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Review Article

Beyond Conventional: Recent Advancement on Floating Drug Delivery Systems: An Approach to Oral Controlled and Sustained Drug Delivery Via Gastric Retention

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ABSTRACT

Gastro-retentive drug delivery system (GRDDS) has gained immense popularity in the field of oral drug delivery recently. It is a widely employed approach to retain the dosage form in the stomach for an extended period of time and release the drug slowly that can address many challenges associated with conventional oral delivery, including poor bioavailability. Different innovative approaches like magnetic field assisted gastro-retention, plug type swelling system, High-Density Systems, muco-adhesion technique, floating system with or without effervescence are being applied to fabricate GRDDS. highlighting their mechanisms of action and applications in targeted drug delivery. Furthermore, recent innovations in materials science and formulation technologies have enabled the development of novel GRDDS with improved biocompatibility, stability, and controlled release profiles. The review also addresses challenges associated with GRDDS, including physiological variability, drug stability, and regulatory considerations, and proposes potential strategies to overcome these obstacles. Gastro-retentive systems extend the residence time in the stomach, improving drug bioavailability, and ensuring maximum drug concentration at the target site. This review explores different gastro-retentive drug delivery systems, including those made from natural and synthetic polymers, and their applications. It also highlights the factors impacting these systems, as well as the challenges in the process and future prospects for their commercialization Additionally, the clinical relevance of GRDDS in the treatment of various gastrointestinal disorders and their future prospects in personalized medicine and targeted therapy are explored.

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INTRODUCTION

The oral administration route has always assumed a role of prominence in therapy due to its well-established advantages. Several factors make this route preferable to patients, and these formulations are also less expensive, easy to transport and store, flexible in terms of the constituents, and ready to administer. However, oral administration faces some physiological constraints due to the heterogeneity of the gastrointestinal system. In addition, several variables change throughout the gastrointestinal tract and greatly influence drug absorption. Among these factors, pH, the commensal flora, gastrointestinal transit time, enzymatic activity and surface area are the most important [2]. Conventional systems are not enough to overcome all the difficulties imposed by the gastrointestinal tract. For instance, they are inappropriate for drugs that are preferentially absorbed in the upper part of the digestive system since conventional formulations do not possess the capacity to face gastric emptying; therefore, they cannot be released in the colon where they stay during the final period of their release time. Therefore, the incomplete release of drugs and the concomitant reduction of dose effectiveness are consequences of the incapacity of the conventional systems to be retained at the stomach level [3]. In order to overcome these adversities, technological researchers have developed pharmaceutical systems that control drug release and the residence time, some of which are already available on the market. The failure in gastric retention with conventional systems has led to the development of oral gastroretentive systems. Such delivery systems were designed to be retained in the upper gastrointestinal tract for a prolonged period of time, during which they release the drug on a controlled basis [2]. The extended contact of gastroretentive systems with the absorbing membrane allows an increase in drug bioavailability. Additional advantages of these systems include (i) an improvement in therapeutic effectiveness, (ii) a reduction in drug loss, (iii) an increase in drug solubility in cases with low solubility in a high pH environment, and (iv) benefits due to the delivery of drugs that act locally in the stomach and duodenum [4]. Several strategies have been studied to formulate successful controlled drug delivery systems that increase the gastric residence time such as bio adhesive or mucoadhesive systems, expandable systems, high-density systems, floating systems, super porous hydrogels, and magnetic systems. This review compiles relevant information about the drugs that can benefit from gastroretention strategies, the factors that influence their gastric retention time, the mechanism of action of gastroretention, as well as their presentation as single and multiple unit systems [4]. In most of the cases, the conventional oral delivery systems show limited bioavailability because of fast gastric-emptying time among many other reasons involved. However, the recent technological development has resulted to many novel pharmaceutical products, mainly the controlled release drug delivery systems to overcome this problem. Gastro-retentive drug delivery system (GRDDS) is one such example where the attribute like gastric retention time coupled with the drug release for extended time has significantly improved patient compliance [4]. Some inherent limitations of the conventional oral drug delivery systems have ignited the interest to this new delivery system. Fast gastric emptying associated with conventional oral medications leads to a bioavailability issue for many drug molecules (e.g., pranlukast hydrate, metformin HCl, baclofen, etc.), of which the main principal site of absorption is the stomach or the proximal part of the small intestine, or have the absorption issue in the distal part of the intestine [5]. Solubility can also be improved by prolonging the gastric retention of drugs that are less soluble in an elevated pH

environment of the intestine [2]. There are many drugs (e.g., captopril, metronidazole, ranitidine HCl, etc.) that are prone to degradation in the colonic area [2]. To attain required therapeutic activity, recurrent dosing is needed for the drugs with short half-lives as they have the tendency of getting eliminated quickly from the systemic circulation. However, an oral sustained-controlled release formulation with additional gastric retention property can avoid these limitations by releasing the drug slowly in the stomach along with maintaining an effective drug concentration in the systemic circulation for an extended period of time. Apart from the systemic action, GRDDS has proved to be effective locally to treat gastric and duodenal ulcers, including esophagitis, by eradicating the deeply buried Helicobacter pylori from the sub-mucosal tissue of the stomach [8,10]. The history of GRDDS formulations dates back to almost three decades [11]. The basic fabrication techniques, including their in vitro characterizations, are also well established. Even in recent times, quite a few reviews have been published on GRDDS [5,12]. These reviews are more focused on the formulation aspects or in vitro characterization studies done by various researchers or overall GRDDS. The industrial aspects covering physicochemical, biopharmaceutical and regulatory considerations of GRDDS [19].

1. Stomach physiology

The stomach is the most dilated part of the GIT and is situated between the lower end of the oesophagus and the small intestine. Its opening to the duodenum is controlled by the pyloric sphincter [17]. To act as a temporary reservoir for ingested food and to deliver it to the duodenum at a controlled rate. To reduce the ingested solids to uniform creamy consistency, known as chime, by the action of acid and enzymatic digestion. This enables better contact of the ingested material with the mucous membrane of the intestines and they're by facilitates absorption. Another perhaps less obvious, function of stomach is its role in reducing the risk of noxious agents reaching intestine [20].

Success of GRDDS relies on the understanding of stomach physiology and related gastric emptying process. Structurally the human stomach is composed of three anatomical regions: fundus, body and antrum (pylorus), as depicted in Fig. 1. After a meal, the average volume of a stomach is about 1.5 l, which varies from 250 to 500 ml during the inter-digestive phases [18]. The part made of the fundus and the body acts as a reservoir of any undigested material, while the antrum performs as the principal site for the mixing action. Being the lower part, the antrum works as a pump for gastric emptying by a propel- ling action. Pylorus acts to separate the stomach from the duodenum and plays a major role in gastric residence time of the ingested materials. However, the pattern of the gastric motility is different for the fasting and fed state [20]. The gastric motility pattern is systematized in cycles of activity as well as quiescence. The duration of each cycle is 90–120 min and it contains four phases, as mentioned in Table 1. The motility pattern of the stomach is usually called migrating motor complex (MMC) [17].

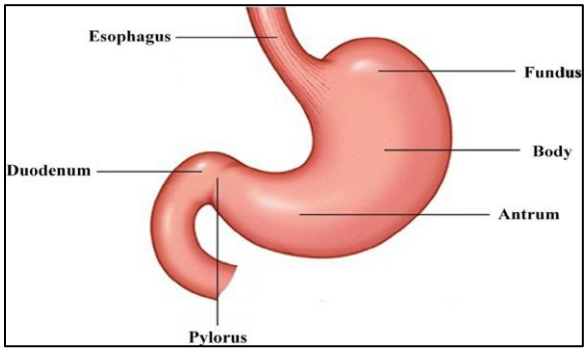

Figure no. 1: Diagram of human stomach

Over the past few decades, pharmaceutical research and formulation development scientists have recognized the potential of site-specific oral drug delivery systems. The stomach site has been identified as a 'depot' for controlled release dosage forms. However, formulation scientists have to consider physiological variations such as gastric residence time (GRT), gastric emptying time (GET), and drug release from the dosage form [7]. Once solid material (food and/or drug) is chewed and swallowed, the oesophagus rapidly transports it to the stomach. The stomach is mainly divided into two parts: the proximal stomach, consisting of the fundus and body, and the distal stomach, consisting of the antrum (or pylorus). The proximal stomach serves as a food reservoir, whereas in the distal stomach the food is processed, forming chyme, and proteins are partially broken down. The distal stomach (pylorus) acts as pump to assist in GE. The rate of GE is influenced by both the volume of food and the composition of the gastric contents. However, the pattern of gastrointestinal motility varies significantly in both fasting and fed states, further influencing the GE time. The fasted state is characterized by an interdigestive series of electrical events, which cycle both through the stomach and small intestine every 2-3 h [7]. This cycling event is termed the migrating myoelectric complex (MMC). The MMC is classified into 4 phases.

Four phases of migrating motor complex (MMC)		
Phases	Description	Duration (min)
Phases I (basal phase)	Idle state without any conc.	30 to 60
Phases II (pre-burst phase)	Intermittent conc.	20 to 40
Phase III (burst phase)	The regular conc. At the maximal frequency causes the good material to migrate distally	10 to 20
Phase IV	Transition period between phase III and phase I	0 to 5

i. Phase I (Basal Phase): This phase lasts about 30-60 min with rare contraction.

ii. Phase II (Pre-burst Phase): This phase lasts about 20-40 min with intermittent action potential and contraction that moderately increase in intensity and frequency as the phase progresses. Later in this phase, there is gastric discharge of fluids and small particles [7].

iii. Phase III (Burst phase): This phase lasts about 10-20 min, with intense and large, regular contractions that last for a short period of 4-6 min. This results in "sweeping" (moving) the undigested materials out of the stomach and

down into the small intestine. Thus, these contractions are also known as the "housekeeper wave."

iv. Phase IV: This phase lasts for a very brief (transitory) period of about 0-5 min in which the contraction between phase III and phase I disperses. This is the transitory period between two different cycles [7].

2. Advantages and Disadvantages of FDDS

A. Advantages of FDDS

- Improves patient compliance by decreasing dosing frequency.
- Better therapeutic effect of short half-life drugs can be achieved.
- Gastric retention time is increased because of buoyancy.
- Drug releases in a controlled manner for a prolonged period.
- Site-specific drug delivery to stomach can be achieved.
- Enhanced absorption of drugs which solubilize only in the stomach [5,6,7].
- Superior to single unit floating dosage forms as such microspheres release drug uniformly and there is no risk of dose dumping [5,6,7].

B. Dis-Advantages of FDDS

- Drugs which have stability and solubility problem in acidic pH cannot be used for GRDDS
- Drugs which are irritant to gastric mucosa. NSAIDs and Aspirin cause gastric lesions.
- Drugs that have absorption throughout GIT are not beneficial for this system
- Variability in gastric emptying time and rate is a major disadvantage.
- Longer time for swelling in hydrogel-based system.
- This system varies with the position of the person [5,6,7].

3. Drug selection criteria for GRDDS:

i. A number of considerations should be made while selecting drugs for Gastro-retentive Drug Delivery Systems (GRDDS) to ensure that the medication is suitable for this kind of delivery system [6].

ii. GRDDS are especially useful for drugs that are poorly soluble and have low permeability in the gastrointestinal tract. These drugs often have limited absorption in the upper GI tract; therefore, prolonging their residence duration can increase their bioavailability.

iii. For drugs with a restricted window of absorption in the stomach or upper small intestine, GRDDS is advantageous. These systems can increase the chance of absorption by making sure the drug remains in the absorption site for a longer period of time.

iv. The stability or solubility of some drugs changes with pH. GRDDS can be designed to release the medication in response to the pH of the stomach, ensuring optimal absorption.

v. Medication that undergoes significant first pass metabolism in the liver may benefit from gastro-retentive delivery. By remaining exposed in the stomach for an extended length of time, the medicine can initially bypass the liver by decreasing metabolism and increasing systemic bioavailability.

vi. Medication with a mechanism of action unique to the stomach, like antacids or those used to treat peptic ulcers or gastro esophageal reflux disease (GERD), is a good fit for GRDDS.

vii. Certain drugs may interfere with meals or respond adversely to pH changes in the stomach. GRDDS can be designed to control the drug's release while food is present or to reduce interactions with food [6].

4. Factors controlling the gastroretentive drug delivery system

The gastric retention time can affect drug absorption. Absorption is often limited to areas

between the stomach and duodenum, and the residence time in this area limits the absorption of drugs. Therefore, the longer the drug stays in contact with the absorbing membrane, more is the rate and extent of absorption. However, the time in the upper part of the gastrointestinal tract is short due to the fast gastric emptying time and generally lasts about 2–3 h. The gastric retention time is, therefore, an important parameter in drug absorption [4]. There are various factors to be considered for the development of gastroretentive dosage forms formulation to prolong the dosing intervals and thus improve patient compliance [9]. They are shown below.

4.1. Factors related to the dosage forms

- Size of the dosage form

To allow the dosage form to pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. In most cases, the larger the dosage form the greater will be the GRT. Due to the larger size of the dosage form, it could not quickly pass through the pyloric antrum into the intestine. Small-size tablets leave the stomach during the digestive phase while the large-sized tablets are emptied during the housekeeping waves.

- Shape of dosage form

Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared to other shapes [9].

- Density of dosage form

Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to the bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of b1.0 g/cm 3 is required to exhibit floating property. However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium [9].

4.2. Food intake and its nature

- Fed & unfed state-under fasting condition

Under fasting conditions, the gastrointestinal motility is characterized by periods of strong motor activity or MMC that occurs every 1.5 to 2 h. The MMC sweeps the undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer [9].

- Food intake & nature of food

Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract influences the gastric retention time of the dosage form. Usually, the presence of food in the gastrointestinal tract improves the gastric retention time of the dosage form & thus, the absorption of drugs increases by allowing its stay at the absorption site for a longer period [9].

- Calorie content

The rate of gastric emptying primarily depends on the caloric contents of the ingested meal. It does not differ for proteins, fats, carbohydrates as long as their caloric content is the same. Generally, an increase in acidity, osmolarity, and caloric value slows down gastric emptying. GRT can be increased between 4 and 10 h with a meal that is high in proteins and fats [9].

- Frequency of feed

The GRT can increase by over 400 min when successive meals are given compared with a single meal due to the low frequency of MMC [9].

4.3. Patient related factors

- Gender

Gastric emptying rate may differ in male & female. Generally, the gastric emptying in women was slower than in men [9].

- Age

Elderly people, especially those over 70 years have a longer gastroretentive time. Thus, gastric emptying time is slowed down [9].

- Posture

The effect of posture on GRT, found no significant difference in the mean GRT for individuals in upright, ambulatory and supine state. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units remained away from the pylorus. However, in supine position, the floating units are emptied faster than the non- floating units of similar size [9].

- Concomitant drug administration

Administration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (e.g. atropine, propantheline), Opiates (e.g. codeine) and prokinetic agents (e.g. metoclopramide, cisapride) can alter gastro retention of oral dosage forms. Anticholinergics like atropine and propantheline increase gastric residence time. Drugs like metoclopramide and cisapride decrease gastric residence time [9].

4.4. Disease state

In gastric ulcer, diabetes, and hypothyroidism there is an increase in gastric residence time. In the case of hyperthyroidism and duodenal ulcers there is a decrease in gastric residence time [9].

4.5. Volume of the GI fluid

The resting volume of the stomach is 25 to 50 ml. The volume of liquids administered affects the gastric emptying time. When the volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids [9].

4.6. Effect of gastrointestinal fluid

On comparison of the floating and non-floating units, it was concluded that regardless of their sizes the floating units remained buoyant on the gastric contents throughout their residence in the GIT, while the non-floating units sink and remained in the lower part of the stomach. Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during the digestive phase while non-floating forms stayed close to the pylorus and were subjected to propelling and retro Pelling waves of the digestive phase [9].

5. Approaches to fabricate gastro-retentive systems

There has been a large development of oral control release and sustain release drug delivery system for gastrointestinal diseases, for prolong absorption of drug. This system improv the bioavailability in Gastroretentive track and maintain an effective drug concentration for prolong time in stomach (GIT). As oral drug (Tablet, Capsule, Pellets) administered orally in stomach there is retention of drug in stomach and release drug in controlled manner. Due to controlled and sustained release the drug will supplied continuously to its absorption site or targeted site [12]. It also a pH base drug delivery system i.e., drug release at the certain pH there is heavy coating of metal which prevent it dissolving from gastric fluid and dissolved at targeted site. Current review deals with various gastro retentive drug delivery system approaches that have been recently become leading methodology in the field of site-specific drug delivery, controlled release drug delivery [8].

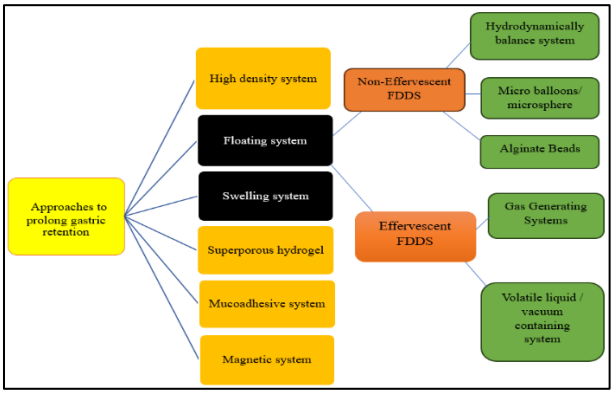

Figure no. 2: Approaches of GRDDS

1. Mechanism of floating systems

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used [12]. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents given in the Figure, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration [12]. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal [12]. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations [12].

F = F buoyancy - F gravity

= (Df - Ds) gv--- (1)

Where, F= total vertical force, Df = fluid density, Ds = object density, v = volume and

g =acceleration due to gravity

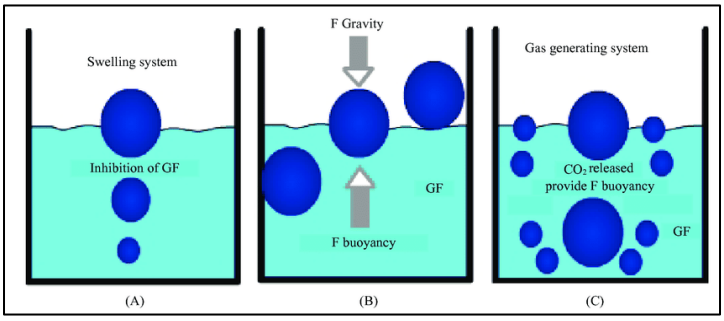

Figure no. 3: Mechanism of floating systems [12]

2. Types of floating drug delivery system

A. Non-effervescent FDDS

a) Hydrodynamically balance system

These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid, and hydration and swelling of the surface polymers produces a floating mass [13]. Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy. Hydro dynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form [13].

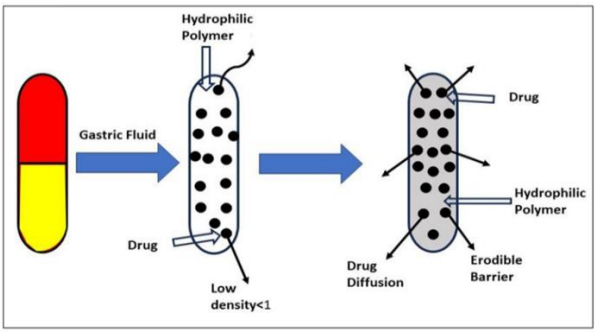

Figure no. 4: Hydrodynamically balanced intragastric delivery system (HBS) [13]

b) Micro balloons/ microsphere

To increase the GRT of the dosage form micro balloons or hollow microspheres with medications in their other polymer displays were made using a straight forward solvent evaporation or solvent diffusion technique. Polycarbonate, cellulose acetate, calcium alginate, Eudragit, agar, low methoxylated pectin, and other polymers are frequently utilized to create these systems [13]. Polymer amount, plasticizer polymer ratio, and formulation solvent all affect buoyancy and medication release from dosage forms. For more than 12 hours, these tiny balloons floated nonstop on the surface of an acidic dissolving medium containing surfactant. Because hollow microspheres combine the benefits of superior floating and multiple-unit systems, they are now regarded as one of the most promising buoyant systems [13].

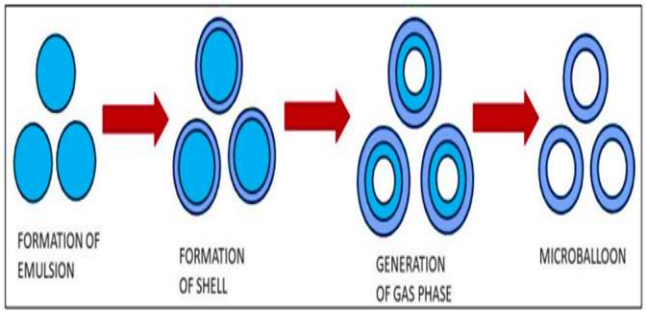

Figure no. 5: Micro balloons/ Microsphere [13]

c) Alginate Beads:

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of 2.5 mm diameter may be prepared by dropping sodium alginate solution into aqueous calcium chloride solution, resulting

in precipitation of calcium alginate resulting in the formation of a porous system capable of maintaining a floating force of more than 12 h. Compared to solid beads, they have a longer period of stay of more than 5.5 h [14].

B. Effervescent FDDS

This approach provides floating drug delivery systems based on the formation of CO_2 gas. It utilizes effervescent components such as sodium bicarbonate ($NaHCO_3$) or sodium carbonate, and additionally citric or tartaric acid. Alternatively, matrices containing chambers of liquids that turns into gas at body temperature could be used. Upon contact with the acidic environment, a gas is liberated, which produces an upward motion of the dosage form and maintains its buoyancy [14]. A decrease in specific gravity causes the dosage form to float on gastric contents. These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), and effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach, carbon dioxide is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinylpyrrolidone coated with hydroxyl propyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc. The various types of this system are as:

Gas generating system

a) Gas Generating Systems**:**

These are matrix type of systems prepared with the help of swellable polymers such as Methyl cellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provide buoyancy to the dosage forms. In single unit systems, such as capsules or tablets effervescent substances are incorporated in the hydrophilic polymer and CO_2 bubbles are trapped in the swollen matrix [14]. In vitro, the lag time before the unit floats is <1 min and the buoyancy are prolonged for 8 to 10 hrs. In vivo experiments in fasted dogs showed a mean gastric residence time increased up to 4 hrs. Bilayer or multilayer systems have also been designed. Drug and excipients can be formulated independently and the gas generating unit can be incorporated into any of the layers. Further refinements involve coating the matrix with a polymer which is permeable to water, but not to CO_2. The main difficulty of such formulation is to find a good compromise between elasticity, plasticity and permeability of the polymer [14].

b) Volatile liquid containing system:

These have an inflatable chamber that holds a liquid, such as ether or cyclopentane, which gasifies at body temperature and causes the chamber in the stomach to inflate. These systems osmotically regulate a floating system with a specified hollow unit. The system has two chambers, the first containing the medicine and the second containing the volatile system. These systems are further classified as follows:

- Intra gastric floating gastrointestinal drug delivery system-

This method includes a flotation chamber filled with vacuum or an inert, harmless gas, as well as a micro porosity compartment containing a medication reservoir [14].

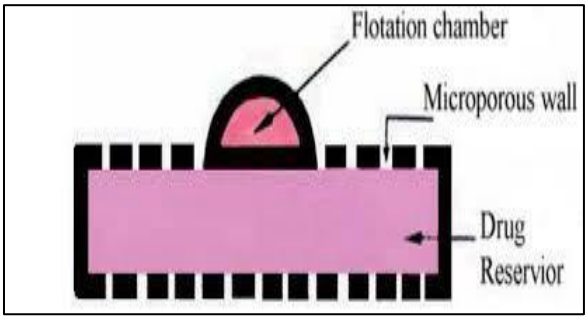

Figure no. 6: Intra gastric floating gastrointestinal drug delivery system [14]

- Inflatable gastrointestinal drug delivery system-

At body temperature, an inflatable chamber holding liquid ether gasifiers to inflate the stomach. The inflatable chamber contains bio erodible polymer filament (e.g., a copolymer of polyvinyl alcohol and polyethylene) that gradually dissolves in gastric fluid, causing the inflated chamber to release gas and collapse [14].

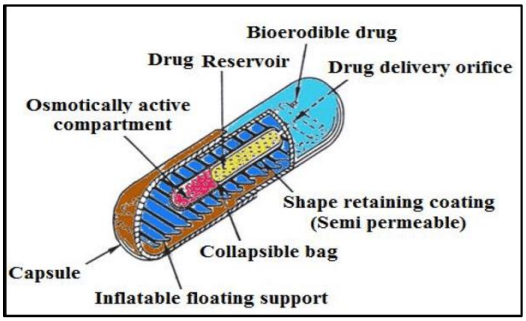

Figure no. 7: Inflatable gastrointestinal drug delivery system [14]

- Intra-gastric osmotically controlled drug delivery system-

It is made up of an inflatable floating capsule and an osmotic pressure regulated medication delivery system. The inflatable capsule disintegrates in the stomach, releasing the osmotically regulated drug delivery system, which is made up of two parts: a drug reservoir compartment and an osmotically active compartment. Working on this method, super porous hydrogels are a good example [14]. The dose form expands to several times its original volume when it comes in contact with gastric fluid. Due to the dose form's bigger size, the gastric contraction slips over the system's surface, pushing the dosage form back into the stomach after the gastric contraction has pushed it to the pylorus [14].

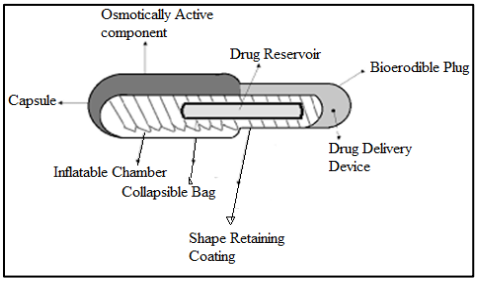

Figure no. 8: Intra-gastric osmotically controlled drug delivery system [14]

c) High-Density Systems:

The high-density frameworks density is going from2.5 to 3.0 g/mL to withstand in vivo peristaltic development and stayed flawless notwithstanding the GIT unsettling influence. The density of the measurements structures is expanded with barium

sulfate, iron powder, titanium oxide, and zinc oxide fuse. The significant downside of this framework is expanded portion size to accomplish high density [10,55].

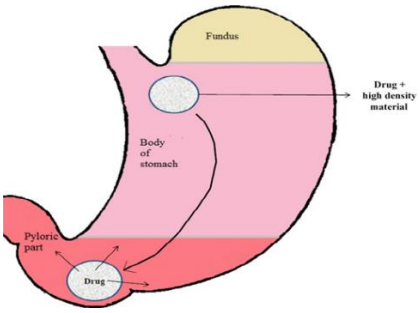

Figure no. 9: Gastro-retentive drug delivery system based on high density [55]

d) Magnetic systems:

In these frameworks, by the use of the attractive outer field the structure of the measurement washed inside the stomach. The dose structure would contain attractively dynamic components. One outer magnet was needed to position on the midsection over the area of the stomach to hold the controlled dose structure set up (Figure no.10). The significant downside of this framework is the absence of patient consistence. The lozenge form would contain magnetically active rudiments. One external attraction was needed to place on the tummy over the position of the stomach to retain the administered medicine in place (Figure no. 10). Though innovative in design, lack of patient compliance was one of the major lapses for in vivo design of this delivery system [10,55].

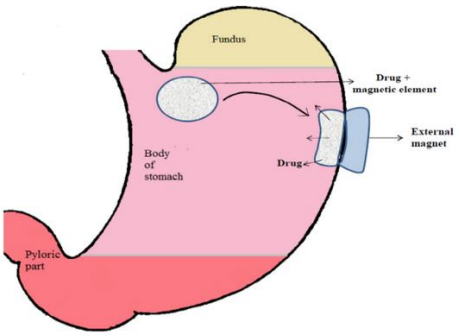

Figure no. 10: Gastro-retentive drug delivery system based on application of magnetic force [55]

e) Modified shape and swelling systems:

Lozenge form to attain sustained- release specific. farther advancement with the preface of swelling and expanding system (Figure no. 11), GRDDS managed to achieve significant success both in vitro and in vivo in order to retain the lozenge form in the stomach. one similar system that was designed to increase in size bigger than the periphery of pyloric sphincter and remain logged there (Figure no. 11). Alternately, the system was named as 'draw type systems' due to their pyloric sphincter blocking trait [55]. Once the polymer came in contact with the gastric fluid, it absorbed water and swelled. The selection of a suitable polymer (or combination of polymers) with an applicable molecular weight/ density grade and swelling parcels enabled the of similar kind of lozenge form has taken place with the preface of new polymers with super-porous nature, causing them to swell to an equilibrium size within a nanosecond. This characteristic rapid-fire lump property (swelling rate is 1100 or further) of the polymer with an average severance size of further than 100 µm occurs due to capillary wetting through several interrelated open pores when the lozenge form comes in contact with GI fluid [10,55].

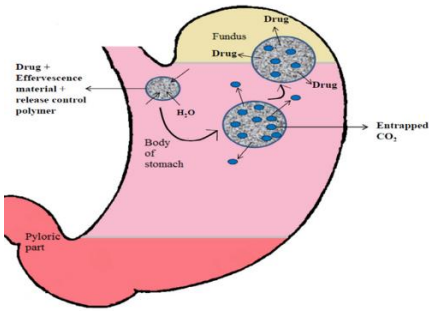

Figure no.11: Gastro-retentive drug delivery system based on combination of polymer swelling and effervescence [55]

f) Bio adhesive/Mucoadhesive systems:

Bio adhesive or muco-tenacious medicine delivery systems were also tried as gastro-forgetful systems. The lozenge form was made to be attached inside the lumen of the stomach wall and survive the gastrointestinal motility for a longer period (Figure no. 12). It was also salutary as a point specific design to promote original medicine immersion in an infected area of the stomach. Muco- tenacious excipients like polycarbophil, lectins, Carbopol, chitosan, carboxymethylcellulose (CMC), pectin and gliadin were reported as expression compositions for this kind of design [55]. The combination of macho- adhesion and floating or swelling medium is being espoused as another new approach for bettered gastro- retention attributes. In- situ gelling fashion (also known as raft forming system) in combination with carbon dioxide bubble ruse was also reported as another case compliance design for gastroretention. This type of delivery system, originally as a result form, contains sodium alginate as in situ gel forming polymer along with carbonates or bicarbonates as bouncy agents. When they come in contact with the gastric fluid, they swell and induce a thick cohesive gel that contains entrapped carbon dioxide bubbles, causing the medicine delivery systems to float. For gastroesophageal influx treatment, raft forming systems are constantly used because of their tendency to produce a subcaste on the upper part of the gastric fluid [10,55].

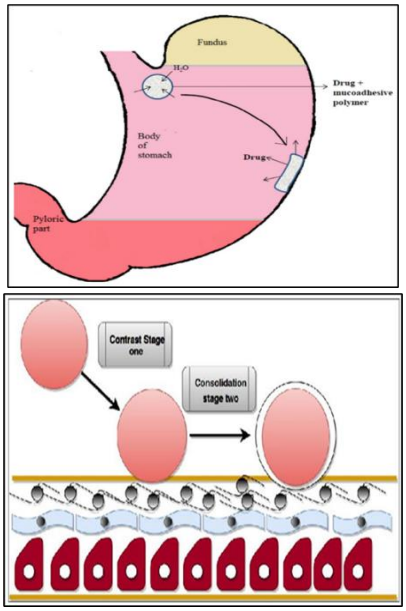

Figure no. 12: A: Gastro-retentive drug delivery system based on muco-adhesion B: bio adhesive/mucoadhesive system [10,55]

The mucoadhesive polymers are very useful excipient in the GRDDS. These polymers can be natural or can be synthetic. Natural polymers are sodium alginate, gelatin, guar gum, Tara gum, karaya gum. Synthetic polymers are HPMC, Carbopol, vinyl pyrrolidine, sodium carboxyl methylcellulose [24].

g) Raft forming systems

These are in situ gelling system gotten by blend with carbon dioxide bubble ensnarement. At first, it is an answer, contains sodium alginate (in situ gel previous) alongside carbonates or bicarbonate's as bubbly specialists. At the point when they interact with the GIFs, sodium alginate grows and produce a thick, strong gel that captures carbon dioxide bubbles, making it skim. They are significantly suggested for the treatment of gastroesophageal reflux [54].

6. Applications of floating drug delivery systems:

- Enhance bioavailability:

The bioavailability of CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption [37].

- Sustained drug delivery:

In this systems dose large in size and passing from the pyloric opening is prohibited. New sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours). Similarly, a comparative study between the Madopar HBS and Madopar standard formulation was done it shown the drug was released up to 8 hours in vitro in the former case and the release completed in less than 30 minutes in the latter case [37].

- Site–specific drug delivery systems:

These systems are particularly advantageous for drugs those are specifically absorbed from the stomach or the proximal part of the small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. It reduces the side effects which are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency [37].

- Absorption enhancement:

Drugs which are having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption [37].

- Minimize adverse activity at the colon:

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance [37].

- Reduce fluctuations of drug concentration:

Continuous input of the drug following controlled release gastro-retentive dosage form administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index [37].

7. Recent studies on various gastro-retentive technologies:

Types of DDS	Purpose	Drug	Polymer	Outcome	Ref.
Floating systems					
Floating in situ gelling system	Increasing drug localization and residence time in stomach	Clarithromycin	Gelling polymer-Gellan gum, floating agent calcium carbonate	Reduced the dose of clarithromycin ten times to show the same therapeutic activity as shown by its suspension counterpart	[43]
Multi-layer coated tablets	Improved localization of drug in stomach	Anhydrous theophylline	HPMC, PEG, Sodium bicarbonate (gas forming agent), Eudragit, ethyl cellulose	The tablets started floating within 7 min and remained in floating state for more than 8 h	[44]
Multiple unit type oral floating alginate beads	Prolonging gastric residence time, targeting stomach cancer and increasing drug bioavailability	5-Fluorouracil	HPMC K15M, gas-forming agent-calcium carbonate	Floating alginate beads of 5-FU showed significant reduction in tumors incidence and number of tumors as compared to pure 5-FU	[45]
Osmotic pump capsule	Prolonging drug action, decreasing frequency of drug administration, and decreasing peak plasma concentration	Famotidine	Polyethylene oxide, cellulose acetate, glycerin, diethyl phthalate	Relative bioavailability of the prepared osmotic pump capsule was found to be 1.605 folds higher as compared to that of the marketed formulation.	[46]
Floating beads	Increasing solubility and bioavailability, providing sustained release and improved localization	Curcumin	Carbopol 980, HPMC	Showed higher efficacy as compared to that of the pure curcumin	[47]
Floating systems	Localizing the drug at the absorption window, providing	Baclofen USP	Sodium CMC, HPMC K4M,	Amount of Polyox WSR 303 and HPMC K4M showed a significant effect on cumulative percent drug release at 6 h Prolonged	[48]

	sustained release		Polyox WSR 303	GRT achieved, and bioavailability increased up to 2.34 times.	
Floating microsponges	Treatment of gastric cancer, inhibiting drug degradation in the intestinal environment	Curcumin	Eudragit S100, and Ethyl cellulose	Pharmacokinetic study showed more bioavailability in microsponges than native curcumin.	[49]
3D-extrusion printing technology	3D-extrusion printing technology	Dipyridamole	HPMC K4M, HPMC E15, MCC PH101	More than 8 h of floating was observed where 30% and 50% infilling showed longer floating time than 70%. The 50% showed exact balance between longer floating time and drug release profile.	[50]
Floating tablets	Providing controlled release property	Ginkolides	MCC, PVP K30	Showed sustained release action for 12 h. In-vivo reports showed GRT in the stomach for about 8 h.	[51]
Floating tablets	Formulating zein-based floating tablets	Captopril	Zein, sodium bicarbonate, magnesium stearate	Radiographic study showed greater than 12 h of GRT, and in-vivo results showed increased MRT and bioavailability	[52]
Multiple-unit floating-bio adhesive cooperative minitablet	Prolonging GRT, improving drug bioavailability	Famotidine	HPMC K4M, Carbopol 971P	Started floating in 1 min and remained in floating state for 8 h T50% value was shown to be 46.54% that depicted good sustained action.	[53]
In-situ gels	Treatment of inflammatory diseases	Budesonide	Pluronic® F-127 (PF127)	Histopathological studies showed that these systems remained intact on TGI mucosa for not less than 4 h. In-vivo studies showed that 16% Budesonide in-situ gel can treat inflammation of the intestine.	[56]

8. Natural gums

Natural polymers, in addition to manufactured cellulose ethers, have been employed as hydrocolloids to successfully control drug release from swellable systems [7]. Natural polymers contain beneficial properties such as biocompatibility and safety, and so have valuable pharmaceutical and biological applications. Natural gums-gellan gum, guar gum, carrageenan's, and xanthan gum along with other polysaccharides like alginates and chitosan and natural polymers like pectin and gelatin are natural hydrocolloids or gel-forming agents that can swell in contact with gastric fluid, maintain relative shape integrity, and have a bulk density less than the gastric content [15,18].

Natural polymers

Natural gums are polysaccharides consisting of multiple sugar units linked together to create large molecules. Gums are frequently produced by higher plants as a result of their protection mechanisms following injury. They are heterogeneous in composition. Upon hydrolysis they yield simple sugar units such as arabinose, galactose, glucose, mannose, xylose or uranic acids, etc. The linear polysaccharides occupy greater volume than branched polymers of comparable molecular weight. Hence, at the same concentration, comparable linear polysaccharides exhibit greater viscosity [22]. Therefore, it is difficult for the heterogeneous gum molecules to move freely without becoming entangled with each other. Also, the natural gums are often known for their swelling properties. This is due to entrapment of large amounts of water between their chains and branches [22]. The polysaccharide gums represent one of the most abundant industrial raw materials and have been the subject of intensive research due to their sustainability, biodegradability and bio-safety. Many natural gums form three dimensional interconnected molecular networks known as "gels". The strength of the gel depends on its structure and concentration, as well as on factors such as ionic strength, pH and temperature. Natural gums are used in pharmaceuticals for their diverse properties and applications. They have good adhesive and laxative properties and are used in dental preparations. They are used as binders and disintegrants in solid dosage forms. In liquid oral and topical products, they are used as suspending, and stabilizing agents [22].

Sr. No.	Natural polymers	Applications in GRDDS
1.	Locust Bean Gum (LBG)	Swelling agent, Mucoadhesive, Sustained effect [23, 24]
2.	Colocasia esculenta gum	Swelling agent, Mucoadhesive, Sustained effect [25]
3.	Psyllium husk	Swelling agent, Sustained effect [26]
4.	Gum karaya	Swelling agent, Mucoadhesive, Sustained effect [27]
5.	Guar gum	Swelling agent, Mucoadhesive, Sustained effect [27]
6.	Limonia acidissima gum	Swelling agent, Mucoadhesive, Sustained effect [26]
7.	Mimosa pudica gum	Swelling agent, Mucoadhesive, Sustained effect [27]
8.	Okra gum	Swelling agent, Mucoadhesive, Sustained effect [25]
9.	Tamarind gum	Swelling agent, Mucoadhesive, Sustained effect [28]
10.	Tara gum	Swelling agent, Mucoadhesive, Sustained effect [28]
11.	Xanthan gum	Swelling agent, Mucoadhesive, Sustained effect [27]
12.	Carrageenan	Swelling agent, Sustained effect [27]
13.	Chitosan	Swelling agent, Sustained effect [32]
14.	Pectin	Swelling agent, Sustained effect [35]

- Locust Bean Gum (LBG)

It is commonly known as Carob bean gum which is obtained from the seeds of the Ceratonia silique Linn a leguminous plant. LBG is composed of a neutral galactomannan polymer. It contains Dgalactose and D-mannose and their proportions vary based on the sources of raw gum materials and the plant's development conditions throughout manufacture. LBG is a more effective gelling, stabilising, and thickening agent, with numerous pharmaceutical applications in the formulation and development of newer drug delivery systems [23, 24].

- Colocasia esculenta gum

Colocasia esculenta is a plant in the Araceae family that is frequently cultivated in Southeast Asia's tropical climates. Underground tubers (corns and cormels) have high glucose content. When water comes into touch with the mucilage of Colocasia tubers, it quickly hydrates and expands. Mucilage from isolated tubers has long-term releasing characteristics and is ideal for use as a swelling polymer in various GRDDS [25].

- Psyllium husk

Psyllium is made from the plant Plantago psyllium, as well as the husk and seed of Plantago ovata. Because of its propensity to create a strong gel in water, psyllium is categorised as a mucilaginous fibre. Biocompatible, inert, swellable, biodegradable, affordable, and widely available, psyllium husk is a good choice. Sterols; unsaturated fatty acids ranging from 5 to 10 % lipids, minute quantity alkaloids, 15 to 18 % proteins, trisaccharide, carbohydrate- splanteose, and 10 to 12 % heteroxylan mucilage are all found in the seed. Because of its release retardant qualities, psyllium husk is a reliable source of GRDDS. Long-term retention of dose forms in the stomach has also been studied [26].

- Gum karaya

Gum Karaya is obtained from Sterculia urens belonging to family Sterculiaceae. Gum Karaya upon acid hydrolysis usually yields D-galacturonic acid, D-galactose and L-rhamnose as principal constituents. It is only marginally soluble in water, 0.1 N HCl, and gastric fluid and slightly insoluble in 95 % ethanol. As gum Karaya has ability to swells in presence of water, it is employed as drug release modifier in many formulations. It has a high rate of erosion and a low hydration capacity. Zero-order drug release is being investigated, as well as matrices erosion [27].

- Guar gum

It is collected from the dried kernels of Cyamopsis tetragonolobus and belongs to the Leguminosae family. Guar gum is recognised by various synonyms such as Cluster bean, Guaran, Calcutta lucerne, Cyamopsis and Guarina [27]. It's a whitish-yellow powder with no odour or taste. Guar gum is water soluble but insoluble in organic solvents. It has the capacity to improve viscosity and is utilised in pharmaceutical industries as a disintegrating agent and binder in tablets [27].

- Limonia acidissima gum

Gum of Limonia acidissima (Rutaceae), often known as wood apple or elephant apple, is a tropical and subtropical tree widespread throughout India. Mucilage is a carbohydrate-rich mucilage derived from tree trunks. When mucilage comes into contact with water, it quickly hydrates and expands. Isolated stem mucilage with long-term releasing characteristics and mucilage suited for use as a swelling polymer in various GRDDS [26].

- Mimosa pudica gum

Mimosa pudica (Mimosaceae), often known as sensitive plant, is a tropical and subtropical undershrub that can be found throughout India. When water comes into touch with mimosa seed mucilage, it hydrates and expands quickly. Using diclofenac sodium as a model medication and mucilage suited for various GRDDS as a swelling and mucoadhesive polymer, the isolated seed mucilage with sustained release capabilities was developed [27].

- Okra gum

Okra gum is obtained from the pods of Hibiscus esculentus. At low concentration, it produces highly viscous mucilage. It is a type of polysaccharide with a hydrophilic character that is now employed as a swellable polymer in various formulations. Okra gum is a tablet binding material that comprises several polysaccharides such as galactose, rhamnose and galacturonic acid. It is used to make tablets with superior friability, hardness, and drug release characteristics. It is more advantageous than various commercial

synthetic polymers since it is safe, biodegradable, chemically inert, non-irritant, eco-friendly, and biocompatible. It is also commonly collected and no toxicological testing is required. Okra gum is used as a release rate modifier in several sustained and controlled release products [25].

- Tamarind gum

Tamarind is a kind of xyloglucan that comes from the tamarind tree seeds, which belongs to the Tamarindus indica family. It is a polysaccharide with a 1:2:3 ratios of galactosyl, xylosyl, and glucosyl. In the pharmaceutical and food sectors, xyloglucan, a key structural polysaccharide found in higher plant main cell walls, is employed as a binder, gel-forming agent, stabiliser, and thickening. Wet granulation technique is used to test the drug release characteristics of tamarind gums utilised in the formulation of matrix tablets. In the production of tablets, several polymer concentrations are used. Increased polymer content leads to a decrease in medication release [28].

- Tara gum

Tara gum is made from the Caesalpinia spinosa seeds endosperm and comes from the Leguminosae family. Tara gum is a white powder with no odour. At a concentration of 1 percent, galactose to mannose (1:3), it results in highly viscous solution. Tara gum is used in the pharmaceutical industry to make gastroretentive controlled release tablets and emulsions for medications such glipizide, carvedilol, metformin hydrochloride, clozapine, and ciprofloxacin hydrochloride, and itopride is a patent claim. Tara gum, when combined with other ingredients, has a good gastroretentive effect and enhances the floating time of the dosage form. It is also used to make an emulsion [28].

- Xanthan gum

Xanthan gum was spontaneously synthesised by the bacteria Xanthomonas campestris. This gum comes in the form of a fine powder or cream that is odourless and free-flowing. This gum contains a stable polysaccharide with a D-glucose backbone similar to that of cellulose. The aqueous solution is stable at wide range of pH (3–12) and temperatures of 10–60 °C in the presence of enzymes, bases, salts, and acids. It's utilised in cosmetics and food goods, as well as oral and topical preparations, because it's non-toxic and non-irritating. It's also employed as a thickening agent, stabilising agent, gelling agent, viscosity modifier, suspending agent, and emulsifier [27].

- Carrageenan

Carrageenan is an anionic gel-forming polysaccharide having high molecular weight. It is isolated from red seaweed species like Eucheuma, Gigartina stellate etc. Is a naturally occurring repeating unit of galactose and 3, 6-anhydrogalactose. Carrageenan is divided into 3 forms based on the degree of sulfation: carrageenan (three-sulfate), carrageenan (di-sulfate), and carrageenan (nonsulfate or monosulfate). They have thickening and release modifying properties [11]. The functional qualities of the carrageenan like bulking, thickening, stabilising and gelling are highly popular choice in food industries. It showed to be beneficial as tablet excipient due to its well compatibility, high stability and persistent viscoelasticity during the process of compression and granulation. Carrageenans are thus appropriate excipients for prolonged release formulations [27].

- Chitosan

It is a cationic polysaccharide composed of glucosamine and N-acetylglucosamine. Deacetylation of chitin derived from crab shells is used to make chitosan. It's non-toxic, biodegradable, and biocompatible. It comes in the form of odourless white coloured powder that is partially soluble in 95 % ethanol and water. It's utilised as a viscosity improver, mucoadhesive, film former, binder in tablets, coating agent, and

disintegrating agent, along with other excipients [32].

- Pectin

Pectin is a safe and cost-effective polysaccharide found in citrus peels and apple pomaces. A complex structure underpins both the extraction procedure and the source pectin. Pectin has a tendency to form gel upon esterification; thus, serves as an important drug carrier in the design of gastroretentive control release formulations [34].

- Peanut husk powder

Peanuts, commonly known as groundnuts and classed as Arachishypogaea in taxonomy, are a legume crop produced primarily for their edible seeds. Peanut husk powder (cellulose 35.7 percent, hemicelluloses 18.7%, lignin 30.2%) is biodegradable, biocompatible, nontoxic, inexpensive, free of unpleasant and side effects, and widely available [35].

9. Hypertension:

a) GRDDS for Antihypertensive Drugs

Uncontrolled hypertension is a major risk factor for stroke, coronary heart disease, left ventricular hypertrophy, arrhythmia, arteriosclerosis, end-stage renal disease, and other life- threatening disorders. According to the World Health Organization, hypertension is the third leading cause of death worldwide [36].

Most of the antihypertensive drugs have short GRT, low BA, and narrow absorption window. GRDDS can be a viable option for management of hypertension as several antihypertensive drugs [37]. It may be beneficial for some of the following drugs having.

- Narrow absorption window, for example, furosemide, atenolol, and diltiazem
- Short half-life, for example, losartan and furosemide
- Instability, for example, captopril at high pH values
- Low solubility, for example, verapamil, furosemide, and propranolol at high pH
- Degradation in the colon.

GRDDS is an approach to prolong GRT, thereby targeting site-specific drug release in the upper GIT for local or systemic effects [37]. This site-specific drug delivery reduces undesirable side effects of administered drug as it can minimize the counter activity of the body leading to higher drug efficiency [36]. GRDDS of antihypertensive drugs may be useful to increase the GRT, BA, henceforth to reduce the dose of the drug, dosing frequency, and increased patient compliance. Hence, to formulate a GRDDS for an antihypertensive drug, to achieve an extended retention in the upper GIT, which may be result in enhanced absorption and thereby improved BA [37].

10. Limitations:

One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach for the drug delivery buoyancy to float here in and to work efficiently. However, this limitation can be overcome by coating the dosage form with bio adhesive polymers, thereby enabling them to adhere to the mucous lining of the stomach wall [35]. Alternatively, the dosage form may be administered with a glass full of water (200–250 ml). Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids. Drugs such as nifedipine, which is well absorbed along the entire GI tract and which undergoes significant first-pass metabolism, may not be desirable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability [1]. Also, there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.

11. CONCLUSIONS:

According to the review of different published literature and detailed investigations on commercial products, it can be concluded that no single gastro-retentive system could be marked as the best suited for any drug candidate. The currently available polymer-mediated non

effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be an effective and rational approach to the modulation of controlled oral drug delivery. This is evident from the number of commercial products and a myriad of patents issued in this field. The FDDS become an additional advantage for drugs that are absorbed primarily in the upper segments of GI tract, i.e., the stomach, duodenum, and jejunum. However, several advantages of GRDDS for patients have been evidenced in the majority of them. Individual drug candidate or a combination of the drugs needs to be assessed case by case regarding the necessary dose and the ease of manufacturing process. Polymer selection remains a critical factor for the formulations that contain high dose. This selection is essential for the compressibility needed to exploit the high doses of the APIs. However, the criteria of ideal polymer should be based on its amount in the dosage form; a minimum quantity that provides a substantial gastric retention should be preferred. Although several approaches like floating, bio-adhesion, effervescence, sinking, magnetic, swelling, etc. have been proposed over the years, reports on their in vivo success have not been captured significantly. Formulation wise, the major trend has been shifted toward the use of swelling polymer matrix together with effervescence in the design of floating delivery systems. Commercially it is emerging slowly as an important novel drug delivery due to many inherent challenges associated with it in spite of the numerous potential benefits offered by this delivery system. In terms of delivering drugs to the systemic circulation along with enhanced effectiveness, it is expected that GRDDS will become more popular in the near future. However, it is necessary to establish their efficacy by properly designed in vivo studies for a specific drug because of the complexity in pharmacokinetic and pharmacodynamic parameters

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