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A COMPREHENSIVE INSIGHT ON GASTRO RETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

The conventional mode of drug delivery faces several challenges in the gastric region such as inappropriate drug release and reduction in dose efficacy that hinders the effective drug delivery from conventional dosage forms. Various physiological obstacles such as short gastric residence time and variable gastric emptying time reduce the efficacy of oral dosage forms. The aim is to fabricate formulations that can deliver the drug to the target organ with higher efficacy and increased bioavailability. Hence, a novel approach has been trending for past several years to deliver the drugs effectively in the gastrointestinal area. The system fabricated to enhance the retention of drugs in GIT is known as gastroretentive drug delivery system. GRDDS provides controlled action and enhances the bioavailability of the drug by prolonging the drug release. These are commonly employed for various gastrointestinal disorders and for site-specific drug delivery. This review summarizes various gastroretentive drug delivery approaches such as magnetic system, floating drug delivery system, bioadhesion etc and discusses the future prospects of GRDDS.

Keywords: Gastroretentive; Floating delivery; Mucoadhesion; Novel drug delivery; Stomach; effervescence

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1. INTRODUCTION

Oral route is the most preferred and convenient route of drug delivery. It is most preferred by patients due to ease of use and convenience for self-administration. Despite all its advantages, drug delivery to gastric region is challenging because of its complex nature and several physiological barriers.[1]

Drugs having absorption window in upper small intestine act as barrier in conventional drug delivery. Because such drugs have short residence time and very short release in the stomach. These difficulties have prompted researchers to design dosage forms with prolonged action. Controlled drug delivery system offers advantages over conventional drug delivery systems such as reduced fluctuation in plasma-drug concentration and at site of action, reduction in dose frequency and thus leads to optimized therapeutic efficiency.[2]

During the past two decades, several controlled drug delivery systems have been designed to act as reservoirs to release the drug at a predetermined rate, but these systems have several limitations such as gastric-emptying rate that varies from person to person and brief gastric transit time (8-12 h). One of the novels in controlled drug delivery is GRDDs (gastro retentive drug delivery system). Dosage forms that can be retained in gastric region are called GRDDs.[3] GRDDs can improve the delivery of drugs having absorption window by prolonging release of drug before it reaches at site of action by using a preventive coating. Various physiological factors such as regional pH, gastric transit time, surface area, enzymatic activity influences absorption of drug in gastrointestinal tract (GIT) and hence these factors can be used to achieve control over absorption.[4]

Drugs having short half-lives, and which gets absorbed in GIT easily are quickly eliminated from systemic circulation and thus requires frequent dosing. To overcome this problem, controlled drug delivery systems in the form of GRDD have been developed which increases the gastric residence time (GRT) and slowly releases the drug in GIT. GRDDs also offers pharmacokinetics advantages like maintenance of constant therapeutic levels and reduced fluctuations.[5] Gastro retentive drug delivery systems (GRDDs) prolongs the gastric residence time of drugs and thus:

- Improves bioavailability
- Reduces drug waste
- Enhances the solubility of drugs that are less soluble in high pH environment.[6]

Several approaches have been used to design gastro retentive drug delivery system, including high density (sinking system), low density (floating system), swellable system, magnetic system, mucoadhesive system and super porous hydrogels.[7] This review gives complete insight of current and future potential of gastro retentive drug delivery system.

2. ANATOMICAL ASPECT OF GASTROINTESTINAL TRACT

The gastrointestinal (GI) tract also known as alimentary canal[8] is a long continuous muscular tube starting from buccal cavity of mouth and terminates at anus[9]. Upper GI

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tract consists of mouth, pharynx, esophagus and stomach and lower GI tract consists of small and large intestines. The GI tract is composed of four concentric layers surrounding the lumen, namely:

- Mucosa
- Submucosa
- Muscularis externa
- Serosa or adventitia[8]

The gastrointestinal tract is mainly divided into three regions:

1. Stomach
2. Small intestine (duodenum, jejunum and ileum)
3. Large intestine (caecum, colon, rectum)

Stomach is a J-shaped organ and can be divided into four regions anatomically:

- Cardia
- Fundus
- Body
- Antrum

Stomach mainly functions to store and mix the food with gastric secretions and then transfer chyme into small intestine through pyloric sphincter.[9]

Secretions of GIT:

Epithelia of GIT is made up of variety of cells which secretes many types of secretions, mainly-

- Mucus
- Other secretions e.g hydrochloric acid and intrinsic factor from parietal cells, pepsinogen from chief cells, gastrin from G-cells.[9]

Mucus: structure, composition and function

Mucus is a complex, viscous, complex secretion synthesized mainly by specialized goblet cells present in the columnar epithelium. Mucus is primarily composed of water (95%) and also consists of other substances such as salts, fatty acids and mucin etc.[10]

The primary function of gastrointestinal mucus is protection of gastric walls from damage by forming gel throughout the gut, mucus is also involved in many diseases process.[10,11]

Most abundant macromolecule in mucus is mucin, glycoprotein found in mucus secretion.[12]

Thickness of mucus layer varies in various organ; stomach has mucus layer of approximately 300 micrometer thickness and jejunum has thinnest mucus layer.[13]

3. PHYSIOLOGICAL ASPECT OF GASTROINTESTINAL TRACT

Stomach is anatomically divided into mainly 3 regions: fundus, body and antrum (pylorus).[14] The proximal region of stomach consisting of body and fundus part serves as reservoir for storage of ingested food while the distal region of stomach consisting of antrum mainly do the mixing action, acting like pump for gastric emptying by propelling actions.[14,15] Gastric emptying occurs in both fasting and fed states, only the pattern of gastric emptying is different.[15] In fasting state, gastric emptying is characterized by interdigestive cycle known as interdigestive myoelectric cycle or migrating myoelectric complex (MMC).[16] Liquid components easily pass through partially constricted sphincted while large food molecules do not pass through it and get retropulsed back into main body of stomach and remain in fed

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state. Fed state usually disturbs this cycle. Various phases of MMC have been summarized in Table 1

GASTRO RETENTIVE DRUG DELIVERY VS CONVENTIONAL DRUG DELIVERY[18]

GRDDS provides several advantages over conventional dosage forms. The main differences between GRDDS and conventional drug delivery have been summarized in Table 2.

FACTORS AFFECTING GASTRIC RETENTION TIME OF DOSAGE FORMS

Variety of factors affect gastric retention time of dosage forms. The important factors affecting gastric retention are illustrated in Figure 1.

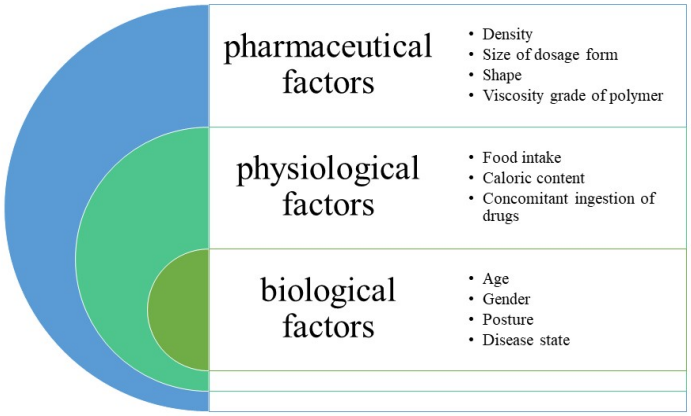

Fig 1: Factors affecting gastric retention

Table 1: Summary of various phases of MMC

Phases of MMC	Duration	Contractions
Phase I (basal phase)	40-60 min	No contractions
Phase II (preburst phase)	20-40 min	Gradual contractions
Phase III (burst phase)	10-20 min	High intensity contractions
Phase IV (short transitional phase)	0-5 min	Short contractions

Table 2: GRDDS vs Coventional drug delivery

S.No	Parameters	Conventional drug delivery	GRDDs
1.	Toxicity	High risk of toxicity	Low risk of toxicity
2.	Patient compliance	less	Patient compliance improves
3.	Drug with narrow absorption window in small intestine	Not suitable	suitable
4.	Drugs having rapid absorption through GIT	not very advantageous	Very much advantageous
5.	Drugs acting locally in the stomach	not very advantageous	Very much advantageous
6.	Drugs which are poorly soluble at alkaline pH	not very advantageous	Very much advantageous
7.	Drugs which degrade in the colon	not very advantageous	Very much advantageous
8.	Dose dumping	High chances of dose dumping	No risk of dose dumping

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- **Pharmaceutical technology factors:**

1. Density of dosage form

Density of dosage form has impact on gastric retention time by two ways: flotation and sinking. In flotation, the density of dosage form is apparently less than that of gastric fluid i.e 1.004g/cm^3. Flotation will increase the gastric retention time. On the other hand, sinking works by having density greater than that of gastric fluid which also increases gastric residence time. For sinking, density of approximately 2.5g/cm^3 is required.[19]

2. Size of dosage form

Size of the dosage is also an important pharmaceutical factor that can help in gastric retention. Size of the dosage form can be changed to increase the gastric residence time for non-floating systems. Increasing the size of the dosage form for values greater than diameter of pyloric sphincter (mean 12.8 ± 7mm) prevents passage of dosage form to duodenum and gastric residence time gets increased.[19] dosage form of diameter more than 7.5mm are found to exhibit GRT.[20]

3. Shape

Shape of the tablet affects gastric retention time. Six shapes of tablets (ring, tetrahedron, cloverleaf, string, pellet and disk) were evaluated in-vivo to calculate GRT. Tetrahedron shape was found to exhibit nearly100 % retention at 24 hr.[21]

4. Viscosity grade of polymer

Drug release from dosage from depends on viscosity of polymer. Low viscosity polymers tend to have better floating properties than high viscosity polymers.[21]

- **Physiological factors:**

1. Food intake

Presence or absence of food in the stomach widely affects GRT. Presence of food in the stomach increases GRT because it increases absorption time of the dosage form by allowing the dosage form to stay for longer time in stomach.[22]

2. Caloric content

As per study done by (JG Moore *et al*, 1984) suggests that increasing meal total caloric content slow down solid food gastric emptying significantly while total caloric content does not influence liquid emptying rates.[23] Diet rich in fat and proteins can increase GRT by 4-10 minutes.[24]

3. Concomitant ingestion of drugs

In fasting state, GI motility is characterized by MMC which sweeps the food from stomach and if timing of administration of dosage form coincides with MMC, then GRT will be short while in fed state, MMC is delayed, so longer GRT.[25]

- **Biological factors:**

1. Age

Elderly people of age on average of 70 years have longer GRT.[26]

2. Gender

Males show less GRT than female counterparts. Men have GRT of 3.4 h while females have longer GRT (4.6h) than males.[27]

3. Posture

Posture of patients (supine and prone) can affect GRT of patients.[28]

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4. Diseased state

Some disease conditions such as gastric ulcer, diabetes, gastroenteritis and hypothyroidism are responsible for slowing the gastric time while disease conditions such as duodenal ulcer increases gastric time.[28]

SUITABLE DRUG CANDIDATES FOR GASTRORETENTION[29,30]

The therapeutic candidates with time-controlled release kinetics can be of interest to prolong the gastric residence time. Such candidates can be drugs, which:

- are locally active in the stomach e.g antacids, misoprostol and antibiotics against Helicobacter pylori.
- are unstable in intestinal or colonic environment e.g captopril
- drugs that are rapidly absorbed from GIT e.g amoxcillin
- having absorption window in the stomach or upper small intestine e.g L-DOPA, riboflavin, furosemide and p-aminobenzoic acid.[29]
- Exhibit low solubility at high pH values e.g diazepam, verapamil HCL.[30]

DRUGS NOT SUITABLE FOR GASTRORETENTIVE SYSTEM[31,32,33]

Drugs having following characteristics are not suitable for gastroretentive drug delivery:

1. Drugs which undergo first-pass metabolism.
2. Drugs which are well absorbed through gastrointestinal tract
3. Drugs that cause irritation of the gastric mucosa.[31]
4. Drugs which have very low acid solubility e.g phenytoin
5. drugs which are unstable in gastric environment e.g erythromycin[32]
6. drugs which are intended for release in the colon e.g corticosteroids[33]

NEED FOR GASTRO RETENTION[34]

- local and sustained drug delivery to the stomach and proximal part of intestine to treat certain conditions
- drugs that are absorbed to variable gastric emptying time
- for the treatment of peptic ulcers caused by H. pylori
- drugs that get absorbed from proximal part of GIT.

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM[35-37]

- Improving local efficiency of drugs in GIT over prolonged period of time
- Reduction in side effects of acidic drugs causing irritation in the stomach
- Reduction in drug waste and administration frequency
- Fluctuation in drug level is not observed and thus, optimum therapeutic plasma concentration is maintained over prolonged period of time
- Increases bioavailability of drugs soluble at acidic pH.
- Provides site specific drug delivery

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DISADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

- Not suitable for the drugs causing lesions
- Bioadhesion in acidic environment and high turnover rate of mucus arises questions about effectiveness of GRDDS
- Floating system with patient of achlorhydria are questionable[38]

POLYMERS USED FOR FORMULATION OF GASTRIC DRUG DELIVERY SYSTEM[39-41]

Synthetic polymers:

Commonly used synthetic polymers for gastroretention are:

- Alginate
- Chitosan
- Hydroxypropylmethylcellulose
- Polyethylene oxide
- Polypropylene
- Ethylcellulose
- Hydroxypropylcellulose
- Polymethacrylates

Natural polymers:

- Guar gum
- Xanthan gum
- Locust bean gum
- Karaya gum
- Tara gum
- Sodium alginate
- Colocasia esculenta gum
- Psyllium husk
- Okra gum
- Chitosan
- Pectin
- Peanut husk powder

DRUGS USED FOR GASTRIC DRUG DELIVERY[42-45]

A variety of active pharmaceutical ingredients are formulated into several dosage forms. A list of active drugs formulated into gastroretentive dosage forms have been summarized in Table 3.

APPROACHES FOR GASTRORETENTIVE DRUG DELIVERY

Different approaches have been used to extend the retention of oral dosage forms in the stomach. Some are formulated as single component system while some are formulated as multi-component system. Main approaches for formulating gastro retentive drug delivery systems include:

- floating system
- non-floating system
- Mucoadhesive system
- Swelling system
- Super porous hydrogel system
- Magnetic system

Various gastroretentive approaches have been illustrated in Figure 2.

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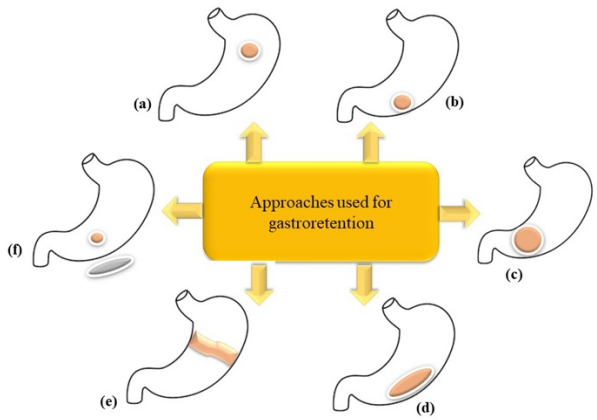

Fig 2: Approaches used for gastroretention

(a) Floating system (b) Non-floating system (c) Swellable system (d) Bioadhesive/ mucoadhesive system (e) Superporous hydrogel (f) Magnet system

Floating system

Floating system is designed to float in the stomach due to low density resulting in prolonged GRT. Floating system is a low-density approach which has bulk density lower than gastric fluids and hence dosage form remains buoyant in the stomach and releases the drug for a prolonged period of time without affecting gastric emptying time. Density of dosage form should be less than that of gastric contents (1.004 g/ml) in FDDS[46].

Classification of floating drug delivery system

- **Single unit floating dosage form**
  - Effervescent system (gas generating system)
  - Non-effervescent system
- **Multiple unit floating dosage form**
  - Effervescent system (gas generating system)
  - Non-effervescent system
  - Hollow microspheres[47-49]
- **Raft forming system**

Effervescent system

Swellable polymers like tartaric acid, HPMC, chitosan, and effervescent compounds like sodium bicarbonate, citric acid, etc. are used to produce the matrix of the effervescent system. Effervescent preparations may improve stomach pH and absorption in the GIT. The cost of an effervescent tablet is more than a regular tablet. Effervescent dosage form (Tablet) containing tartaric acid, citric acid, or sodium bicarbonate. When reacting in the stomach, carbon dioxide is produced, leading to the production of effervescence. The effervescent makes the tablet dose form less dense and more floatable in the stomach fluid. Sodium bicarbonate is used to create effervescent (carbon dioxide) handled in a 0:76:1 ratio with citric acid. The drug storage system in the body. When effervescent are created in a drug reservoir, the medication releases in a controlled or sustained manner.

a) Gas Generating system:- The effervescent system includes the gas generating system. As a result, this method also relies on the effervescent reaction, which releases carbon dioxide when sodium bicarbonate and citric acid mix. When a medication is caught in a hydrocolloid layer, its specific gravity and density are reduced, causing it to float above the gastric contents after gas releases,

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gas creation, or carbon dioxide (effervescent) production[50].

b) Volatile Liquid or Vaccum System:- Recent developments in gastro-retentive medication delivery systems include the use of volatile liquid and vacuum systems. This system has an inflatable chamber that is loaded with volatile oils that gasify at body temperature, such as ether and cyclopentane. after the medication is released, discharges of volatile liquids. A bio-erodible polymer plug made of polyvinyl alcohol, polyethylene, etc. might also fill the inflatable chamber[51].

Non effervescent system

Matrix-forming polymers including polymethacrylate, polyacrylate, and polystyrene as well as highly swellable and gel-forming substances like polysaccharide and hydrocolloids are used in the creation of non-effervescent systems. as a dosage-form non-effervescent medication Orally taken medication (such as a tablet, capsule, or pellet) comes into touch with the stomach fluid Stomach pH ranges from 1 to 3 pH, swelling and bulking up, and losing less than 1 density. Non-effervescent dose forms have a gel-formed structure that serves as a reservoir and allows to release in control for an extended period of time. The best non-effervescent formulations have pores on the surface, which create an osmatic state that causes the dosage form to inflate significantly more than other oral dosage forms when it reacts with gastric fluid. The dosage form is pushed into the pylorus by the gastric concentration in the stomach as a result although swelling as a result of the pressure passing through it and returning to the surface. as a result, dose form possesses a high absorption rate, slow drug release, and float on the surface of stomach juice[52].

Raft forming system

The raft forming system is mainly used for the treatment of gastric esophageal reflux diseases. In raft forming system there is formation of viscous cohesive gel when comes in contact with gastric fluid. Due to which overall portion of the liquid gel swells and form a continuous layer called as raft, on the surface of gastric fluid. Raft forming system includes carbonate / bicarbonate due to which dosage form become bulky and are responsible for liberating carbon dioxide to make system less dense. In raft forming system the gel forming agents are sodium alginate which converts in to raft after reacting with gastric fluid and also prevent reflux of gastric content in to the esophagus. The principal use of the raft-forming technology is the management of GERD, or stomach esophageal reflux illnesses. When the viscous cohesive gel in the raft-forming mechanism comes into touch with the stomach fluid, it forms. Consequently, the liquid gel, overall fraction enlarges and forms on the surface of the stomach fluid is a continuous layer known as a raft. Because of the carbonate and bicarbonate in the raft-forming system, dosage forms bulky and are in charge of releasing carbon dioxide to reduce system density. On a raft During the gel-forming process, sodium alginate transforms into a raft responding to gastric juices and preventing the reflux of gastric contents into the esophagus[53].

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Non-floating system

The dosage form of a gastro-retentive drug delivery system in a non-floating drug delivery system does not float in the stomach but rather remains there by a different process. Having bioadhesive and mucoadhesive qualities, the medication may settle down in the stomach. This system dosage form releases the medication in a sustained manner, as well as at the intended spot. It is also a pH-dependent medication delivery device; at a particular pH, it dissolves.

Mucoadhesive system

These were created to carry out drug absorption in a site-specific way. This strategy employs bioadhesive polymers that stick to stomach mucosal epithelial surface, resulting in extend the period of gastric retention. Several mechanisms of adhesion include:

1. Bioadhesive polymer's capacity according to wetting theory to disperse and bring about close contact with mucus layers.

2.Mucin's physical entanglement and the notion of diffusion interpenetration of a strand with a soluble polymer embedding mucin strands in polymer structures[54].

According to the absorption theory, bioadhesion results from secondary forces including hydrogen binding and van der wall forces. According to electronic theory, electrostatic attraction exists.a network of glycoproteins called mucins, and bioadhesive substance. Polymers used as bioadhesive:- Sodium Alginate, HPMC, PAA, Chitosan, PEG, Dextrin, Tragacanth, Sucralfate.

Swellable system

These are the dose forms, which after ingesting enlarge to a point where they cannot leave through the pylorus. Therefore, the dosage form remains for a longer time in the stomach. length of time. The names of these systems include 'plug type systems' because they display the a propensity to stay logged at the pyloric sphincter if their diameter exceeds when inflated, they measure about 12–18mm. The harmony between the duration and scope of the degree of cross-sectional area maintains swelling connecting between the chains of polymers. A high swelling is delayed by the degree of cross-linking system's capacity to preserve its physical integrity for a long time[55].

Magnetic system

A dosage form for magnetic systems consists of an internal magnet, excipients, and the active medicinal component. To manage the positioning of the dosage form containing an internal magnet, an extracorporeal magnet is positioned above the stomach. Moreover, the GRT may be impacted by the extracorporeal magnet's magnetic field strength previous research have claimed that magnetic pills increase GRT and bioavailability. Groning and co used magnetic acyclovir tablets in a trial on human volunteers with and without an external magnetic sphere. The authors noted that there was an increase in plasma drug content and GRT in the extracorporeal magnet is present[56].

Superporous hydrogel system

These expandable systems are classified separately because they differ greatly from traditional types. Superporous hydrogels

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with an average pore size are used in this method to enhance the GRT> 100 micrometers, enlarge to its equilibrium size due to the quick water intake by within a minute capillaries dripping countless pores that are openly linked. They enlarge considerably are large (swelling ratio: 100 or greater) and intended to be strong enough mechanically to endure pressure by contracting the stomach. Here is suggested by a hydrophilic co-formulation particle of substance[57,58].

VARIOUS NEW APPROACHES FOR GASTRORETENTIVE DRUG DELIVERY

Microsponges:

Microsponges are modern gatsroretentive dosage forms having spherical structure and are mainly composed of interconnected channels. These provide better drug loading capacity, minimal dose dumping, more stability and cost effectiveness as compared to other gastroretentive dosage forms[59,60].

Gastroretentive microballoons:

Microballoons (Hollow microspheres) have been approved as a viable therapy for gastric retention. Microballoons are spherical empty particles with no core that can linger in the stomach for extended periods of time. These are non-effervescent type of gastroretentive dosage forms. These possess better floating properties, as well as they can incorporate multiple units. Due to low density, they remain buoyant in stomach for long period of time. When they come in contact with gastric fluids they form gel which prevents fluid penetration into the device and consequent drug release[61,62].

MARKETED FORMULATIONS OF GRDF[42-44,63,64]

Gastroretentive dosage forms have been used over several years and hence numerous namrketed products have been formulated and summarized in Table 4.

PATENTS ON GRDDS

Several gastroretentive dosage forms and delivery systems have been patented and are summarized in Table 5.

CLINICAL TRIALS

A lot of in vitro and in vivo studies are being carried out to assess the effectiveness of gastroretentive dosage forms. These in vivo studies have been summarized in Table 6.

APPLICATIONS OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

- **Gastric retention delivery systems on treatment of H.pylori infection : -** One of the most prevalent harmful bacterial illnesses, Helicobacter pylori (H. pylori), affects an estimated 50% of the world's population. In addition to peptic ulcers, gastric lymphoma, and acute chronic gastritis, it is linked to the onset of the dangerous gastroduodenal disease. illustrates the H. pylori-induced stomach ulcer mechanism in a simple manner. H. pylori is primarily found in the gastric mucosa or at the junction of the mucous layer and the stomach's antral epithelial cells. The H. pylori genome has been associated with abnormal stomach acid production and premalignant histological characteristics. The diagnosis and management of peptic ulcer disease

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have undergone a radical change as a result of the identification of this bacteria. The majority of antibacterial drugs have low H. pylori minimum inhibitory concentrations (MIC) in culture. Additionally, treating H. pylori infection in vivo with just one antibiotic does not work. This is as a result of the antibiotic's low concentration, instability in the acidic gastric fluid, and little time spent in the stomach. Low concentrations of the antibiotic reach bacteria underneath the mucosa. The total eradication of H. pylori requires the use of many antibiotics in combination with an anti-secretory drug, however these regimens are not entirely successful. The other issues are with patient adherence, side effects, and bacterial resistance. To effectively eradicate H. pylori from the stomach in addition to the multi-antibiotic therapy, various therapeutic approaches have been investigated[65,66]

Example:- Floating tablets :-Diltiazem, Fluorouracil, Isosorbide dinitrate.

- **Maximize the bioavailability:-**For dosage types that require extended activity, gastro-retentive floating drug delivery systems are used to enhance drug bioavailability during the extended action period.
- **Sustained Drug Delivery**:- Since HBS systems can stay in the stomach for a long time, they can release the medication over a lengthy period of time. Thus, these approaches can address the issue of short stomach residence time associated with an oral CR formulation.These systems can float on the gastric contents since they have a bulk density of< 1. These systems are not allowed to pass through the pyloric aperture because of their size, which is relatively considerable.
- **Drug Delivery System act on specific site:-**Gastro retentive floating drug delivery systems function correctly in certain drug delivery system locations and offer suitable actions that provide Vantages for dosage type by these systems, which is different from other systems that are absorbed from the belly. The controlled drug delivery system is more affordable, provides the necessary local curative dosage levels, and limits the systemic sensitivity to environmental factors. The circulation of the drug reduces the negative effects. Given the availability of stomachic from a targeted delivery system, it may also be possible to reduce the frequency of doses for medications like furosemide and vitamin B2. The stomach and duodenum are where furosemide is absorbed most readily. A monolithic floating dosage form with an extended stomach residence duration and enhanced bioavailability has reportedly been created. The AUC obtained with the floating tablets was almost 1.8 times greater than that of the regular furosemide pills[67].
- **Absorption Enhancement**:- Potential choices for floating drug delivery systems include medications with low bioavailability due to site-specific absorption from the upper gastrointestinal tract, which would increase their absorption .

- **Decreased the adverse activity of the colon:-** Reduce the amount of medication that enters the colon by holding the dosage form within the gastro-retentive system[68].

FUTURE PERSPECTIVE

One of the biggest problems facing the pharmaceutical business, particularly for medications that are absorbed from the upper section of the intestine, is the GRT of the traditional dosage form. The shortcomings of conventional dose forms will be mitigated by the development of GRDDS, though more work is required to fix its flaws. Numerous studies on GRDDS have been conducted to date using single-system techniques such floating, expandable, and mucoadhesive systems. Even though various GRDDS technologies have been extensively explored to achieve successful gastroretentive systems, most have their own limitations. The variation in GRT, especially in the fed and fasted states, is still one of the main challenges faced by many formulation scientists. No single approach might be the best for resolving the problems. Therefore, it is desirable to explore suitable GRDDS that can overcome the limitations of a single approach. Using combination approaches such as expandable and effervescent floating systems, mucoadhesive and floating systems, swellable and even though numerous GRDDS technologies have been thoroughly investigated to provide effective gastroretentive systems, the most of them have their own drawbacks. One of the biggest problems that many formulation scientists are still dealing with is the variance in GRT, particularly in the fed and fasting stages. not one the most effective strategy for fixing the issues. Consequently, it is advisable to investigate suitable GRDDS that are able to go over the restrictions of a single strategy. Using many strategies, such as such as effervescent and mucoadhesive floating systems, extensible and swellable floating systems.

Understanding the effects of formulation and process variables on the essential quality features of GRDDS is another crucial component for enhancing GRDDS. Floating behavior, a crucial quality aspect of GRDDS, swelling, in vitro drug release, gel strength, mucoadhesive strength, mucoadhesive time capacity, hydrogel porosity, tensile strength, and friability of the tablet. From a formulation perspective, it is essential for the logical creation of formulations to comprehend polymer behavior and its role in the ingestible dosage type. Additionally, choosing an adequate polymer concentration is also crucial for creating such dosage forms.In this context, the quality by design (QbD) approach can be a practical tool for examining how formulation and process variables affect the crucial quality features of GRDDS. With the use of the QbD methodology in the pharmaceutical areas, there has been a sizable change in the comprehension and management of the manufacturing procedure, which significantly reduces the possibility of product failure.

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Table 3: Drugs used for gastric drug delivery through several dosage forms

S No.	Dosage forms	Active pharmaceutical ingredient
1.	Powder form	cinnarizine
2.	Tablets (floating system)	Captopril, amoxicillin, ampicillin, theophylline, fluorouracil, verapamil, diltiazem, rifampicin, ofloxacin, ranitidine, propranolol HCl, norfloxacin, metoclopramide HCl, gabapentin, metoprolol succinate, clarithromycin
3.	Granules (floating system)	Prednisolone, diclofenac sodium, indomethacin
4.	Microspheres (floating system)	Ibuprofen, aspirin, griseofulvin, terfenadine, diltiazem HCl, aceclofenac, cimetidine, cephalexin
5.	Liquid alginates (floating system)	Aluminium hydroxide, magnesium carbonate
6.	Gel beads (calcium pectinate)	Famotidine, calcium pectinate
7.	Capsules (floating system)	Misoprostol, diazepam, nicardipine, L-DOPA and benserazide, verapamil
8.	Nanoparticles (mucoadhesive)	fluconazole
9.	Minitablets	furosemide
10.	Microballoons	riboflavin

Table 4: Marketed gastroretentive dosage forms

Dosage form	Brand name	Active ingredient	Manufacturing company
Floating capsule	Valrelease®	Diazepam	LaRoche, USA
Effervescent floating liquid alginate preparation	Liquid Gaviscon®	Aluminium hydroxide	Reckitt Benckiser Healthcare, UK
Floating CR capsule	Madopar®	L-DOPA and benserazide	Roche products, USA
Raft forming system	Almagate Flot Coat®	Aluminium-magnesium antacid	Pierre Fabre Medicament, France
Gas generating floating system	Cifran OD®	ciprofloxacin	Ranbaxy, India
Bilayer floating capsule	Cytotec®	Misoprostal	Pfizer, UK
Coated multi-layer & swelling system	Baclofen GRS®	Baclofen	Sun Pharma, India
Effervescent floating system	Zanocin OD®	Ofloxacin	Ranbaxy, India
Colloidal gel forming FDDS	Conviron®	Ferrous sulphate	Ranbaxy, India
Polymer based swelling technology: AcuForm™	Metformin GR®	Metformin hydrochloride	Depomed, USA
Floating liquid alginate preparation	Topalkan®	Aluminium-magneium antacid	Pierre Fabre Drug, France
Bioadhesive tablets	Xifaxan®	Rifampicin	Lupin, India
Effervescent floating system	Riomet OD®	Metformin Hydrochloride	Ranbaxy, India

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Effervescent and swelling based floating system	Prazopress XL®	Prazosin hydrochloride	Sun Pharma, Japan
Floating system- CR capsule	Prolopa HBS®	Levodopa and benserazide hydrochloride	Roche, UK
Erodible matrix based system	Cipro XR®	Ciprofloxacin hydrochloride and betaine	Bayer, USA
Foam based floating system	Inon Ace Tables®	Simethicone	Sato Pharma, Japan
Gastroretention with osmotic system	Coreg CR®	Carvedilol	GaxoSmithKline, UK
Floating and swelling system	Cafeclor LP®	Cefaclor	Galanix, France
Floating and swelling system	Tramadol LP®	Tramadol	Galanix, France
Polymer based swelling technology	Gabapentin GR®	Gabapentin	Depomed, USA
Polymer based swelling technology	proQuin XR®	Ciprofloxacin	Depomed, USA
Polymer based swelling technology	Glumetza®	Metformin hydrochloride	Depomed, USA
Floating and swelling system	Metformin HCl®	Metformin hydrochloride	Galanix, France
Expandable system (unfolding)	Accordion Pill®	Carbidopa/levodopa	Intec Pharma, Israel
Extended release tablets	Kombiglyze XR®	Metformin, saxagliptin	Bristol Myers Squibb
OROS	Covera HS®	Verapamil Hcl	DURECT Corporation, USA
Geomatrix™	Sular®	nisoldipine	Skyepharma, shionogi Pharma Inc., UK
Gas generating floating tablets	Oflin OD®	ofloxacin	Ranbaxy, India

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Table 5: Patents granted for GRDDS

Patent no.	Formulation	Inventor name	Publication year
US9801816	GR dosage form extended-release of acamprostate	Bret Berner, Cuiping Chen	2017
US9561179	Controlled release floating pharmaceutical compositions	Catherine Castan, Philippe CAISSE	2017
US9393205	GR tablets	Varinder Kumar, Shavej AHMAD, Romi Barat Singh	2016
US 9314430	Floating GR dosage form	Pascal Grenier, Alain Nhamias, Guy Vergnault	2016
US 20160338949	Stabilized GR tablets of pregabalin	Varinder Kumar, Shavej AHMAD, Romi Barat Singh, Kaushal NAYYAR,Mohan Prasad	2016
US 20150231084	Osmotic floating tablets	Varinder Kumar, Shavej AHMAD, Romi Barat Singh, Ajay Kumar SINGLA	2015
US 20150366832	GR dosage form for carbidopa	Nadav Navon, Eytan Moor, David Kirmayer, Elena Kluev, Giora Carni	2015
US 9119793	GR dosage form of doxycycline	Douglas A. Bakan, Waranush Jitpraphai	2015
US 8974825	A pharmaceutical composition for the GI drug delivery system	Harshal Anil Jahagirdar, Rajesh Kulkarni, Shirish kumar Kulkarni	2015
US 8808669	GR extended release composition of the therapeutic agent	Ramesh Muthusamy, Mohan Gopalkrishna Kulkarni	2014
US 8586083	GRDDS comprising an extruding hydratable polymer	Hassan Mohammad	2013

Table 6: Clinical trials conducted on GRDDS

S.No.	Intervention / treatment	Condition	Study type	Phase	Sponsor	Identifier
1.	Memantine hydrochloride	Healthy subjects	Single center, open-label, single dose	Early phase I	Lyndra Inc.	NCT03468543
2.	Soctec capsule	Healthy subjects	Interventional	Early phase I	Skye Pharma AG	NCT02335515
3.	Gastric-Retentive Gabapentin (Gralise)	Complex Regional Pain Syndrome	Single group assignment	NA	Massachusetts General Hospital	NCT01623271
4.	Memantine hydrochloride	Healthy subjects	Single centre, open label, single dose study	Early phase I	Lyndra Inc.	NCT03711825
5.	Furosemide	Healthy subjects	Randomized, crossover design	I	LTS Lohmann Therapie-Systeme AG	NCT01887379
6.	Zaleplon	Insomnia	Randomized, crossover design, quadruple	II	Intec Pharma Ltd.	NCT01277107

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CONCLUSION

The analysis of many published works and in-depth research on commercial products led researchers to the conclusion that no specific gastro-retentive system could be deemed the most effective for any given drug candidate. However, the bulk of them have shown that GRDDS has a number of patient benefits. Regarding the required dose and the simplicity of the manufacturing process, each medication candidate or drug combination must be evaluated individually. For formulations containing high doses, polymer selection is still an important consideration. The compressibility required to utilize the high doses of APIs depends on this choice. But using a minimum amount of a polymer that exhibits significant stomach retention still meets the criteria for the perfect polymer. Floating drug delivery system consist of swelling polymer matrix together with effervescence. Despite, many potential advantages afforded by this delivery system, it is only slowly becoming a significant innovative drug delivery system commercially due to several inherent problems involved with it. It is anticipated that GRDDS will gain in popularity in the near future due to its improved ability to transport medications to the systemic circulation. However, because the pharmacokinetic and pharmacodynamic factors for each medicine are complex, it is vital to demonstrate their efficacy through well-designed in vivo research.

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CONFLICT OF INTEREST

Nil

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