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REVIEW ON SEVERAL APPROACHES INVOLVING GASTRO-RETENTIVE DRUG DELIVERY SYSTEM

KUMAR R[1], SUGUMARAN A[2*], DUTTA G[1] AND NARAYANASAMY D[1]

1: Department of Pharmaceutics, SRM College of Pharmacy, SRMIST, Kattankulathur, Tamil nadu 603203, India

2: Department of Pharmaceutical Sciences, Assam University, Silchar, 788011, Assam, India

***Corresponding Author: Dr. Abimanyu Sugumaran: E Mail: abipharmastar@gmail.com**

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ABSTRACT

Any drug delivery technique must deliver a therapeutic dose of medicine to the desired location in the body while also maintaining an effective plasma drug concentration for a certain time period. Incomplete drug release results in a shorter duration of action of the dose form and a decreased bioavailability of the medication. A gastro retention medication delivery device is employed to circumvent this issue. The point of this study is to look at the various medication delivery techniques for gastro-retention that have been utilized to increase the therapeutic effect of pharmaceuticals with a short therapeutic window, are unsteady at basic pH, are soluble in acidic medium, and are active locally in the stomach. The anatomy of the stomach, the factors affecting GRDDS, and the various GRDDS techniques currently used in gastric retention drug delivery systems, such as hydrodynamically balanced systems, super porous hydrogel systems, magnetic systems, muco-adhesive systems, high-density, low-density systems and micro balloon systems are discussed in detail, along with their applications and advantages. Additionally, it considers prospective approaches for increasing stomach retention duration in fasting and fed states. In summary, this research sheds light on existing and future perspectives on gastric retention medication delivery systems.

Keywords: Effervescent system, FDDs, GRDDs, HBS, Stomach

INTRODUCTION

Oral administration is the most commonly used method of medication delivery. Approximately half of all drugs on the market are delivered orally, which has several benefits, including fewer patient complaints, as well as being easy, inexpensive, and safe to use **[1]** . However, drawbacks such as a brief stomach retention period, a short half-life, and rapid elimination from the circulatory system are present. As a result, they need repeated doses to achieve the desired therapeutic effect. Oral sustained-controlled-release preparations were developed to circumvent this constraint by gradually releasing the medication into the intestinal system while keeping an efficient drug concentration in systemic circulation for a prolonged duration. This decreases the frequency of doses and boosts the drug's bioavailability. This is especially beneficial for medications that are absorbed through the digestive system **[2]**. These pharmaceutical administration systems have two significant drawbacks: 1) a brief gastric retention time (GRT) and 2) an unpredictably brief gastric emptying time (GET). Both of these variables may contribute to poor drug clearance in the absorption zone of pharmaceutical formulations leading to a decrease in the effectiveness of the supplied dosage **[3]**. The medicine delivery system must achieve a longer stomach retention time by producing a site-specific orally administered controlled release dose form. Extended stomach retention may boost the bioavailability of the medications. Drug waste was reduced, and The solubility of medications which are less soluble in high pH conditions has been improved **[4-6]**. Gastro retentive drug administration (GRDD) is a technique for prolonging the time a drug spends in the stomach, allowing for site-specific medication delivery for local or systemic effects in the upper part of the gastro intestinal tract. This delivery mechanism has the ability to stay in the digestive system for a long duration, significantly increasing the drug's gastric retention time **[7, 8]**. Drugs that have a low absorption rate in the lower GI tract, are unstable and poorly soluble at alkaline pH, have a short half-life and act locally in the gastro - intestinal tract **[9–12]** . Over the last few decades, numerous GRDD techniques have been developed and refined, including high-density systems, low density system, super porous hydrogels, magnetic, ion-exchange mucoadhesive, raft-forming and expandables systems **[11–14]**. The present research examines many gastro-retentive strategies that have emerged as cutting-edge methodologies in recent years, as well as their future prospects.

ANATOMY OF THE STOMACH

Since the stomach is so crucial in the GRDDS, full knowledge of stomach physiology and anatomy is necessary for the successful design of gastro-intestinal medication formulations. The structure of the anatomy of the stomach is shown in **Figure 1**. The stomach is divided into two sections: the proximal stomach's fundus and body, and the distal stomach's antrum and pylorus. The stomach's main function is to temporarily hold food, break it down, and thereafter gently pass it down the duodenum **[15, 16]**. The fundus and body largely serve as storage areas for indigestible fiber, whilst the antrum functions as a pushing pump that assists non stomach clearing **[15, 17, 18]**.

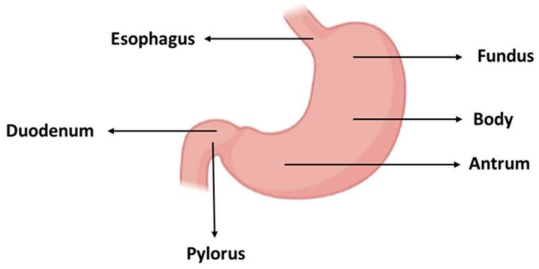

Figure 1: Stomach Anatomy

The pH of the stomach is important in the digestion of several nutrients and serves as a first line of defence against many microorganisms. The stomach serves as a reservoir for stronger acids and has the lowest pH of any portion of the digestive system. The stomach pH is 1-3, the pH of the small intestine is 5-7.5, the pH of the large intestine is 7.9-8, and the rectum pH is 7.5-8 **[19]**. The surface of the intestinal epithelium is lined with intestinal epithelial cells (IECs). Where it plays a crucial function in food digestion, nutrient absorption, and protecting the gut from different bacteria. External nourishment, such as amino acids, is required for the growth, maintenance, and operation of the IECs **[20]**. Gastric retention time is the amount of time it takes for stomach contents to reach the small intestine.The longer the stomach retention period, the more medication is absorbed in the GI tract. The system's stomach retention period is determined by the size and density of the dose form. The dosage form will float on the gastric medium if its density is lower than the gastric content. Floating behaviour necessitates a density of less than 1 g/ml. The presence or lack of food influences the stomach's retention time. The duration of gastric retention is lengthened when food is present by slowly releasing the medicine in the stomach for a considerable amount of time **[18]**. The time it takes for the stomach to empty out of the stomach is referred to as the gastric emptying time. Many

pathogenic variables impact gastric emptying, including nutritional consumption, exercise, illness status, and stress **[21]**. Stomach emptying happens during both eating and fasting periods, although the order in which it happens varies a lot. Throughout the fasting period, an interdigestive sequence of electrical events in the stomach and small intestine repeats every 90–120 minutes **[15]**. The pyloric sphincter thickens to roughly 19 mm. As an outcome, particles smaller than the pylorus' width can readily escape to the duodenum during the interdigestive phase **[22, 23]**. Motor activity starts 5 to 10 minutes after a meal and lasts as long as the food is still in the stomach in the fed state, possibly delaying stomach emptying **[24]**.

The system floats on the stomach content when the dosage form density is lower than the gastric content, and the density of the dosage form has little or no influence on the gastric emptying time of floating or non-floating tablets. The length of gastric retention is influenced by the presence of food in the stomach.While density has just a tiny impact **[25]**.

Gastro retentive drug delivery system

GRDDS (Gastro Retentive Drug Delivery System) are a new technique for the oral controlled-release administration of a variety of medicines **[26, 27]**. GRDDS is a way of prolonging stomach residence time to target site-specific drug distribution in the gastrointestinal system for local or systemic effects **[7]**. These systems can stay mostly in the stomach for a prolonged enough time to deliver the active drug from a gastric juice formulation. Their use has various benefits, including enhanced medication absorption and lower drug blood level fluctuations, which results in improved treatment efficiency and fewer side effects and also the possibility of enabling stomach-specific action. These systems are capable of delivering medications at the absorption site at an appropriate rate over an extended length of time **[28–30]**. GRDDS are useful for medications with limited absorption in the lower gastrointestinal tract, low solubility at alkaline pH, a short half-life, and local action in the upper gut **[24, 31]**. There are several techniques to delivering gastroretentive drugs. These contain high-density systems, low density system, super porous hydrogels, magnetic, ion-exchange, mucoadhesive, raft-forming and expandables systems. Conventional drug delivery systems have low bioavailability and may not be able to overcome difficulties provided by the gastrointestinal tract (GIT), such as partial drug release, reduced dosage effectiveness, and the need for repeated doses. As a result, the disappointment of traditional drug delivery methods to keep medications in the stomach can result in GRDDS **[32]**.

Different methodologies have been developed to increase stomach gastric retention. Some medications are available in single-unit and multiple-unit dose formats. GRDDS are divided into two categories: floating and non-floating. Classification of GRDDS is shown in **Table 1**.

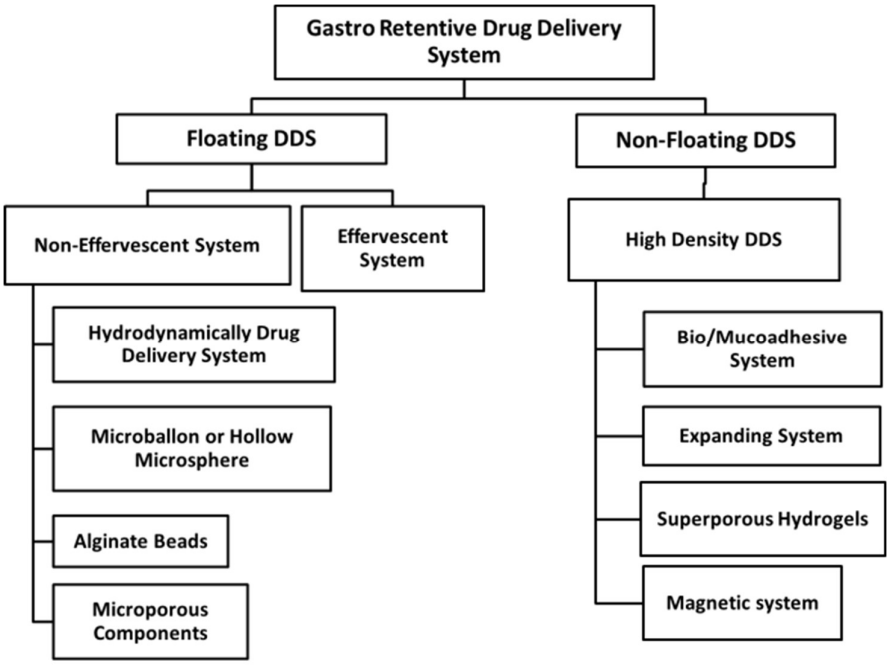

Table 1: Represent classification of GRDDS

Advantages:

Bioavailability of medication may be greatly increased for those metabolised in the upper gastrointestinal tract, especially when compared to non-gastrointestinal drug delivery systems **[33]**. Drugs with short half-lives may be enhanced; this decreases dose frequency and alleviates patient complaints. The gastro retention system has more advantages than the traditional dosage form because it eliminates gastro retention time (GRT) and gastric emptying time (GET). Because its bulk density is smaller than that of the stomach fluid, the system is intended to float on it without impacting the intrinsic rate. Gastro retention medications may cause sustained and extended release of drug from the dosage form, resulting in local effects in the stomach or small intestine. As a result, they're useful for treating stomach and small intestine problems.The use of site-specific medication delivery minimises the likelihood of undesired side effects. The gastro retention dose type decreases medication concentration volatility and its impact **[34]**.

Factors affecting:

The stomach's anatomical structure contains peculiarities that should be considered while designing a gastro-

retentive delivery system. The function of the gastro-retentive system is influenced by a variety of factors. These characteristics are classified into three categories: pharmacological, physiological, and patient-related. Factors influencing medicine include: For effective Gastro Retentive Drug Delivery Systems , excipients and polymers impact is difficult to recognize on different formulations, formulations, as well as the size, shape, weight, volume, and dimensions of the formulations **[35, 36]**. Physiological factors Extrinsic variables such as meal composition, frequency of consumption, caloric content, physical activity, posture, and sleep have been observed to impact drug GRTs in the gastric track in numerous investigations. The presence or absence of food in the stomach affects the dose form's gastric residence period. Food in the GIT often prolongs the retention duration of the dosage form, allowing the drug to spend more time at the site of absorption **[37–39]**. The Patient Factors: GRDDS may be affected by patient-related characteristics such as sexual orientation, age, sickness, and psychological state **[40]**. The motility of the stomach decreases with age, lengthening the time necessary for the stomach to empty. Females' stomach clearance rates are often slower than men's **[40]**. The patient's emotional state may have an effect on GRDDS. It has been shown that sad people have a slower stomach emptying rate, but anxious people have a quicker rate **[37, 41]**. Dosage and medication forms are indicated in **Table 2**.

Table 2 Dosage and Medication Forms

Dosage	Drugs Form
Tablet forms	'Amoxycillin, Chlorpheniramine,Verapamil, Theophylline, Ampicillin, Furosemide, Ciprofloxacin, Diltiazem, Acetaminophen,Captopril, Acetylsalicylic acid, Nimodipine, Prednisolone, Isosorbide mononitrate, CinnarazineandFluorouracil'
Capsule forms	'Nicardipine, Propranlol,, Misoprostal, Chlordiazepoxide, Furosemide, Diazepam andUrodeoxycholic acid'
Granule forms	'Indomethacin & Prednisolone& Diclofenac sodium'
Microsphere forms	'Griseofulvin & Aspirin & Ketoprofen & Iboprufen & Terfenadine'
Film forms	'Cinnarizine'

Floating drug delivery system

Floating drug delivery systems (FDDS) also known as hydrodynamically controlled systems have a low density and enough buoyancy to float above stomach contents without jeopardising stomach emptying over the course of a lengthy time. While the stomach contents is floating, the drug is softly released at the rate required for it to exit the system. The stomach's residual system is cleansed once the medicine has been removed. As a result, stomach retention is longer and therapeutic concentration variations in the circulation are better managed **[42, 43]**. Floating tablets containing aqueous extracts of

liquorice, for example, may be developed as a method of increasing gastrointestinal residence time and thereby boosting bioavailability. Floating tablets of aqueous licorice extract show considerable promise as an alternative to the standard dose form **[44]**. A minimum degree of floating force (F) is also needed to keep the dosage form afloat on the surface of the meal, in addition to the minimum stomach content required to achieve the buoyancy retention principle **[45]**. Granular, pellets, pills, tablets, bilayer films, and hollowed microspheres have all been used to build floating systems **[46]**. Two formulation factors are used in this study; effervescent and non-effervescent systems, to distinguish floating drug delivery methods **[35]**. **Figure 2** depicts the mechanism of floating tablets.

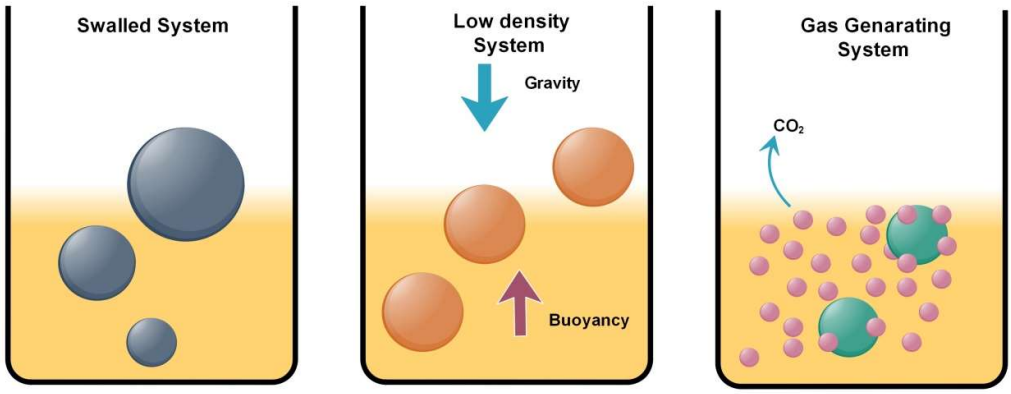

Figure 2: Mechanism of floating tablets

Effervescence system

Matrix-based systems are used in these systems. The preparation employs swellable polymers such as methylcellulose and Chitosan, as well as additional effervescent chemicals such citric acid, sodium bicarbonate and tartaric acid **[47]**. When these chemicals come into contact with stomach material, CO2 is released and imprisoned in a swelling hydrocolloid. This makes the dosing more buoyant. A swellable, asymmetric triple-layer table was used to produce the delivery approach **[48, 49]**. There are two kinds of effervescent systems: volatile liquid-holding systems and gas-producing systems. One benefit is the integration of a high number of active substances. In active dose form, one effervescence pill is equivalent to three to ten ordinary tablets. Effervescence pills may be used by patients who have difficulties swallowing. Many effervescence tablets contain a flavor, so they taste better than non-effervescence powder versions **[50–52]**. Many studies have shown that effervescent pills and

powder are absorbed more effectively than traditional dose forms. It is related to the production of carbon dioxide during the process, which improves the absorption of active substances by modifying paracellular pathways **[53–55]**.

Non effrervescence system

This technique employs polysaccharides, gelling or very swellable cellulose hydrocolloids, and matrix-creating polymers such as polycarbonate, polyacrylic acid, polystyrene and polymethacrylate. When taken orally, it comes into contact with stomach acids and has a bulk density of 1 this active component expands. The air is trapped inside the enlarged matrix and provides buoyancy. The ensuing inflated gel-like structure acts as a reservoir, enabling the gelatin mass to deliver drugs continuously. When the dosage form comes into contact with stomach fluid, it expands to several times its original volume; the gastric contraction forces the delivery system to the pyloric sphincter. Because of the greater size of the dose form, it does not reach the pylorus. As the contractions move over the system's surface, The dose form returns to its original position in the stomach **[56–58]**. A Captopril non-effervescent floating tablet formulation was developed. Captopril is a medication that is used in conjunction with an Angiotensin Converting Enzyme (ACE) Inhibitor used to treat high blood pressure, heart problems, and diabetic nephropathy **[59]**.

Colloidal gel barrier systems (Hydrodynamic balanced systems)

This method increases the amount of medicine that can be absorbed in solution form by extending the time that the medicine is in the stomach. It doesn't do much more than mix the medicine with gel-forming hydrocolloids to keep it floating on top of the stomach contents. Some of the ingredients in this system are cellulose-based hydrocolloids like hydroxypropyl methylcellulose (HPMC), polysaccharides, and other materials that make up a matrix. These materials are called "matrix-forming polymers." **[60]**. When the hydrocolloid in the system comes into interaction with the gastrointestinal fluid, it hydrates and forms a gel barrier. A hydrodynamically balanced tablet of itopride was made. This system is made for oral drugs that are specific to a certain part of the body and have a lower bulk density than gastric fluid. This makes the dosage forms float in the stomach, which helps the drug stay there longer **[61]**. Itopride hydrochloride is the drug of first choice for treating upper dyspepsia. It is a prokinetic drug that helps the intestine move by blocking dopamine D2 receptors and blocking acetylcholine esterase **[62]**.

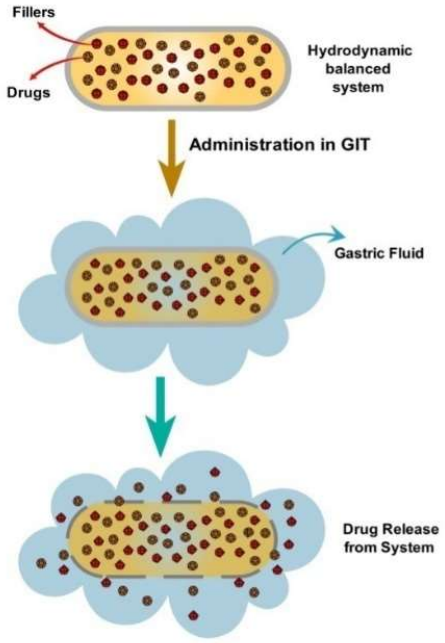

Figure 3: Mechanism of hydrodynamic balanced system

Micro porous compartment systems:

In this device, drug reservoir is encased within a microporous compartment with pores running along the top and bottom walls. The outer walls of the device were totally secured to prevent undissolved drugs from coming into direct contact with the stomach surface. The delivery system floats in the stomach juice due to trapped air in the stomach's flotation chamber. The medicine is dissolved by the gastric juice that enters through the aperture, allowing the dissolved drug to be delivered continuously into the intestine **[63]**. Stomach fluid penetrates into the opening to the degree that it stops the medicine from being absorbed &transports the dissolved medication into the intestine to be absorbed **[64]**. Microporous bilayer osmotic tablet for colon-specific administration A microporous bilayer osmotic tablet which contains dicyclomine hydrochloride and diclofenac potassium for colon targeting to treat irritable bowel syndrome was created using a unique oral medicine delivery technique **[65]**.

Floating microspheres/micro balloons

The most effective buoyant method is hollow microspheres, commonly known as micro balloons. It is made up of a core hollow region inside the microsphere. The hollow microspheres are manufactured using a new solvent and have medicine in their exterior polymer laye **[66, 67]**. The drug was suspended in an ethanol/dichloromethane solution, and an

enteric acrylic polymer was fed through an agitated polyvinyl alcohol (PVA) solution at 40 degrees Celsius. The gas phase in the dispersed polymeric droplet is produced by the evaporation of dichloromethane generated in the inner chamber of the polymer and drug microsphere. For more than 12 hours, the microball floated at the top of an acidic dissolving solution containing surfactant **[42]**.

Alginate beads

Alginates are polysaccharide polymers derived from brown seaweed (Phacophycae). When alginate is exposed to stomach acid, it precipitates into a low-density, viscous gel with a pH near to neutral in seconds or minutes **[68]**. CO_2 is released by the sodium bicarbonate in the alginate-antacid formulation when the pH changes, and it is retained in the alginate gel and floats to the top of the stomach contents like a raft **[68, 69]**. As a result, Direct and quick acid pocket/film neutralisation may be achieved using alginate-based formulations including sodium bicarbonate **[70]**. Freeze-dried calcium alginate has recently been used to create floating dose formulations with multiple units. When a sodium alginate slurry was added to a calcium chloride aqueous medium, calcium alginate precipitated, resulting in beads in the form of spheres with a thickness of around 2.5 mm. These beads were separated, frozen with liquid nitrogen, and then freeze-dried at -40 degrees Celsius for 24 hours, resulting in a porous system with a structure that lasted more than 12 h. For at least 5.5 to 10 hours, the floating beads stayed in place **[50]**.

High density system

In comparison to stomach fluid, high-density systems have a higher density. Excipients frequently used in these systems include iron powder, BaSO4, ZnO, and tiO_2 **[15]**. While the patient is standing upright, little high-density pellets fall to the bottom of the stomach and become lodged in the folds of the antrum. An antrum density of around 2.5 g/cm3 seems to be required for a considerable lengthening of gastric residence duration **[71]**. To survive its peristatic motions, the abdominal rogue and cable are kept in the abdominal rogue and cable. To complete these formulations, the drug is either coated with a substantial core or combined with ingredients such as metal powder,. However, the usefulness of this method has not been shown in humans, and it is not being sold **[24]**. One of the key disadvantages of this kind of technology was the larger dosage size necessary to reach that high density **[72]**. **Figure 4** depicts a high density system for gastro retention drug administration.

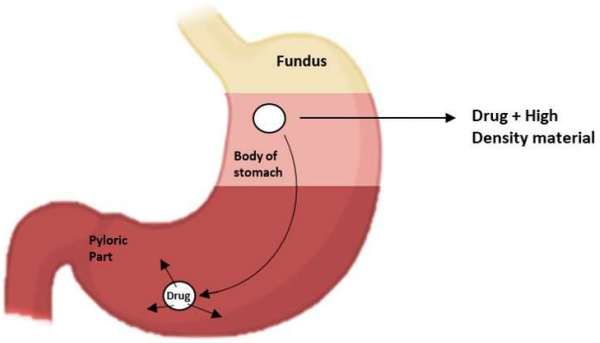

Figure 4: High density system

Expandable systems

The devices were first used in animal medicine, but their applications were later expanded to include people by increasing the number or shape of the devices. The GRT of expandable delivery systems may be enhanced **[73]**. In order for the system to function well, three main designs must be addressed: restricted space for simple oral intake, increased shape in the belly to restrict passing it via the valve, and system quantity reduction upon total dose forms to assist outflow **[27, 28, 74]**. The ability of this mechanism to restrict the valve makes it helpful. It is sometimes referred to as a "plug-type system." Swelling and unfolding are two methods of system expansion that allow for capacity and form modifications **[74, 75]**. GRDDS had substantial success both in vitro and in vivo by introducing swelling and expanding mechanisms to maintain the dose form in the stomach **[76, 77]**. One such system, described by Bolton *et al*. **[78]**, was intended to grow beyond the diameter of the pyloric sphincter and stay logged there. Because of their pyloric sphincter blocking property, the devices were sometimes dubbed "plug type systems." The polymer absorbed water and inflated when it came into contact with the stomach fluid **[74, 78, 79]**. The dosage form was able to achieve sustained-release features by selecting a suitable polymer with an appropriate molecular mass grade and swelling properties **[80]**. The discovery of innovative super-porous polymers that can expand to their maximum size in under a minute has resulted in further progress for this kind of dosage form. When the dosage form comes into contact with GI fluid, capillary wetting through many interconnected open pores causes the polymer's characteristic rapid swelling property (swelling ratio of 1:100 or above) with an average pore size of more than 100µm to occur **[72]**. In order to keep the dosage form's delayed release profile, it is crucial to choose a decomposable chemical with the appropriate material mass, thickness, and swelling properties **[27, 81]**. Expandable systems, on the other hand, have a few drawbacks, including difficulty

storing easily hydrolyzable disposable polymers; difficulty manufacturing and may not be economical; difficulty managing physical reliability; and the possibility of gut barrier, abdominal hold, and gastritis **[27, 74, 82]**.

Bioadhesive system

In 1984, Park and Robinson proposed the mucoadhesive/bioadhesive system **[83]**. It was constructed to attach to the epithelial cells of the stomach, hence prolonging the GRT of the medicinal molecule **[9, 15]**. Drugs are combined with a bioadhesion polymer, which might be natural or synthetic, in this way. The contact formed between the polymers and the epithelial surface promotes mucoadhesion **[84]**. This is usually broken down into two stages: first contact and subsequent consolidation. Mucoadhesion is a complicated and unknown mechanism, but numerous explanations have been offered. Electronic theory is based on the fact that mucoadhesive and biological materials have opposing electrical charges.When two materials collide, electrons are exchanged, forming a double electronic layer at the interface where the attractive forces inside this electronic double layer operate. The wetting hypothesis is applicable to liquid systems that have an attraction to the surface and spread across it. The contact angle, for example, may be used to determine this affinity. According to the general rule, the lower the contact angle, the stronger the affinity **[85]**. The contact angle should be equal to or near zero in order to establish the mucoadhesive strength. The wetting hypothesis is applicable to liquid systems that have an attraction to the surface and spread across it. The contact angle, for example, may be used to determine this affinity. According to the general rule, the lower the contact angle, the stronger the affinity. To offer appropriate spread ability, the contact angle should be equal to or near to zero **[86]**. Gastrointestinal bioadhesion dosage forms, pellets, spheres, films, caps, and tabs have all been produced and reported in the literature. Some of the most commonly used mucoadhesive polymers include carbopol, chitin, sodium alginate, hydroxypropylmethylcellulose, tween 80, propylene glycol, and poly (acrylic acid) **[15, 27, 87]**. Mucoadhesive polymers let pharmacological chemicals attach to mucosal surfaces, increasing the duration of the medicine at the desired place. An effective bioadhesion chemical is non-irritating and non-toxic, inert, attaches to the mucosal surface, has site selectivity, and interacts with mucus. A polymer's mucoadhesive properties and contact force are determined by its molecular mass, shape, elasticity of the polymer molecules, hydrogen-bonded ability, and cross-linking density **[88]**.

Several research studies have concentrated on merging flotation and bioadhesive qualities to develop mucoadhesive floating DDS, which extends the dosage form's stomach residence period. The researchers created a hollow-bioadhesive psoralen microsphere and microspheres with strong mucoadhesive properties and high buoyancy. According to pharmacokinetic studies, the medicine mostly in microspheres also had a longer clearance half-life and a lower clearance rate.

The mucus content changes based on the location of the mucous membrane. In this system, precise targeting may be challenging. Furthermore, high stomach moisture and rapid mucus turnover may limit polymer bioadhesion. Furthermore, there is a substantial chance of oesophageal adhesion, which might lead to a collatral lesion **[27, 38]**.

Magnetic system

An innovative concept was proposed to keep the dose form inside the stomach by using a magnetic field **[89]**. Magnetically active materials would be included in the dose form. The dose form contains active therapeutic chemicals, inert substances, and a trace of internal magnet. Above the colon, an endoscopic magnet is inserted to track the insertion of the active ingredient with an internal magnet **[15]**. **Figure 5** depicts a magnetic system for gastro retention drug administration. The location and strength of the extracorporeal magnet may have an effect on GRT **[90]**. Magnetic tablets have been proven in studies to improve GRT and bioavailability **[14, 91]**. Gastric retention duration and blood plasma concentration were both doubled when an extracorporeal magnet was applied. Bio-adhesive granules containing ultra-fine ferrite were developed and tested in rabbits **[92]**. It shows that a1700 gauss external magnetic field could hold all the particles in the gastrointestinal tract for over two hours. Furthermore, accurate magnet positioning might be challenging **[90]**. One of the primary obstacles to the in vivo design of this delivery system was a lack of patient cooperation, despite its revolutionary design **[89]**. Magnetic systems have received limited investigation, and their therapeutic use has yet to be established. As a consequence, future research into these technologies should concentrate on their medicinal potential.

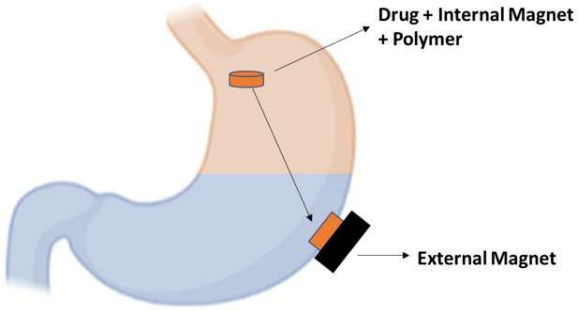

Figure 5: Magnetic system

Superporous hydrogel systems

In 1998, a new form of water-absorbent copolymer was introduced, superporous hydrogel. Because of its strong mechanical strength and elastic qualities, this system has acquired popularity in constraint formulation **[93]**. A superporous hydrogel is a three-dimensional network of hydrophilic polymers with many supersized pores. Capillary soaking via linked open holes causes the superporous hydrogel to expand. A "superporous hydrogel" is a hydrogel with pores that are hundreds of micrometres in size **[94]**. method for the preparation of superporous hydrogel:

1. The Porosigen Method 2. Method of phase separation 3. Technique of cross-linking 4. technique of gas blowing. These formulations include monomers such as acrylic acid, hydroxyl ethyl methyl acrylate, and polyvinyl alcohol; foam stabilisers such as pluronic F127 and silvet L7605; and foaming agents such as sodium bicarbonate and sodium carbonate. Hybrid agents include natural polymers such as sodium alginates and sodium carboxymethyl cellulose, as well as synthetic polymers such as poly vinyl alcohol **[94].**

Raft forming system

A raft-forming system is another kind of GRDDS. To create delayed drug delivery, effervescent excipients are combined with gel-forming. The emphasis is on inducing localised reactions since floating rafts act as barriers between the oesophagus and the stomach. As a consequence, they might be employed to effectively control peptic ulcer disease **[15, 94]**. Sodium alginate is used as a gelatinous material polymer and a gas-generating component. An acid modifier and $NaHCO_3$ are utilized. Carbon dioxide is created as a consequence. This decreases the bulk density of the system, enabling the raft to float on the stomach fluid **[94]**. In vitro controlled-release studies were conducted on numerous excipients to assess their floating activity, and a floating raft device for mebeverine HCl sustained release was constructed. As it swells and

entraps CO2 bubbles created by calcium carbonate contact with stomach fluid **[27]**. It forms a thick and sticky gel. The raft should remain in the bowels for many hours, allowing the medicine to be released gradually **[24]**.

Application

Except for the restricted absorption of pharmaceuticals by the intestinal wall, floating drug delivery offers a wide variety of applications for medicines with limited bioavailability. It preserves the dosage close to the absorption sites, resulting in increased bioavailability. Here's a run down of what they are: Sustained Drug Delivery: Because FDDS might stay in the stomach for an extended period of time, the medicine can be administered gradually. As a consequence, these approaches may address the problem of a restricted stomach residency length in an oral controlled-release formulation. These systems may float on the fluids of the gastrointestinal tract because their bulk density is less than one **[90]**. Site-specific drug delivery: These methods are especially effective when it comes to medications like riboflavin and furosemide, which are mostly processed in the stomach or the proximal region of the small intestine. According to this study, bioavailability was increased by developing a homogeneous floating dose form with a longer stomach contact time. The Area Under the Curve (AUC) of the floating tablets was about 1.8 times that of regular furosemide pills **[92]**. Drugs having restricted availability owing to site-specific intestinal absorption, such as those from the gastrointestinal tract, might be created as floating delivery devices to improve absorption **[91]**. GRDDS's marketed product is shown in

Table 3: Marketed products of GRDS

Technology	Drug	Product	Company
Effervescent floating liquid suspension	Aluminum hydroxide, magnesium carbonate	Gaviscon®	Glaxo Smith Kline, India
Floating tablets	Cipro floxacin	Cifran® OD	Ranbaxy, India
Gas generating tablets	ofloxacin	Zanocin® OD	Ranbaxy, India
Bilayer floating capsules	misoprostol	Cytotec®	Pharmacia, USA
Colloidal gel forming	Folicacid,Ferrous sulphate	Coviron®	Ranbaxy, India
Floating capsule	Diazepam	valrelease®	Roche, UK
Floating system	simethicone	Inon Ace®	Sato Pharma, Japan
Floating liquid alginate	Aluminum and magnesium	Topalkan®	Pierre Fabre Medicament, France
bi-layer floating tabelts	baclofen	Baclofen® GRS	Sun Pharma, India
Floating capsule	Levodopa and benserazide	Madopar® HBS	Roche, UK
Floating tablets	Metformine hydro chloride	Riomet® OD	Ranbaxy, India
Floating tablets	tramadol	Tramadol® LP	Galenix, France
Effervescent and swelling based floating system	prazosin hydro-chloride	Prazopress® XL	Sun Pharma, Japan

Future Aspect

In the pharmaceutical industry, gastro retention time for upper intestine absorbed drugs is one of the most complex. While additional study is required, the creation of GRDDS will help overcome current dosage form limitations. Single-system studies have been done on 'floating systems, expandable systems and mucoadhesive systems'. While several Gastro Retention Drug Delivery System solutions have been carefully researched, they all have limitations. Many pharmacologists struggle with changing GRT, particularly between fed and fasting states. Neither option may work. As a result, GRDDSs exist that transcend a single approach. Increase the use of extensible carbonated floating systems, bioadhesive buoyant systems, and mucoadhesive high-density systems. The stomach's physiological conditions, such as appetite and eating, are less influenced by dual-functioning units. GRDDS research should focus on enhancing dosage form retention in the stomach during fasting. Because the medication dose, polymer composition, and manufacturing requirements of a gastroretentive delivery system vary depending on the product, each system must be evaluated individually. **[22]**. To improve the GRDDS quality, first understand how preformulation factors affect the important quality criteria. GRDDS is floatable. In vitro release, tablet compressive strength, and friability Polymer activity and function are critical for creating gastroretentive drugs. When creating pharmaceutical formulations, it is vital to choose the best polymer absorption. QbD may be used to investigate the impact of dosage form changes on GRDDS parameters. Quality by Design (QbD) has revolutionised the pharmaceutical industry's understanding and management of production methods. It reduces quality issues **[13]**. The magnetic system may be a gastroretentive mechanism. Clinical studies are currently being completed. As a result, future magnetic system research must focus on clinical applications to determine whether they can be used on humans. Extracorporeal magnets may also detect the taken dose form by inserting magnetic devices into the superporous hydrogel system. This may help forecast stomach emptying and medicine transit times. Radiography and scintigraphy, for example, can measure dose from acid output in vivo **[24]**.

CONCLUSION

Conventional dosage forms have reduced bioavailability due to the partial release of drugs during the stomach retention period. Because of the short half-life and quick clearance from systemic circulation of medications absorbed in the stomach, they must be administered on a frequent basis. To address this issue, the oral sustained-

release formulation was developed in order to extend the stomach retention time while maintaining a stable drug plasma concentration in the circulatory system. Gastro retention drug delivery systems have a lot of promise when it comes to improving the bioavailability of medications given in the stomach. Although this review paper addresses a range of approaches, such as muco adhesive, magnetic, super hydro-porous, micro-ballon and high- and low-density systems, their clinical use is unclear. Future GRDDS procedures may need to focus on a combined strategy to increase the product's pharmacological quality. A QbD technique may also be used to get a better understanding of how formulation and process parameters affect product performance.

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Conflict of interest:

The authors, hereby, declare that there is no conflict of interest.

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