: For this strategy to work, the dosage forms' density must be higher than that of the stomach's normal contents (1.004 gm/cm^3). To create these preparations, the active substance is either coated onto a dense core or combined with inert materials such as iron powder, barium sulfate, zinc oxide, and titanium oxide. These materials can add a density of between 1.5 and 2.4 gm/cm^3. A density of roughly 2.5 gm/cm3 seems necessary for a considerable prolongation of stomach residence time [16-19]. However, the efficacy of this system in humans has not been shown, and no system has been commercialized **Fig. 10**.

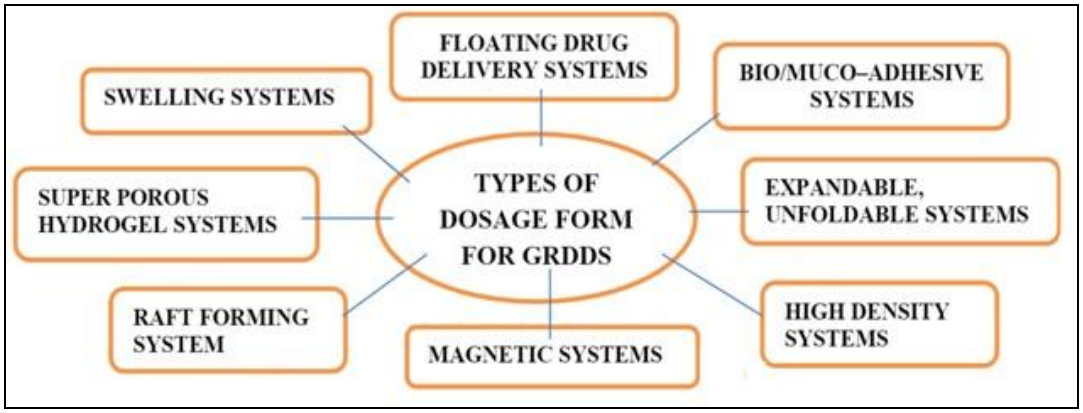


FIG. 10: GASTRORETENTIVE TECHNIQUES

The various types of these systems are as follows:

Single-layer Floating Tablets: This drug has a bulk density of less than one and is combined with a hydrocolloid that forms a gel when exposed to stomach acid to create a single-layer tablet having these characteristics. These dosage forms are buoyant because the inflated polymer has trapped air inside them **Fig. 11**.

Bilayer Floating Tablets: The two layers of a bilayer tablet are used to control the drug release rate.

The immediate-release layer releases the first dose, while the sustained-release layer floats in the stomach because it absorbs gastric fluid and keeps its bulk density below unity.

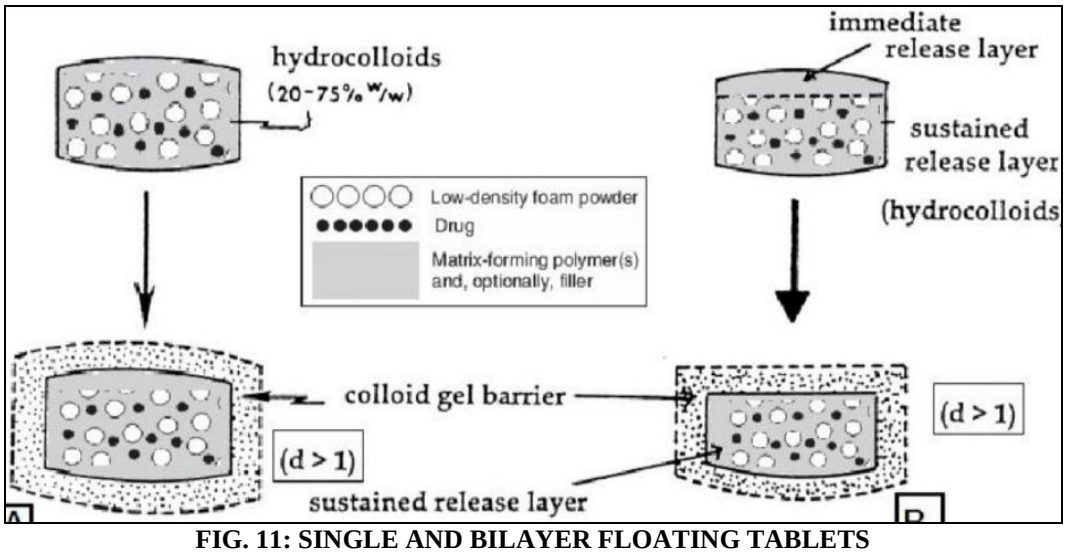


FIG. 11: SINGLE AND BILAYER FLOATING TABLETS

Floating Drug Delivery Systems: Floating drug delivery devices are one of the most effective means of establishing stomach retention and appropriate pharmaceutical bioavailability. These administration forms are most effective when used with drugs that have a narrow absorption window in the stomach or upper small intestine. Because of its lower bulk density compared to gastric fluids, it

has the potential to float in the stomach for an extended period of time without affecting the gastric emptying rate, and the drug is released gradually and at the correct rate. When a drug is swallowed, it first enters the stomach and then leaves via the residual system. Thus, the GRT was improved, and the inter-individual variance in plasma drug concentration was reduced. The major requirements for a floating drug delivery system are:

1. As a reservoir, it needs to slowly release its contents while keeping its specific gravity below that of the contents of the stomach (1.004-1.01 gm/cm^3).
2. There needs to be a cohesive gel layer formed.

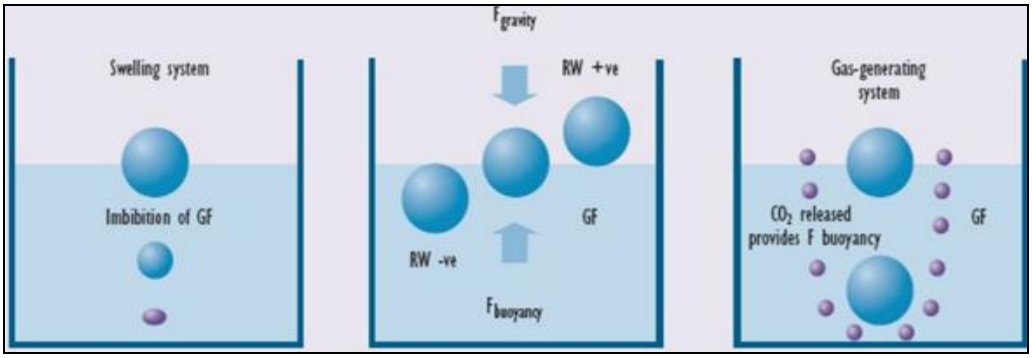


FIG. 12: MECHANISM OF FLOATING DRUG DELIVERY SYSTEM

The intrinsic low density might result from air entrapment (via methods like hollow chambers) or the incorporation of low-density materials (e.g. fatty materials, oils, or foam powder). These procedures were used to develop single- and multi-unit systems of floating dosage forms: **Fig. 12**. Polypropylene foam powder, matrix-forming polymers, medicine, and filler have all been proposed as part of a single-unit floating system. The exact regulation of the ensuing drug release patterns is possible in conjunction with the good floating behavior of these devices. Constipation and pain may result from single-unit dosage forms sticking together or becoming stuck in the gastrointestinal tract.

In contrast, multi-unit floating systems have been shown to reduce both inter- and intra-subject variability in medication absorption and the danger of dose dumping, making them a potentially attractive alternative. Drugs can be released more steadily and for a longer period of time using multiple-unit floating systems like the air compartment multiple-unit system, HM prepared using the emulsion solvent diffusion method, microparticles based on low-density foam powder and beads prepared using the emulsion gelatin method. Non-effervescent and effervescent methods, both based on the notion of buoyancy, have been employed to develop a floating pharmaceutical delivery system.

Volatile Liquid Containing Systems: The two halves of this system are divided by a flexible, impermeable, and pressure-sensitive bladder. The first compartment is for the drug, while the second is for the volatile liquid. To keep the GRT steady during medication administration, an inflatable chamber filled with a liquid (such as ether or cyclopentane) that gasifies at body temperature may be used. Inflatable devices may be designed to expel themselves from the stomach after a specified amount of time by including a bioerodible plug composed of polyvinyl alcohol, polyethylene, or another substance that progressively dissolves. Device inflates, releasing medicine slowly into stomach fluid.

Intragastric Floating Gastrointestinal Drug Delivery System: In these devices, the drug reservoir is housed in a microporous compartment, and a floatable chamber that can be evacuated or filled with air or a harmless gas causes the chamber to expand in the stomach **Fig. 13**.

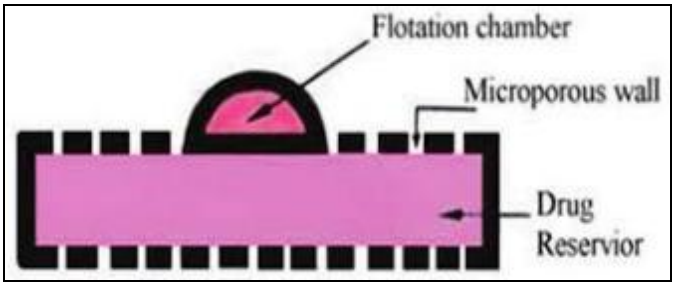


FIG. 13: INTRAGASTRIC FLOATING GDDS

Inflatable Gastrointestinal Delivery System: A drug or polymeric matrix impregnated with a drug serves as the drug reservoir, which is placed into the inflation chamber before being wrapped in a gelatinous capsule. Bio-erodible polymer filament (copolymer of PVA, polyethylene) gradually dissolves, causing the drug reservoir to retain in the gastric fluid, resulting in controlled drug release. The inflation chamber contains a volatile liquid (e.g., ether, cyclopentane, *etc*.) that gasifies at body temperature, causing the chamber to inflate **Fig. 14**.

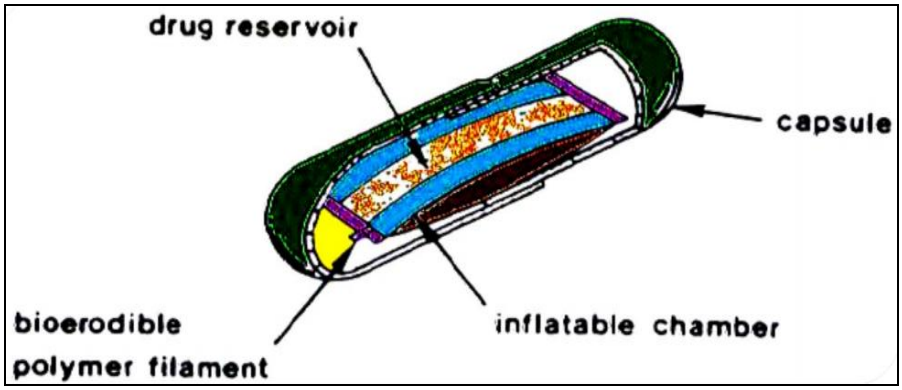


FIG. 14: INFLATABLE GDDS

Intragastric Osmotically Controlled Drug Delivery System: This method consists of a drug delivery device controlled by osmotic pressure and inflatable floating support. The capsule's quick disintegration in the stomach frees the drug delivery system that is governed by osmosis and enters the stomach. An osmotic pressure-controlled medication delivery system consists of a drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is surrounded by a foldable, pressure-sensitive bag that is airtight, watertight, and equipped with a drug delivery hole. Osmotic active salt is contained in a semi-permeable container at the heart of the device. The constant absorption of water from GI fluid into the stomach's osmotically active compartment via a semi-permeable barrier allows the osmotically salt to dissolve. Following exposure to osmotic pressure, the collapsible bag's reservoir compartment contracts, releases the medication solution formulation via the delivery hole. The bio-erodible plug in the floating support causes the support to deflate after a certain length of time. The deflated drug delivery system is then removed from the stomach **Fig. 15**.

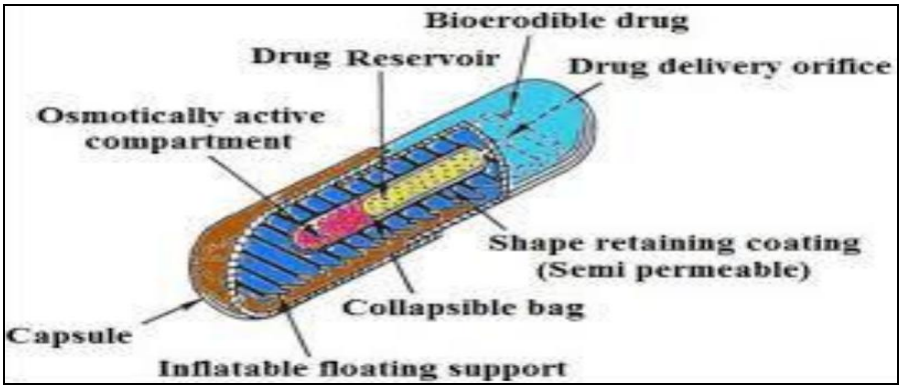


FIG. 15: INTRAGASTRIC OSMOTICALLY CONTROLLED DDS

Gas Generating System: Floatability might potentially be produced by the creation of gas bubbles. Carbon dioxide (CO_2) may be generated locally by combining carbonates or bicarbonates with an acid, such as stomach acid, citric acid, or tartaric acid. It has been shown that a stoichiometric ratio of 0.76:1 between citric acid and sodium bicarbonate is best for gas generation. Another possibility is a liquid matrix that turns into a gas at body temperature. Such strategies have been used in both standalone and multi-part structures **Fig. 16.**

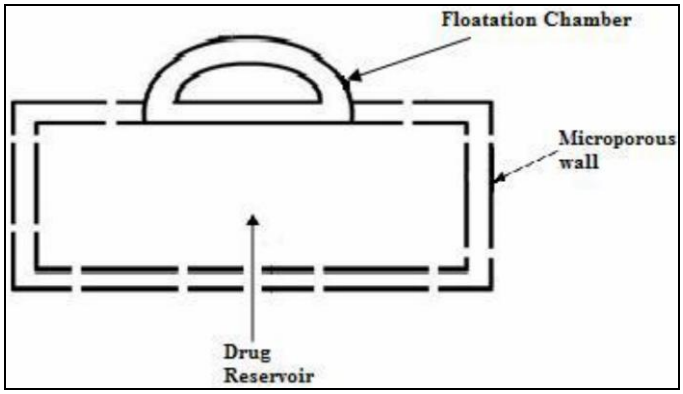


FIG. 16: GAS-FILLED FLOATATION CHAMBER

Steps Involved in Floating of Dosage Form:

1) Penetration of water

2) Generation of CO_2 and floating

3) Dissolution of drug

Non-effervescent Systems: Non-effervescent floating drug delivery methods often use polymers such as polyacrylate, polycarbonate, polystyrene, and polymethacrylate, as well as hydrocolloids of the cellulose type, polysaccharides, or matrix-forming polymers. One way to preserve its relative shape and bulk density below unity in the gastrointestinal environment involves mixing the drug closely with a gel-forming hydrocolloid that comes into touch with stomach fluid after oral administration. Because the polymer expansion traps air, these dosage forms may float. Common excipients used in these setups include polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide, and polycarbonates. It's possible that subtypes of this system exist.

Hydrodynamically Balanced Systems: Sheth and Tossounian coined the phrase "hydrodynamically balanced systems" to describe these setups. One such strategy uses a pharmaceutical that uses gel-forming hydrocolloids to prevent the drug from sinking to the bottom of the stomach. This unit dose contains one or more hydrophilic polymers that may form a gel. Hydroxypropyl methylcellulose, hydroxy ethylcellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, polycarbophil, polyacrylate, polystyrene, agar, carrageenans, and alginic acid are only some of the excipients used in the creation of these systems.

In most cases, the polymer is administered alongside other drugs in a capsule containing a hydrodynamically stable system. The capsule shell dissolves upon contact with water, and the expanding gelatinous barrier provides the dosage form with long-term buoyancy in gastric juice. The dosage form keeps the surface hydrated and buoyant because the constant surface erosion allows water to enter the inner layers. Formulations that employ fatty excipients have a low density, which protects them against erosion. In the 1980s, consumers could buy the system-based product Madopar LP®. Polymer influence on drug release profile relies on equilibrium between drug loading and polymer effect on drug release profile. Many different strategies have been tried and investigated to improve the performance of hydrodynamically stable floating devices **Fig. 17**.

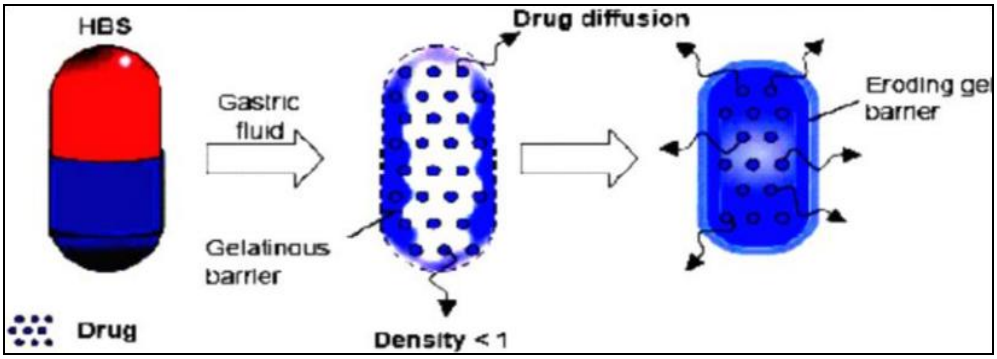


FIG. 17: HYDRODYNAMICALLY BALANCED SYSTEMS

Microballoons / Hollow Microspheres (HM): Simple solvent evaporation or solvent diffusion/evaporation procedures were employed to create HM loaded with medications in their other polymer shelf, hence extending the GRT of the dosage form. Some of the most common polymers used in creating such systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S,

agar, and low methoxylated pectin. Form formulation variables such as the total quantity of polymers employed, the plasticizer polymer ratio, and the solvent influence flotation and drug release. The microballoons floated continuously in an acidic dissolving liquid with surfactant for more than 12 hours. Due to their ability to combine the advantages of a multiple-unit system with outstanding flotation, HM is presently considered one of the most promising buoyant systems.

Methods of Preparation of Hollow Microspheres: HM's hollow interior is manufactured by solvent diffusion and evaporation methods. After dissolving the polymer in an organic solvent, the drug is either dissolved or disseminated throughout the solution. To create an oil-in-water (o/w) emulsion, the pharmaceutical solution is emulsified into an aqueous phase that contains polyvinyl alcohol. After a stable emulsion has been made, the organic solvent is evaporated by either increasing the temperature under pressure or by constantly swirling the mixture. Since the droplets have a cavity created by the polymer precipitation at the o/w interface after the solvent has been removed, they are able to float **Fig. 18**.

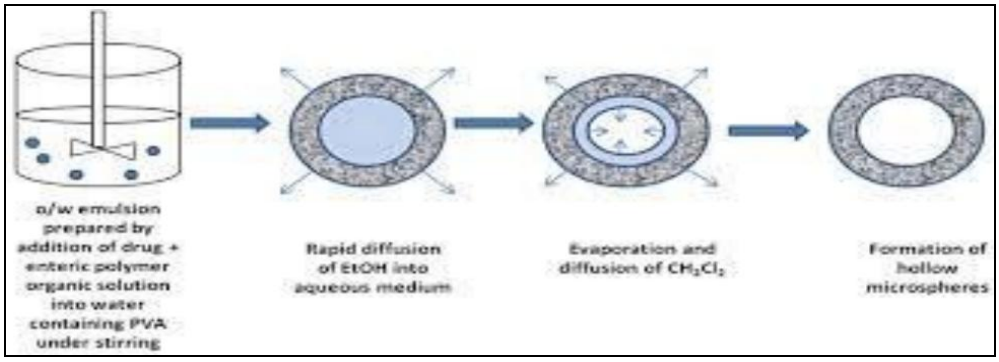


FIG. 18: HOLLOW MICROSPHERES (MICROBALLONS)

Advantages of Hollow Microspheres: It helps patients remember their medication by decreasing dosing frequency. Continuous drug release enhances bioavailability despite the first-pass effect because it reduces plasma drug concentration fluctuations and keeps the drug concentration where it should be. Buoyancy raises GRT. Medicines that are only soluble in the stomach are absorbed more effectively. Prolonged, steady medication delivery with precise timing. The stomach may be a site-specific distribution area for certain drugs. Microspheres are preferable to single-unit floating dosage forms because they provide uniform drug release and eliminate the risk of dose dumping. Because to the slow release, stomach upset is prevented. Drugs with a shorter half-life could be more effective in treating these conditions.

Microporous Compartment System: For this technique to be effective, a medication reservoir must be enclosed in a microporous compartment with pores along the top and bottom walls. Its exterior walls were completely sealed to prevent the undissolved drug from coming into touch with the stomach lining. Thanks to the air stored in the flotation chamber, the delivery system may float freely in the stomach contents. Down the opening, gastric juice may dissolve the medicine before carrying it through the intestines for absorption.

Effervescent (Gas Generating) Systems: Floatability might be achieved by creating gas bubbles. These buoyant systems use swellable polymers like polysaccharides (like chitosan) and effervescent components (e.g., sodium bicarbonate, citric acid, or tartaric acid). According to research, citric acid and sodium bicarbonate have a 0.76:1 stoichiometric ratio, which is optimal for gas generation.

As a result of the released carbon dioxide, the formulation will float harmlessly in the stomach. Floating systems based on ion exchange resin technology, a mixture of sodium alginate and sodium bicarbonate, and multiple-unit dosage forms that produce gas (carbon dioxide) when ingested have all been reported.

Likewise, floating mini capsules with a core of sodium bicarbonate, lactose, and polyvinyl

pyrrolidone (PVP) coated with HPMC have been described. Moreover, multilayer and bilayer systems have been constructed in **Fig. 19**.

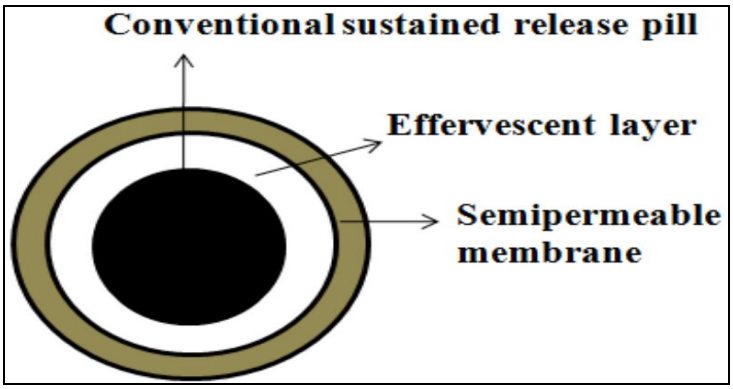


FIG. 19: EFFERVESCENT (GAS GENERATING) SYSTEM

Any of the layers may include the gas-generating chemical, and the medications and the excipients can be produced independently. One modification involves covering the matrix with a polymer that allows water through but blocks carbon dioxide. Finding the sweet spot between the polymers' elasticity, flexibility and permeability is the primary problem with these formulations (**Fig. 20**.

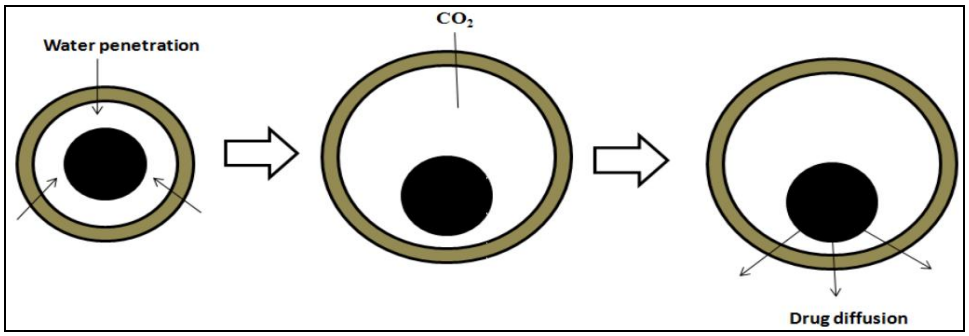


FIG. 20: DRUG RELEASE FROM EFFERVESCENT (GAS GENERATING) SYSTEMS

Bioadhesive or Mucoadhesive Drug Delivery Systems: Bioadhesive, drug delivery devices, are used to increase drug absorption at a particular place in the body. This technique uses bioadhesive polymers, which might potentially adhere to the stomach's epithelial membrane. Because of this, they promote longer-lasting gastric retention **Fig. 21**.

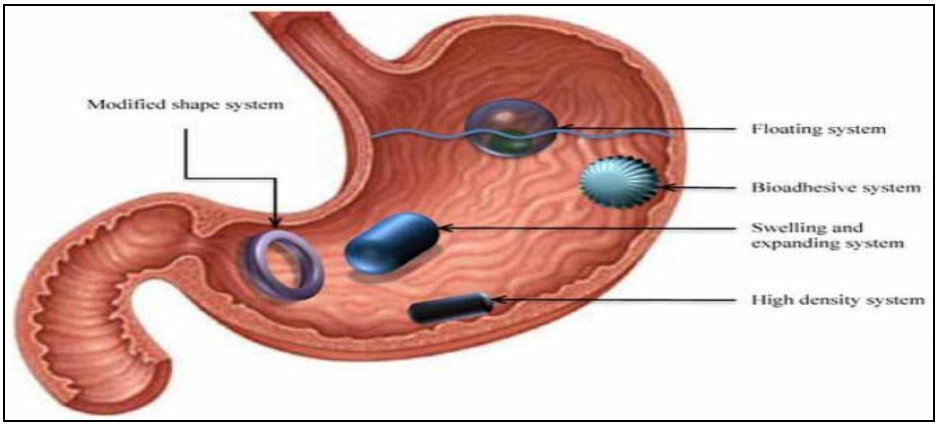


FIG. 21: BIO-ADHESION SYSTEM

Adhesion is based on the fact that a dosage form may adhere to the mucosal surface via a variety of mechanisms **Fig. 22**. These are the mechanisms:

- First, there's the "wetting" theory, which is predicated on the idea that bioadhesive

polymers may spread and make intimate contact with mucosal layers.

- Second, diffusion theory proposes that mucin strands get physically entangled in flexible polymer chains or that mucin strands interpenetrate the porous structure of the polymer substrate.
- Thirdly, the absorption hypothesis states that bioadhesion is caused by weaker forces, such as Vander Waal forces and hydrogen bonding.
- The fourth possibility is the "electron theory," which states that the bioadhesive material and the glycoprotein mucin network are attracted to one another due to electrostatic forces.

Many different substances are used for bioadhesion, including polyacrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG), and polylactic acid. Some of these polymers are effective in creating bioadhesive, but keeping it in place is challenging because of the rapid mucus turnover in the digestive system.

There are various types of mucoadhesion:

Hydration-Mediated Adhesion: Hydrophilic polymers, which have mucoadhesive properties due to their high water absorption and subsequent stickiness, are used for this purpose. For this bio/mucoadhesive drug delivery system to have prolonged gastroretention, the polymer's rate of degradation must also be considered.

Bonding-Mediated Adhesion: Physical-mechanical and chemical bonding are only two of the methods used to secure polymer adherence to mucus or epithelial cell surface.

When an adhesive substance is inserted into the mucosa's creases and folds, it may cause the mucosa to fuse together mechanically. Primary (covalent) and secondary (ionic) chemical linkages exist (ionic).

Receptor-Mediated Adhesion: Polymers may bind to specific receptor sites on the surface of cells, extending the half-life of dosage forms in the stomach. Tomato lectins are only one example of a plant lectin that interacts specifically with sugar groups in mucus and on the glycocalyx.

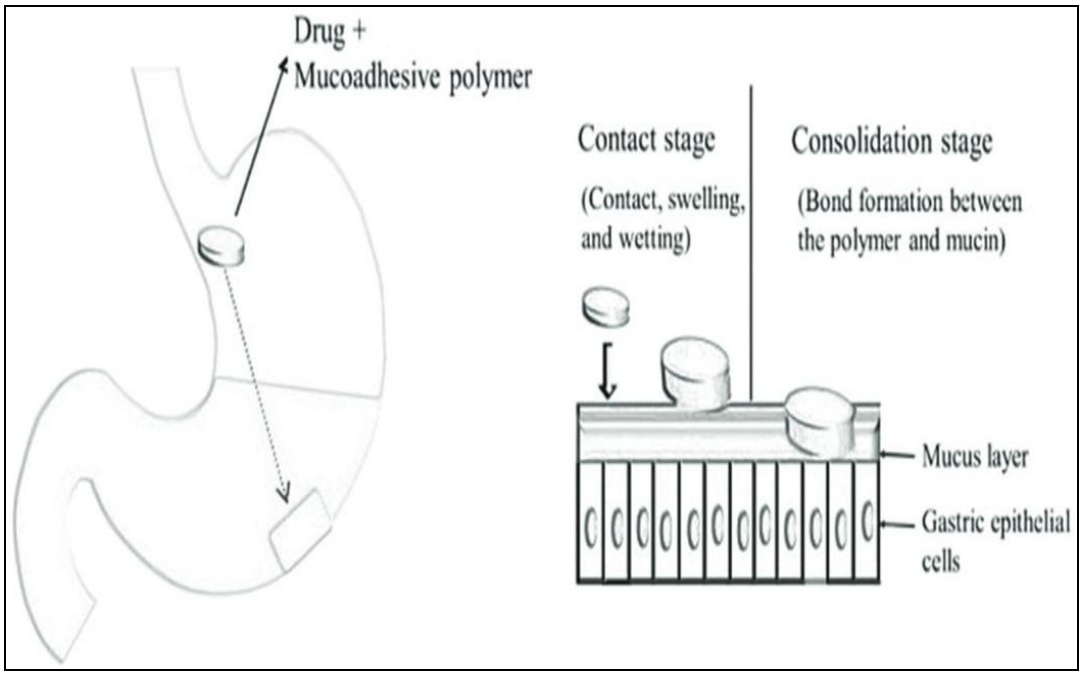


FIG. 22: MUCOADHESIVE DRUG DELIVERY SYSTEM

Polymers Employed for Mucoadhesion:

Synthetic Polymers: Various grades Polyethylene oxide like WSR 301, 301, N10, Coagulants, *etc*. Cellulose derivatives (methylcellulose, ethyl-cellulose, hydroxy ethylcellulose, Hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose. Poly (acrylic acid) polymers (carbomers, polycarbophil). Poly

(hydroxyl ethyl methyl acrylate). Poly (vinyl pyrrolidone). Poly (vinyl alcohol).

Natural Polymers:

(a) Tara gum

(b) Sodium alginate

(c) Karaya gum

(d) Guar gum

(e) Xanthan gum

(f) Locust bean gum

Expandable, Unfoldable and Swellable Systems: It is possible for a dosage form to make it through gastric transit if it is bigger than the pyloric sphincter. However, whether taken alone or in combination, the dosage form must be manageable enough to be swallowed without causing gastrointestinal obstruction **Fig. 23**.

FIG. 23: UNFOLDABLE AND SWELLABLE SYSTEMS

As a result, their configurations are needed for the development of an extensible system to increase GRT:

They come in three sizes:

1) A little pill for oral administration

2) A larger gastro retentive pill

3) A third tiny pill for elimination once the device has discharged its contents **Fig. 24**.

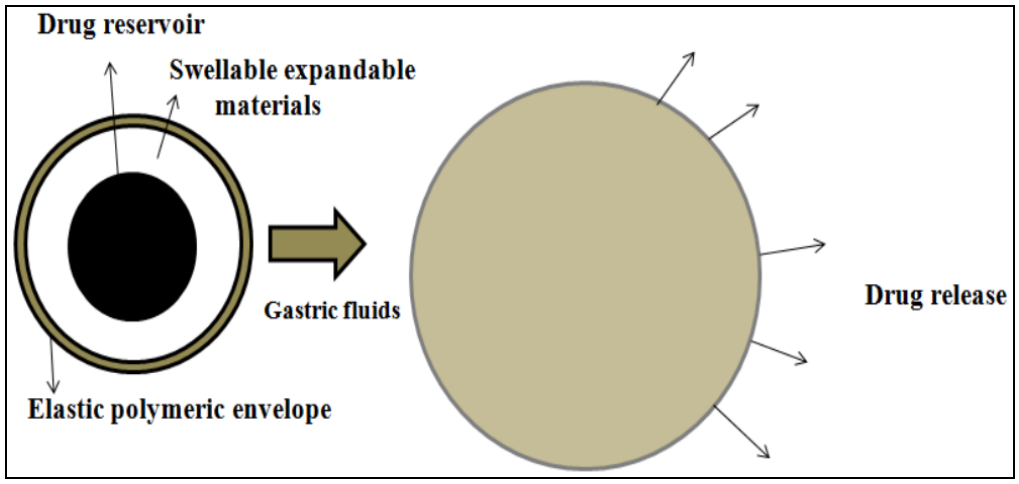


FIG. 24: DRUG RELEASE FROM SWELLABLE SYSTEMS

Greater gastroretentivity is achieved by combining a large dosage size with a very rigid dose form that can withstand the peristalsis and mechanical contractility of the stomach. Recently, there has been a lot of research and development effort put into the idea of using foldable and swellable devices to distribute gastroretentive drugs effectively. Systems that can be unfolded are made using biodegradable polymers. Bioerodible polymer is compressed into a capsule that extends into the stomach, and the resulting structures range from tetrahedrons and rings to planner membranes (4-label discs and 4-limbed crosses) **Fig. 25**. Swellable systems are also kept in the GIT due to their mechanical properties. The diminution is due to the absorption of osmotic water, and the dosage form is small enough to be dissolved in gastric juices. The challenges of storing rapidly hydrolyzable, biodegradable polymers, the short-term mechanical shape memory for the unfolding system, and the high production costs all work against the widespread use of expandable systems. Blockage, intestinal adhesion, and gastropathy may occur if single-unit expandable medication dosage forms are retained for a lengthy period of time due to their rigidity and size.

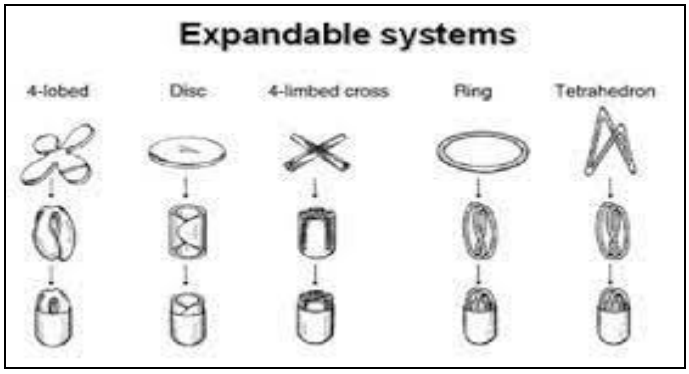


FIG. 25: GEOMETRICAL SHAPES OF GASTRORETENTIVE PATCH

Super porous Hydrogel Systems: There is enough difference between these expandable systems and others that they deserve their own classification. To improve GRT, super porosity hydrogels with an average pore size of >100 miter may absorb water rapidly by capillary wetting through many linked open holes and expand to equilibrium size in under a minute. They are built to grow to an enormous size (a swelling ratio of 100 or more) and withstand the force of the stomach contracts. This is inferred from the co-formulation of hydrophilic particle material.

High-density Systems: These components that have a density of 3 g/cm^3 are stored in the stomach's rugae and can withstand the peristaltic waves. Systems with a density higher than 2.4–2.8 g/cm^3 may be retained in the stomach's lower region. Manufacturing such systems with a large amount of medicine (>50%) and reaching the required density of 2.4-2.8 g/cm^3 is technically tough, which is the most significant drawback of such systems. Diluents such as barium sulfate, zinc oxide, titanium dioxide, and iron powder may be used to create such high-density formulations **Fig. 26**.

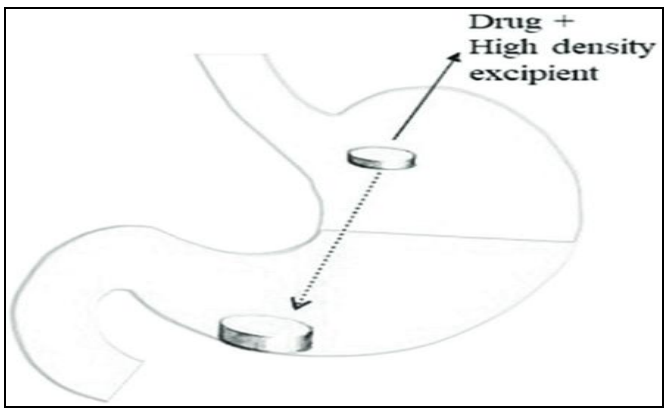


FIG. 26: HIGH-DENSITY SYSTEMS

Swelling Systems: After being ingested, these dosage forms swell to a size that precludes them from being absorbed by the pylorus. Due to this, the dosage form remains in the stomach for a much longer period of time. These devices are commonly called plug-type systems because they become trapped at the pyloric sphincter. Polymeric matrices stay in the stomach for hours after being consumed. In order to achieve controlled and prolonged drug release, it is necessary to choose a polymer with the ideal molecular weight and swelling properties.

When exposed to stomach acid, the polymer absorbs the fluid and swells. Due to the physical-chemical crosslinks in the hydrophilic polymer network, these polymers expand substantially. These crosslinks prevent the polymer from dissolving, which protects the structural integrity of the dosage form. To some extent, the quantity and duration of swelling are controlled by the degree of crosslinking between the polymeric chains. If the system is highly crosslinked, its swelling capacity is decreased, and its physical integrity is maintained for longer.

In contrast, a low degree of crosslinking causes extensive swelling followed by rapid polymer breakdown. The correct quantity of cross-connecting is necessary to keep swelling and breakdown in check. The swelling system will lose its integrity owing to a loss of mechanical strength caused by abrasion or erosion when the membrane ruptures from constant expansion, or it may burst into small fragments. These systems may deteriorate in the presence of stomach fluids to the point that the device may no longer attain or sustain the expanded configuration after a certain amount of time **Fig. 27**.

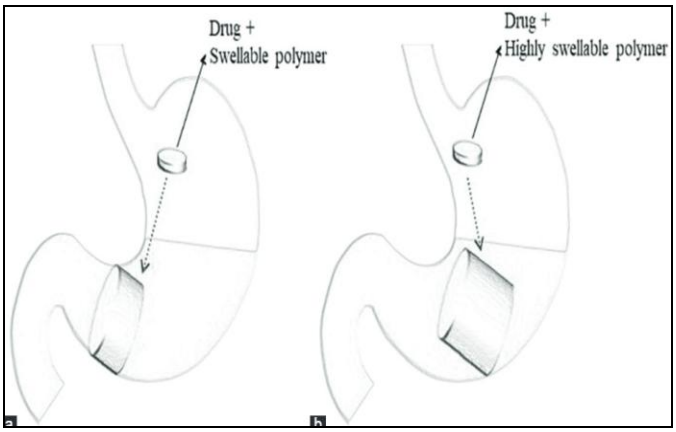


FIG. 27: SWELLABLE SYSTEM

Raft Forming Systems: These systems allow for sustained drug release and are fabricated using gel-forming polymers and effervescent excipients. These gadgets are great for delivering a contained effect since they restrict the connection between the esophagus and the stomach. Therefore, the technique has the potential for treating conditions including GERD and peptic ulcers. Upon contact with gastric juices, these systems swell and form a viscous cohesive gel, forming a continuous layer called a raft. Sodium alginate, sodium bicarbonate, and acid neutralizer all generate a gas-generating gel in the new antacid raft-building technology. The raft floats atop the stomach fluid because carbon dioxide is being produced, reducing the bulk density of the system. The drug may be continually delivered as the raft floats on the stomach fluid for many hours. When it comes to administering antacids, these rafts really shine. These systems are susceptible to MMC because of their poor mechanical strength **Fig. 28**.

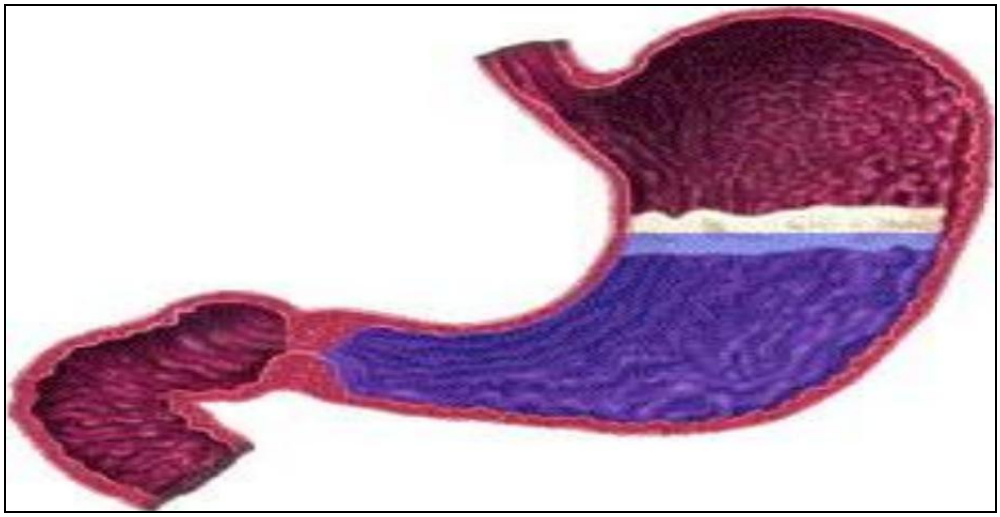


FIG. 28: SCHEMATIC ILLUSTRATION OF THE BARRIER FORMED BY A RAFT-FORMING SYSTEM

Magnetic Systems: This approach of bettering GRT works on the premise that the dosage form has a small internal magnet and that a magnet is then placed on the abdomen over the stomach site. Although it seems that the magnetic system works, the placement of the external magnet is critical and might put the patient at risk of not using it **Fig. 29**.

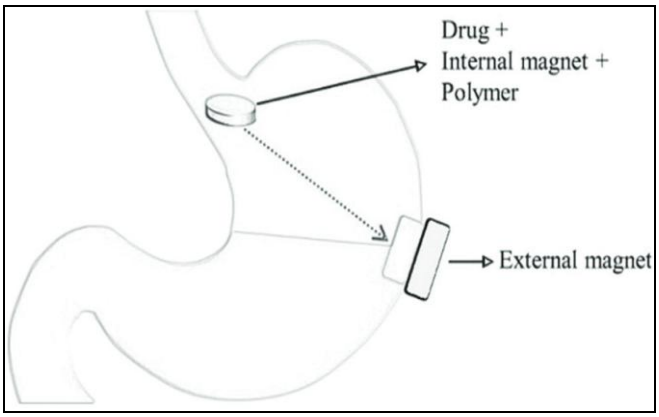


FIG. 29: MAGNETIC SYSTEM

Applications of Floating Microspheres: Floating microspheres may be used to transport drugs with narrow absorption windows, such as antiviral, antifungal, and antibiotic drugs (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines). Floating Indomethacin microspheres, for example are highly useful for rheumatoid arthritis sufferers because they allow for regulated release of the drug while reducing the major side effect of stomach discomfort.

Floating microspheres excel when it comes to administering drugs with low solubility or insolubility. It is generally known that the transit time becomes a crucial factor affecting drug absorption as a medication's solubility decreases since there is less time available for dissolution. For weakly basic drugs that are poorly soluble at an alkaline pH, HM may confine such pharmaceuticals to the stomach, preventing solubility from becoming the rate-limiting step in a release. The positioned gastric release is helpful for drugs like verapamil hydrochloride that are absorbed quickly and completely in the stomach.

Floating microspheres with gastroretentive properties will change the absorption profile of the active drug, increasing its bioavailability. By facilitating local drug release and producing high drug concentrations at the gastric mucosa, HM may considerably enhance stomach pharmacotherapy for treating stomach and duodenal ulcers, gastritis, and esophagitis. HM has recently been reported to entrap medications such as prednisolone, lansoprazole, celecoxib, piroxicam, theophylline, diltiazem hydrochloride, verapamil hydrochloride, riboflavin, aspirin, griseofulvin, ibuprofen and terfenadine [20].

Advantages of Gastroretentive Drug Delivery Systems:

Enhanced Bioavailability: The bioavailability of riboflavin CR-GRDF is much greater than that of non-GRDF CR polymeric formulations. Medication absorption and transit through the gastrointestinal system are only two processes that act together to determine the total quantity of drug absorption [21, 22].

Enhanced the First-pass Biotransformation: A prolonged rather than a bolus input of the medication to the metabolic enzymes (cytochrome P450, in particular CYP3A4) may greatly boost the pre-systemic metabolism of the tested substance, analogous to the increased effectiveness of active transporters with capacity restricted action.

Sustained Drug Delivery / Reduced Frequency of Dosing: Input from CR-GRDF that is both steady and slow may trigger a pharmacokinetic flip-flop, allowing for less frequent dosing of medications with a short biological half-life. This quality is associated with better treatment outcomes due to higher patient compliance.

Targeted Therapy for Local Ailments in the Upper GIT: Treatment of the stomach and small intestine locally may benefit from a more prolonged and stable release of medicine from the GRDF. It is possible to attain local therapeutic medicine concentrations using this route of administration, although very little quantities of the drug are absorbed and distributed systemically.

Reduced Fluctuations of Drug Concentration: After CRGRDF therapy, continuous drug infusion produces blood drug concentrations within a narrower range than instant release dose forms. This means that drug effects are more consistent and that undesirable effects related to peak concentrations are less likely to occur. This is of paramount significance for drugs with a narrow therapeutic window.

Improved Selectivity in Receptor Activation: Because different drugs activate different types of receptors at varying doses, it's important to keep such concentration changes to a minimum for optimal pharmacological efficacy.

Reduced Counter-activity of the Body: When a medication disrupts the body's regular physiologic processes, the body often replies with a rebound activity that lessens the drug's effect. The drug's therapeutic effectiveness may be improved by slowing its absorption into the body since this decreases the likelihood of adverse effects.

Extended Time over Critical (Effective) Concentration: For drugs with non-concentration-dependent pharmacodynamics, such as beta-lactam antibiotics, the clinical response is not associated with peak concentration but rather with the amount of time spent at a critical therapeutic concentration. By maintaining blood levels above a threshold concentration for an extended period of time, the pharmacological effects and therapeutic outcomes may be improved using the sustained route of administration.

Minimized Adverse Activity at the Colon: When medicine is held in the stomach's GRDF, less of it makes its way to the large intestine. This means that the drug's potential gastrointestinal side effects could be avoided. For beta-lactam antibiotics, whose presence in the colon leads microorganisms to acquire resistance, this pharmacodynamic aspect supports GRDF formulation.

Site-specific Drug Delivery: A floating dosage form may be an effective delivery system for poorly absorbed drugs in the upper small intestine. Maintaining adequate local therapeutic levels while reducing systemic exposure is achieved by the controlled, slow delivery of the medicine to the stomach. This lessens the drug's potentially harmful effects on blood flow. Plus, the longer stomach availability of a site-guided administration method may lead to less frequent dosing.

MERITS OF FDDS:

Sustained Drug Delivery: The GRT of many different medications may be significantly extended by using an FDDS since it can remain in the stomach for several hours. It is projected that uniform and steady blood levels of medication may be achieved with the administration of a single dose of medication that releases active components over a lengthy period of time, thanks to the expected extension in stomach retention.

Site-specific Drug Delivery: Pharmacological targeting to the stomach seems useful for any medications aiming to have a sustained local impact on the gastroduodenal wall. Examples include Helicobactor pylori eradication, which requires many drugs to be taken multiple times daily and has low patient compliance. By reducing the dosage and the number of times it is administered, FDDS has the potential to make the therapy more stable.

Pharmacokinetic Advantage: It's important to note that any solute created in the stomach will empty with the fluids and be available for absorption throughout the whole surface of the small intestine. This should be highly useful if an absorption window opens up in the first part of the proximal small intestine. The relative bioavailability of a drug may be increased by increasing the dose, which is possible when the total GIT time is longer. The bioavailability of furosemide was significantly increased (42.9% vs. 33.4% and 29.5%, respectively, when supplied as a floating dosage form, compared to the commercially available tablet (Lasix®) and the enteric product (Lasix® long). Theophylline, which is better absorbed in the upper GIT, also saw an increase in bioavailability. For ostensibly similar reasons, tranilast and verapamil, two other medicines with limited bioavailability, were also included in FDDS [23].

Advantages of Gastroretentive Drug Delivery Systems: Compared to non-GRDDS, this GRDDS may significantly increase the bioavailability of therapeutic medicines, especially those metabolized in the upper GIT. The extent of drug absorption is influenced by a number of factors related to drug digestion and transport in the gastrointestinal tract. A pharmacokinetic reversal may occur with SR for drugs with a short half-life, allowing for less frequent dosing and higher patient compliance.

They may be used to solve the issues with GRT and GET, which is an improvement above the standard approach. These gadgets are designed to float on top of gastric fluids without affecting the intrinsic rate of absorption since their bulk density is lower than that of gastric fluids.

Drug release from dosage forms that offer local therapy in the stomach and small intestine may be prolonged and more consistent when administered through a gastroretentive route of administration. Therefore, they are useful for treating conditions affecting the stomach and small intestine.

Drug systemic exposure may be minimized or eliminated by the use of gastroretentive dosage forms, which are slowly released and so assure effective local action at the site of disease. As a result of this targeted administration of medicine, unwanted side effects are mitigated to a greater extent.

Gastroretentive dosage forms lessen the peaks and valleys in medicine concentration and effect. Therefore, adverse effects associated to peak concentrations and depending on concentrations may be shown. Because of the importance of this for drugs with a narrow therapeutic window.

Drugs are more effective when given gastroretentiveally because the body has less time to mount a counter-activity. If variations in drug concentrations can be reduced, selective receptor activation may be enhanced. Gastroretentive doses have a slow release rate, thus the medication stays at a high concentration for a longer length of time, which has greater pharmacological and chemical implications [24].

Characterization: The following are the parameters that are used to evaluate the gastroretentive expandable system:

Unfolding Time: Folded in a zigzag fashion, the two films were then put in individual containers. In vitro dissolution studies were performed using the USPXXIII Apparatus 1 (Basket) spinning at 100 rpm and 900 mL of aqueous hydrochloric acid at a pH of 1.2 at 37±0.5°C. Six capsules were utilized

in each case. The baskets were taken away and the videos were examined for unfolding behavior at 5, 10, 15, 20, 30, 60, 120, 240, 480, and 720 minutes [25, 26].

Uniformity of Weight: Ten 4-cm × 2-cm patches were removed from each plate after each formulation was prepared in triplicate. The weight was calculated using a Shimadzu digital balance. The average and standard deviation were determined for each formula.

Thickness: The thickness of the patch was measured using a digital screw gauge. The mean and standard deviation for each formulation were calculated.

Folding Endurance: Folding endurance was measured by counting the number of times a patch could be folded in the same spot before tearing.

Drug Content: After placing the film in a 100 mL volumetric flask with 0.1 N HCL solution, we let it sit for 24 hours while stirring periodically. Following filtration, the filtrate is diluted with 0.1 N HCl and subjected to ultraviolet light.

Resultant Weight: Bulk density and floating time are two of the most important aspects of buoyancy. However, a single estimate of density is inadequate to explain buoyancy since density fluctuates with changes in resultant weight as a function of time.

Matrix tablets, such as those made from bicarbonate and matrix polymer, tend to float at first because of the gas produced and trapped within, but their weight eventually shifts when some of the medication is released, and the outside of the matrix polymer erodes away.

Buoyancy Lag Time: When a dosage form is added to a dissolving liquid, the time it takes to float to the surface is measured. These factors may be evaluated during the dissolving test.

Floating Time: Most of the buoyancy experiments are done in 37°C Simulated Gastric Fluid. The dosage form's floating time is the time it takes to dissolve completely in the solubilizing medium.

Swelling Index: Films were tested in triplicate using stomach fluid simulators to measure edema (pH 1.2). A film was weighted at the outset (W1), then immersed in a 37°C medium for 360 minutes (W2). The swelling ratio was determined as:

$$(W2-W1) / W1$$

Water Uptake: It is a proxy for the swelling capacity of a matrix. At certain intervals, the dosage form is removed and the patient's weight is recorded.

$$\text{Water uptake} = WU = (Wt – Wo) \times 100 / Wo$$

Where, Wt = weight of dosage form at time t. Wo = initial weight of dosage form.

In-vitro **Mucoadhesion:** The film's ability to adhere to the stomach mucosa was evaluated three times using a twin beam physical balancing. The wet film was brought into touch with dry film attached to the bottom surface of another Teflon cylinder suspended from the left arm of the balance by withdrawing a 5 g weight from the right pan of the balance. The right pan was loaded with weights until the film detached from the mucosal surface, and then the balance was left in that position for three minutes. The greater the pan's weight, the greater the bioadhesive force required to separate the film from the mucosa. The force of the adhesion was calculated using the formula:

$$\text{Force of adhesion (N)} = (\text{Bio adhesive strength}/ 1000) \times 9.81$$

In-vitro **Mucoadhesive Time:** The duration of film dissolution from goat stomach mucosa in 0.1 N hydrochloric acid was evaluated (pH 1.2). It was evaluated using an *in-vitro* dissolving device and an *in-vitro* adhesion testing approach.

Goat stomach mucosa was bonded together for 5 minutes under pressure using a 0.1 N HCl buffer and cyanoacrylate adhesive in a beaker of dissolving equipment with a 3 cm diameter. At 37±0.5°C, the time required for the mucoadhesive film to separate from the mucosal membrane was measured by rotating the dissolving equipment assembly at an appropriate speed.

Tensile Strength: To determine the tensile strength of the polymeric film, it was sandwiched between corked linear iron plates. The film was sandwiched between two corked linear plates. A pulley system was in place, with one end of the film attached to an iron screen and the other to a free-moving

thread. The pan at the trailing end of the tread was gradually loaded with increasingly heavier objects. A pointer placed on the tread was used to determine the film's elongation. A critical mass was reached, breaking the film. The following equation was used to determine the tensile strength:

Tensile strength (Kg / mm^2) = Force at break (Kg) / Initial cross sectional area of the sample (mm^2)

Elongation at Break: Force and elongation were calculated after the shattered films. Film samples that were broken off at the end, rather than in the middle, were not included in the observations. Six distinct types of measurements were taken for each formulation.

***In-vitro* Dissolution Study:** Experiments on *in-vitro* dissolution were performed using a USP dissolution device (Basket apparatus).

The 75 mg of ranitidine equivalent was packed into firm gelatin capsules measuring 2 cm × 4 cm in a zigzag pattern. The rate at which the basket was spun was measured at one hundred revolutions per minute. We used 900 ml of 0.1 N HCl as the dissolving medium (pH 1.2).

Timed withdrawals of the sample and subsequent volume replenishment with new dissolving media kept the sink state constant. Samples of 10 ml were taken at regular intervals until drug release was complete. The quantities were swapped out for new dissolving media at appropriate intervals to keep the sink condition constant. Different aliquots were analyzed using a UV-Spectrophotometer at different wavelengths **Fig. 30**.

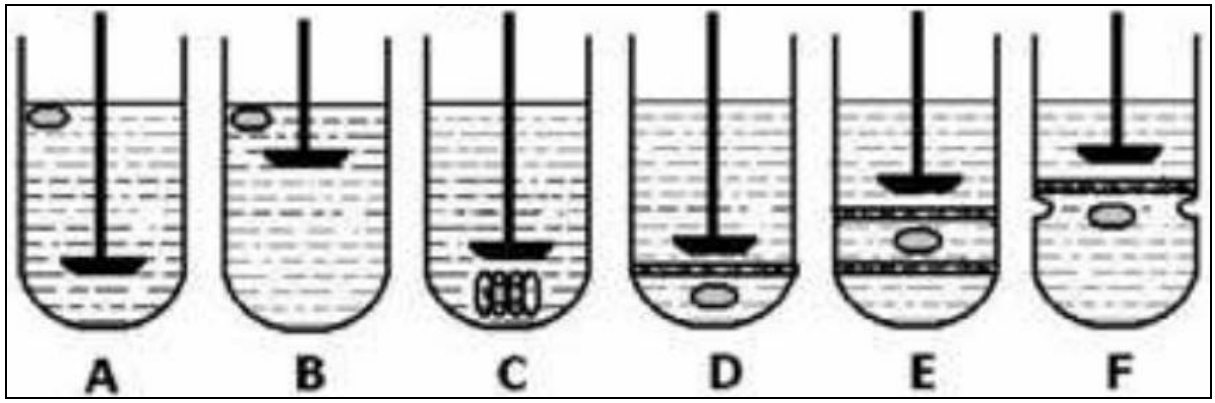


FIG. 30: VARIOUS TYPES OF MODIFICATION IN DISSOLUTION ASSEMBLY

Specific Gravity: To determine the specific gravity, one may utilize the displacement method using analytical grade benzene as the displacing medium. To ensure constant buoyancy, the system uses a stainless steel basket suspended from a Sartorius electronic balance by means of a metal thread. Submerging the floating object to a certain depth in a water bath prevents water loss due to evaporation. Using RS 2332C interphase and sarto wedge software, the balance could calculate the buoyancy force acting upward and transmit the data to a remote personal computer. Lotus® spreadsheets may potentially take up the balance sheet data in real-time. Experiments on floating kinetics were conducted in 900 mL of stomach-like fluid (pH 1.2) at 37°C, with readings obtained every 30 seconds and a baseline recorded and subtracted from each reading. A holder at the base of the dissolving basket allowed the downward force to be measured **Fig. 31**.

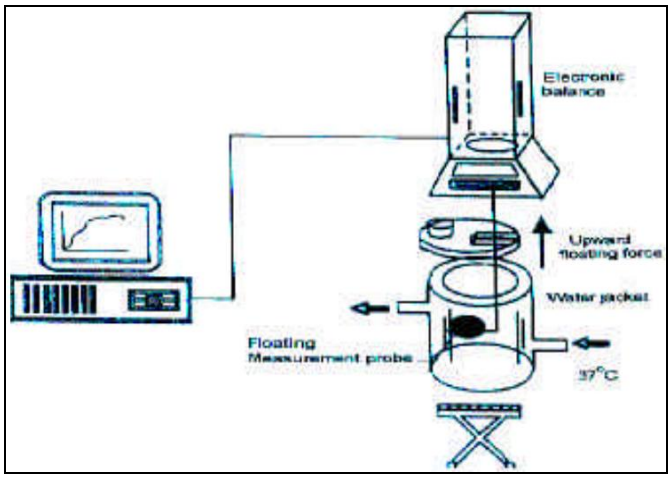


FIG. 31: CONTINUOUS FLOATING MONITORING SYSTEM

G-Scintigraphy: Gamma-emitting radioisotopes compounded into control release dosage forms have become the gold standard for evaluating healthy volunteers with gastroretention. A little amount of a stable isotope, such 68Sm, is included into the production of a dosage form. Major drawbacks of gamma Scintigraphy include the patient's exposure to ionizing radiation, the method's inability to provide detailed topographical information, the technique's low resolution, and the difficulty and high expense of making radiopharmaceuticals.

Radiography: This method is the gold standard for determining gastroretentivity in preclinical studies. The primary advantages of this method over gamma Scintigraphy are its inexpensive price and simple implementation. Even though X-rays are useful, their use is on the decline because of stringent regulations on exposure levels and the frequent need of huge amounts. One common contrast agent is barium sulfate.

Gastroscopy: Fiberoptic and video technologies, as well as peroral endoscopy, are covered. It is advised to use gastroscopy to physically assess the effect of the stomach environment on the FDDS, or to remove the DDS for a more complete inspection outside of the stomach.

Ultrasonography: A variety of abdominal organs could be seen thanks to the ultrasound pulses' reflected acoustic impedances across the contact, which varied greatly. There is no severe acoustic mismatch between most dose forms and the physiological environment at the point of interaction. Because of this, ultrasonography is seldom used to identify FDDS. The intragastric location of the hydrogels, the degree of solvent penetration into the gel, and the gastric wall-FDDS interaction during peristalsis were all analyzed.

Magnetic Resonance Imaging (MRI): Stomach emptying, motility and intragastric distribution of macronutrients, as well as pharmacological models, are just some of the areas where MRI has emerged as a helpful tool in recent years. MRI's advantages include its ability to detect abnormalities in soft tissues with high accuracy, its high temporal and special resolution and its lack of ionizing radiation. For better organ delineation and study, non-toxic paramagnetic and supramagnetic MR imaging contrast chemicals may be utilized to boost or dampen the signal of interstitial fluids and tissues.

^{13}C Octanoic Acid Breath Test: GRDDs use ^{13}C-octanoic acid. After ingesting octanoic acid, a chemical reaction occurs in the stomach, releasing carbon dioxide gas that is breathed. The ^{13}C-isotope will take the place of the crucial carbon atom in CO_2. Therefore, the time it takes for $^{13}CO_2$ gas to be detected in exhaled air may be referred to as the stomach retention duration of the dosage form. When the dose form is absorbed and digested, it causes no reaction and produces no CO_2. Therefore, the cost of this method is lower than that of similar ones.

Natural Polymers:

Hydrocolloids (20%-75%): They may be anionic, synthetics, or non-ionic, like modified cellulose derivatives, hydrophilic gums. *E.g.*, Acacia, Agar, Chitosan, Casein, Bentonite, Veegum, Gellan gum, Sodium CMC, Pectin, MC, HPC, HPMC K4 M, HPMC K15 M, Eudragit S100, Calcium alginate, HPMC K100 M, Eudragit, Propylene foam, Ethylcellulose, Polyethylene oxide, β-Cyclodextrin, Polyethylene glycol, Sodium alginate, PVA, Polycarbonate, Carbopol, PVP, E4 M, Acrylic polymer and CP 934P [27].

Inert Fatty Materials (5%-75%): Edible, inert fatty materials with specific gravity <1 can reduce the formulation's hydrophilic property and therefore increase buoyancy. E.g., Fatty acids, Beeswax, Gelucires® 39/01 & 43/01, long-chain fatty alcohols, etc.

Effervescent agents: Citric acid, Sodium bicarbonate, Tartaric acid, Citroglycine, DiSodium Glycine Carbonate, etc.

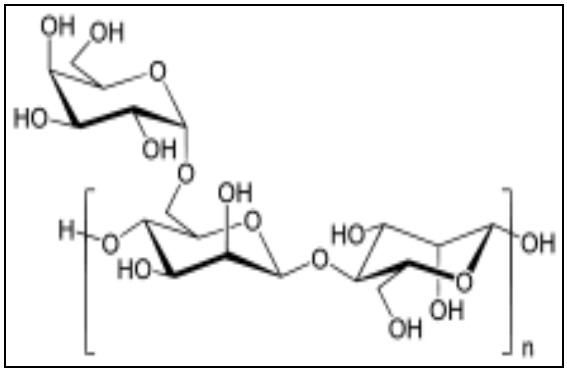
Release Rate Accelerants (5%-60%): Lactose, Mannitol, etc.

Release Rate Retardants (5%-60%): Dicalcium phosphate, Talc, Magnesium stearate, etc.

Low-density Material: Polypropylene foam powder.

Buoyancy-increasing agents (up to 80%): Ethylcellulose.

Guar Gum: Guar gum is a naturally occurring galactomannan polysaccharide. Fast hydration and expansion of guar gum in cold water allow for the creation of colloidal dispersions with a high viscosity even at low concentrations. This gelling property delays drug absorption, making it a useful carrier for extended-release drugs. As a polymer and disintegrant, guar gum is used in pharmaceuticals to create systems that allow drugs to float in the body.

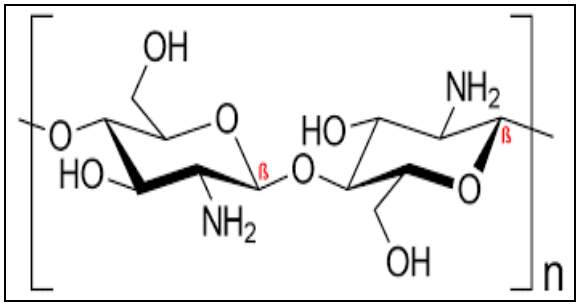


Properties of Guar Gum: Soluble in both warm and cold water, it is insoluble in most organic solvents. Powerful hydrogen-bonding characteristics, secondly. Exceptional thickening, emulsifying, stabilizing, and film-forming qualities. Rheological manipulation capabilities.

Advantages of Guar Gum in Floating Drug Delivery System: Extending the time a drug spends in the stomach and boosting its absorption have both been linked to polymer swelling. *In-vitro* drug dissolving studies showed that guar gum formulations were insensitive to changes in stirring speed, with no discernible effects on the dissolution profile.

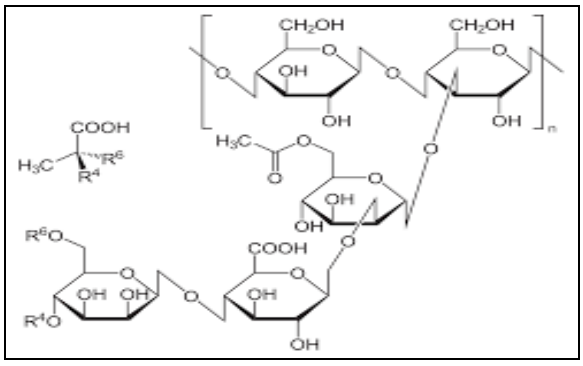
Chitosan: Chitin may be converted into chitosan, a natural and adaptable polymer, by a deacetylation reaction. Some of its biological features include not being poisonous, breaking down into naturally occurring substances in the body, being safe, being hemostatic, being anti-cancerogen, being anti-cholesteremic, and being biocompatible. Because of its bio-adhesive and antibacterial properties, this polymer is well-suited for targeted delivery. Chitosan is insoluble at neutral and alkaline pH values because it has a high molecular weight polycationic weak base with a pKa value of around 6.2-7.0 for the D-glucosamine residue. When put to a pH of 1.2 acidic solution, it becomes buoyant in nature and offers controlled release.

Increasing the chitosan film's thickness has the potential to slow the discharge rate.



Advantages of Chitosan: Using chitosan granules or chitosan laminated preparations may be helpful in the creation of DDS that lessens the effect of gastrointestinal transit time. Most Hallow microcapsules floated for more than 12 hours when exposed to stomach acid. The drug release followed zero-order kinetics and was controlled by diffusion and erosion processes.

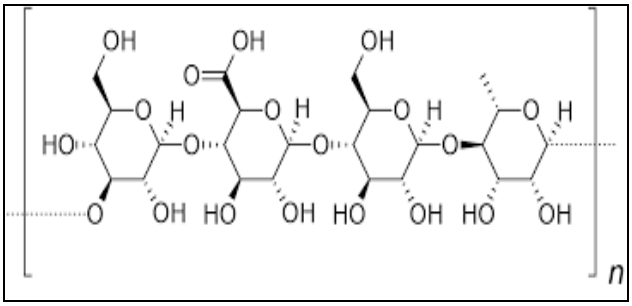
Xanthan Gum: To produce xanthan gum, the bacteria *Xanthomonas campestris* are fermented carbohydrates in pure culture. This results in a high molecular weight extracellular hetero-polysaccharide. Xanthan is a kind of polysaccharide that has a very long chain and several trisaccharide side chains. Gum is also stable in alkaline and acidic conditions and can withstand the presence of salts without dissolving or becoming brittle.



Advantages of Xanthan Gum: One of its functions is to modify the rate at which a drug is dissolved in a solution. It dissolves in water. Low concentrations have a high viscosity. It may allow for the controlled release of medicines with zero-order kinetics. Tablets made with xanthan gum and

citric acid may maintain buoyancy for more than twenty-four hours.

Gellan Gum: Gellan gum, also known as guar gum, is an anionic, high-molecular-weight extracellular linear polysaccharide composed of glucuronic acid, rhamnose, and glucose. Superior flavor release, gel strength, stability, process versatility, excellent clarity, powerful film-forming, and thermally reversible gel qualities are some of this gum's benefits. Gellan gum is a fermentation by-product of *Spingomonas elodea*.

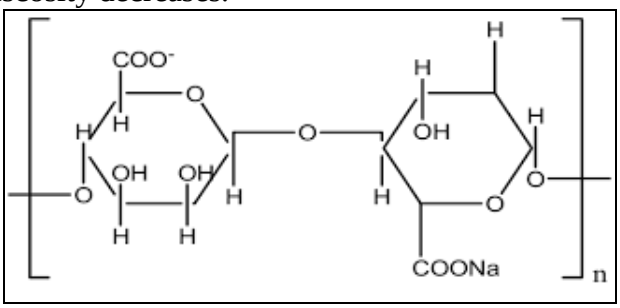


Advantages of Gellan Gum: It has excellent stability, taste release, and gel strength. A gel is produced when positively charged ions are added. It is a staple in the food industry as a stabilizer and thickener.

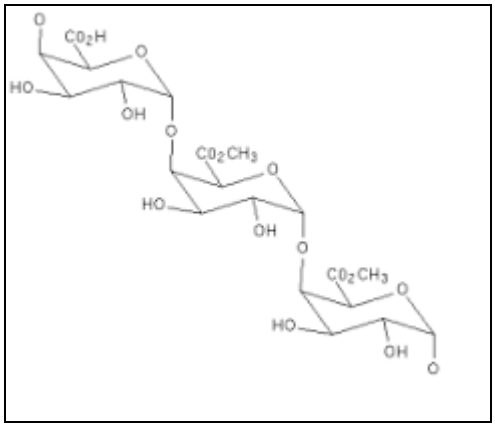
Sodium Alginate: There has been research into and use of sodium alginates as emulsion stabilizers, suspension agents, tablet binders, and tablet disintegrants. Sodium alginate is mostly composed of the sodium salt of alginic acid, a polyuronic acid including D-mannuronic acid and L-guluronic acid residues.

Sodium alginate was analyzed for its molecular weight and its block structure. Aqueous solution with a pH of 7.2 (1%) acidity/alkalinity Insoluble in water, ether, chloroform, and ethanol/water mixtures over 30%. Soluble in ethanol (95%), but not ether or chloroform.

It also has a poor solubility in aqueous solutions with a pH below 3 and in other organic solvents. A sluggish dissolution in water results in a thick colloidal solution. Sodium alginate comes in a variety of commercial grades, each of which results in water solutions of varying viscosities. A 208°C aqueous solution with a viscosity of 20-400 mPa s (20-400 cP) has a concentration of 1% by weight (w/v). Viscosity may be affected by concentration, pH, temperature, and the presence of metal ions. When the pH of a liquid increases over 10, its viscosity decreases.



Pectin: Pectin, a polysaccharide extracted from apple pomaces and citrus peels, is safe and inexpensive. The acid is a D-galacturonic acid with 1–4 glycosidic bonds. Pectin is a promising candidate for pharmacological treatment, for example as a drug carrier for controlled release applications, because of its gel-forming abilities, which vary with the degree of esterification and molecular size.



Advantages of Pectin: Pectin gel beads are an effective method for controlling drug release in the gastrointestinal tract. Pectin is used in the food industry as a prebiotic, a cholesterol regulator, an anticancer agent and a fiber source.

Synthetic Polymers: In recent years, synthetic polymers have become more important in the pharmaceutical industry. There are several uses for synthetic polymers, including adhesives and film coating agents. Polymers may have a wide variety of functional groups because to their huge size as macromolecules. Semi-synthetic polymers are a hybrid between natural and synthetic polymers [28].

The list of synthetic polymer used is as follows:

1. Hydroxypropyl methylcellulose.

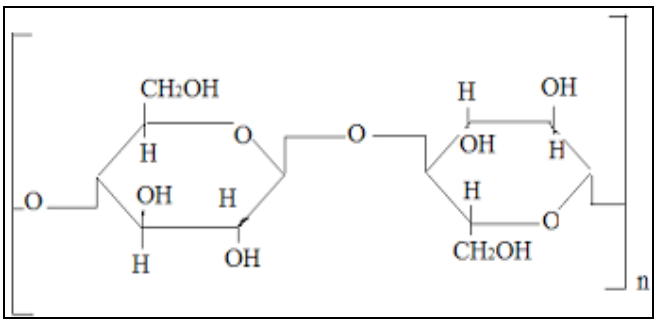
2. Eudragit.

3. Ethylcellulose.

Disadvantages of synthetic polymer are as follows:

1. Expensive pollution of the environment.
2. Both short-term and long-term negative outcomes.
3. It has low biocompatibility.
4. The local reaction and the inflammatory response

Hydroxypropyl Methylcellulose: Polymers such as hydroxypropyl methylcellulose ethers may bind, hold water, thicken, film-form and even act as a lubricant and a lubricant. These compounds are odorless, colorless, and completely soluble in water. The semi-synthetic, inert, viscoelastic polymer is used as an excipient and controlled-delivery component in oral medications and may be found in a wide variety of consumer products.



Properties: These are some of the more general features of Hypremellose. Each type exhibits these traits to varying degrees, and some may also exhibit other traits that are especially helpful in certain contexts.

1) Apparent density: 0.25~0.70g/cm^3.

2) The refractive index =1.336.

3) Surface tension: 42 to 56mn/m.

4) Solubility: dissolve in water and some solvent.

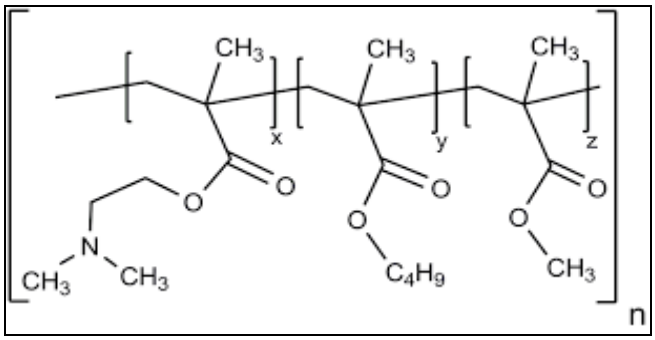
Advantages:

1. One of the most common polymers in the world, and it dissolves in water.

2. It has the properties of a thickener, a film forming, and a water retainer.

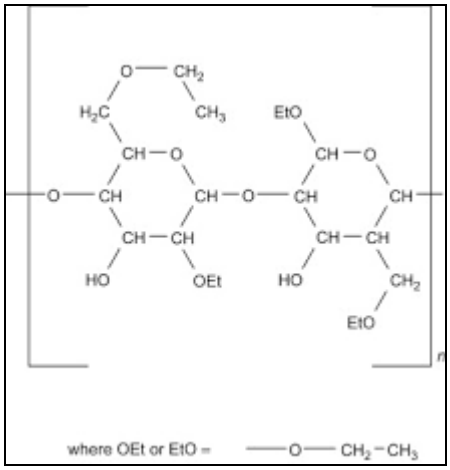
3. For oral dosage forms, a hydrophilic matrix is the simplest SR approach.

Eudragit: Film-coating agents made from polymethacrylates (Eudragit) are often used in capsule and tablet manufacturing. Depending on the kind of polymer used, films with varying solubility qualities may be produced. Soluble in stomach fluid at pH 5 and below. Eudragit RL, RS, NE 30D, NE 40D, and NM30D are used to provide water-insoluble film coatings for SR items. Since, Eudragit RL films let more light and air through than Eudragit RS films, films with varying permeabilities may be made by mixing the two types. However, Eudragit L, S and FS types are put to use as enteric coating agents due to their resistance to stomach fluids. Eudragit L is soluble at pH >6, whereas Eudragit S and FS are soluble at pH >7. Similarly, other types of enteric coatings are soluble at lower or higher pH values. Binders made from polymethacrylates are used in both water-based and organic wet granulation techniques. Higher concentrations (5-20%) of dry polymer are used to control the release of an active component from a tablet matrix. The use of solid polymers between the percentages of 10 and 50% is possible in direct compression processes. New gel formulations for rectal administration and the matrix layers of transdermal delivery systems have both been developed using polymethacrylates polymers.



Ethylcellulose: Ethocel (Ethylcellulose polymers) has been widely used in the pharmaceutical industry for over 50 years. Numerous pharmaceutical applications have found use for ethylcellulose: bitter active taste masking; moisture protection; stabilization; extended-release multi

particulate coating; micro-encapsulation of actives; extended-release binder in inert matrix systems; solvent; extrusion granulation and micro-encapsulation. Ethylcellulose is a fantastic polymer for use in developing timed-release pharmaceuticals. It expands in the presence of gastric juice but is insoluble at any of the pH levels seen in the body. Accordingly, it fits the bill for enhanced patient adherence. For instance, the polymer chains in Ethocel 4, Ethocel 10 and Ethocel 45 are of different lengths.



Various Dosage Forms of GRDDS:

Floating Microspheres: Rosiglutazone, Cefpodoxime, Cefuroxime and Nateglinide

Floating Granules: Lacidipine, Ranitidine, Simvastatin, Metopropalol and Atorvastatin

Films: Cinnarizine

Floating Capsules: Celecoxib, Pioglutazone, Diazepam, Furosemide, Misoprostol, L-dopa, Benserazide, Ursodeoxycholic acid, and pepstatin

Floating Tablets: Alfuzosin, Losarten, Proapnalol, Ofloxacin, Glipizide, and Loratidine

Mucoadhesie System: Venlafaxine, Famotidine, Metformin, and Metoprolol [29].

Challenges Involved in GRDDS: Since, GRDDS are only active in the stomach, they must be kept there. Keeping the dosage form in the stomach or upper region of the small intestine for a prolonged amount of time until all of the drug from the system is released at a controlled pace is, thus, the most challenging component of making GRDDS. Diverse factors affect how quickly or slowly the stomach empties. Dosage and whether or whether the stomach has been empty or full are the two most crucial considerations. The rate at which one's stomach empties after eating depends on a number of factors, including the kind of food consumed, the number of calories consumed, the person's gender, and their age. Calorically and fat-dense meals impede gastric emptying as well. Individual factors such as age, gender, dosage form size and shape, disease state, and body mass index affect the GRT. The GRT is also affected by the pylorus. Another fact is that canine and avian species (among others) have a pylorus that is smaller and a peristaltic movement that is opposite to that of humans. The motility pattern of the stomach is altered in response to undernourishment and other factors such as indigestible polymers and fatty acid salts, which reduce the pace at which food is expelled from the stomach. Therefore, the results must be drawn cautiously [30].

Specific Studies Recent Studies: Metformin hydrochloride was employed to make a floatable gastroetentive tablet using a gas-generating agent and a gel-forming hydrophilic polymer developed by Basak *et al*. The formulations' floating properties and *in-vitro* drug release were enhanced. In an *in-vitro* drug release experiment, the SR of metformin hydrochloride from these tablets was controlled, with 96-99% released after 8 hours [31].

Using two distinct grades of Methocel K100 (HPMC K100) and Methocel K15, Jaimini *et al*. developed famotidine effervescent pills that float (HPMC K15). These grades' gelling abilities were examined. Tablets made with Methocel K100 have improved buoyancy over those made with Methocel K15M. As the citric acid content declined, the delay in the floating effect increased. Both the non-Fickian transport of the medication from the tablets and the extended release of the drug from the tablets were confirmed [32].

Badve *et al*. developed a method to encapsulate diclofenac sodium into hollow calcium pectinate beads for floating-pulsatile release during chronopharmacotherapy. The floating pulsatile concept was developed to increase the stomach residence time of a dosage form with a lag phase followed by a burst release. In this research, researchers suggested using hollow calcium

pectinate microparticles as a floating pulsatile drug delivery system for disease chronotherapy [33].

A new floating, swelling, bioadhesive administration technique for SR ofloxacin was developed by Chavanpatil *et al*. Different combinations of release-retarding polymers, such psyllium husk, HPMC K100M, and a swelling agent, crosspovidone, were tried and tweaked to provide a 24-hour release profile. *In-vitro* studies found that the drug release mechanism was non-Fickian and instead followed Higuchi kinetics [34].

Rahman *et al*. created a bilayer-floating tablet (BFT) for captopril via direct compression. HPMC K-grade and an effervescent citric acid and sodium bicarbonate mixture make up the floating layer. The release layer included either just captopril or captopril in combination with a number of polymers. These polymers included HPMC-K15M, PVP-K30, and Carbopol 934. As predicted by the Higuchi release model, the formulation did not undergo appreciable changes in appearance, drug content, floatability, or *in-vitro* dissolution pattern after three months of storage at 45°C/75 percent RH [35].

Due of phenoporlamine hydrochloride's short half-life in the body, Xiaoqiang *et al*. developed an SR tablet. Three floating matrix tablets were prepared using a gas-forming agent. We used HPMC K4M and Carbopol 971P to make the hydrogel system. After sodium bicarbonate was added to the matrix, the tablets floated for nearly 6 hours on top of stomach simulation fluid. All of the tablets showed non-Fickian diffusion in the stomach fluid model, with dissolution profiles [36].

To control the rate and location of meloxicam release, Sharma *et al*. developed a multiparticulate floating pulsatile drug delivery system out of porous calcium silicate and sodium alginate. Prepared bead crushing strengths varied between 182g and 1073g [37].

Microspheres of HPMC and ethyl cellulose were created by the solvent evaporation method by Srivastava *et al*. The microspheres' structure and surface morphology were analyzed using optical and scanning electron microscopy. Microspheres maintained their buoyancy for almost 10 hours while dispensing their medicine slowly over 8 hours. *In-vitro* studies showed that the medication was released from the microspheres in a controlled manner due to diffusion. Daily dosing with a gastroretentive ofloxacin dosage form was developed by Chavanpatil *et al*. The delivery method was created using a SR formulation with swelling and floating properties to increase stomach retention. The formulations, which included psyllium husk, HPMC K100M, crosspovidone, and combinations of these polymers, were evaluated for their capacity to float, remain stable, contain the intended amount of medicine, and release that drug at the intended rate [39].

Jain and colleagues developed controlled release to improve GRT without directly irritating the stomach lining. Calcium silicate (FLR) was used as the porous carrier, repaglinide and a Eudragit polymer were added, and then the resulting microspheres were suspended in an emulsion solvent diffusion technique. Forty studies examined how various formulation and processing variables affected the outcome [40].

The ranitidine tablets that Patel and colleagues created floated during testing. We used Avicel PH 102 and Tablettose 80 as fillers. Drug release from hydrophilic matrices and floating properties were shown to be significantly affected by viscosity [41].

Muthusamy *et al*. used an emulsion solvent diffusion method to create lansoprazole floating micropellets with the drug to carrier ratios of 1:1, 1:2, and 1:3. Different carriers including HPMC, methylcellulose, and chitosan were used. The yield for micro pellets increased to 82%. The drug-to-chitosan ratio of 1:1 resulted in excellent integration efficiency and a high percentage of lansoprazole release from micropellets *in-vitro*. Particles varied in size from 327 to 431 nm [42].

Sato *et al*. investigated the pharmacoscintigraphic assessment of riboflavin-containing microballons for floating drug delivery systems in healthy human volunteers. They discovered that microballons were highly effective at increasing drug bioavailability, leading to longer-lasting pharmacologic activity [43]. Dave *et al*. created a ranitidine HCl delivery method that is gastroretentive. As gel-forming agents, guar gum, xanthan gum, and HPMC were

employed. As a gas-generating agent, sodium carbonate was used.

The effects of citric and stearic acids on the drug release profile and floating characteristics were studied. A low quantity of citric acid and a large amount of stearic acid was shown to favor the prolonged release of ranitidine HCl [44].

Sato *et al*. used an emulsion solvent diffusion technique to create microballons from enteric acrylic polymers mixed in dichloromethane and ethanol. Urinary excretion was used to study the pharmacokinetics of riboflavin. The riboflavin release characteristics of MB produced by combining it with HPMC in various ratios were enhanced [45].

Using polycarbonates as drug carriers and emulsion (o/w) solvent evaporation methods, Umamaheshwari *et al*. produced floating microspheres containing acetohydroxamic acid. The impact of polycarbonate concentration on particle shape, size, entrapment efficiency, and drug release rate was investigated [46].

El-Gibaly *et al*. used chitosan and a negatively charged surfactant, sodium dioctyl sulfosuccinate, to create floating microcapsules containing melatonin. The floating microcapsules' properties were comparable to those of non-floating microspheres. According to the findings, the floating hollow microcapsules generated may be a promising gastroretentive-controlled release medication delivery method [47].

Streubel *et al*. created a single-unit, floating, controlled drug delivery system made of polypropylene foam powder and matrix-forming polymers, which they physiochemically analyzed. The low density of the extremely porous foam powder resulted in excellent *in-vitro* floating behavior of the tablets [48].

Joseph *et al*. colleagues created piroxicam microspheres that could float in the simulated stomach and intestinal fluid. A solvent evaporation method was used to make the microspheres. In vitro release of piroxicam from polycarbonate microspheres in simulated stomach fluid at 37°C revealed no notable burst impact, with an incorporation efficiency above 95% [49].

Choi *et al*. made floating beads out of a sodium alginate solution using $CaCO_3$ or $NaHCO_3$ as a gas-forming agent. For CO_2 gas and gel production, the solution was dropped into a 1 % $CaCl_2$ solution containing 10% acetic acid. The impact of the gas-producing agent on the size and floating characteristics of the beads was studied. $CaCO_3$ outperforms $NaHCO_3$ as a gas-forming agent in the production of alginate beads, according to the findings [50].

El-Kamel *et al*. used an emulsion solvent diffusion method to create floating microparticles of ketoprofen. The researchers employed four different Eudragit S 100 (ES) ratios to Eudragit RL (ERL). The amount of medication retained in the floating microparticles reduced as the ERL concentration increased. In all tested mediums, the formulation having a 1:1 ratio of the above-mentioned polymers had a significant proportion of floating particles [51].

CONCLUSION: Drugs with poor bioavailability may benefit from GRDDS because of their potential to increase absorption and absolute bioavailability by targeting the upper gastrointestinal tract for drug delivery. Because of the intricacy of pharmacokinetics and pharmacodynamics, in vivo experiments are required to establish the optimum dose form for a given medicine. Research using GRDDS might also be used to eliminate H. pylori, the pathogen widely accepted as the root cause of chronic gastritis and peptic ulcers.

Even though this microorganism is highly resistant to many medicines, complete eradication calls for sustained high concentrations of antibiotics inside the stomach mucosa for a considerable time. The physiology of the stomach is a critical consideration. When the medication is taken (before, during, or after a meal) is crucial. However, creating a pharmaceutically viable gastroretentive dose form is a considerable challenge for modern pharmaceutical science. The pharmaceutical distribution mechanism requires a lengthy stay in the stomach, which is counter to the stomach's normal physiology. There are many different types of GRDDS (high density, floating, expandable or unfoldable or swelling, superporous, bioadhesive, magnetic systems, etc.), each with its

own benefits and drawbacks. A great deal of work is being put into developing several GRDDS types at the moment. Because of this, pharmacotherapies of all types stand to benefit from their growing prominence in the near future.

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