IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
November 2023 Vol.:28, Issue:4

Innovations in Drug Release: A Review on Gastroretentive Drug Delivery Systems

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Sanoj Rajan*[1], Sneha Susan Sunny[2], Mohasin S[3], Jeffisha F[4]

Doctor of Pharmacy, Department of Pharmacy Practice, East West College of Pharmacy, Vishwaneedam post, Magadi Main Road, Bharath Nagar, BEL Layout, Bengaluru, Karnataka 560091 India.

Submitted: 22 October 2023
Accepted: 27 October 2023
Published: 30 November 2023

Keywords: Floating delivery, gastro retentive system, gastroprotection, sustained drug release

ABSTRACT

Due to patient compliance and simplicity of administration, English oral delivery of drugs was the most widely used modality. Any medicine taken orally has a shorter bioavailability due to the longer time it spends in the stomach. For medications with a limited window of absorption, poor stability at high alkaline pH, and enhanced solubility at low pH, gastroretentive drug delivery systems (GRDDS) have recently attained widespread adoption. Through the development of a drug delivery system that is kept in gastric fluid and releases its active ingredients in the stomach, this approach generates a medication that improves its efficacy. Effervescence agents, mucoadhesive polymers, magnetic materials, bouncy boosting excipients, and procedures that create plug-like devices that resist stomach emptying are a few approaches used to achieve gastric retention of medicines. This study describes the developments in the technologies investigated, their clinical relevance, and drug delivery techniques, along with their enormous potential future applications. Their acceptance into the pharmaceutical industry is an important factor to consider, as the majority of researched strategies have issues and are therefore undervalued to beat clinical trials. To achieve the system with the envisioned activity, the appropriate technology must be chosen for the task at hand using a suitable system of action. This review gives a succinct summary of several characteristics of recently developed approaches for GRDDS.

INTRODUCTION

Despite ongoing advancements in medication delivery techniques, oral administration remains popular due to patient comfort and simplicity of use. Drug delivery systems are used for maximizing the therapeutic index of the drug and also for reducing the side effects. The most preferred route is the oral route especially for the administration of therapeutic drugs because the low cost of therapy and ease of administration leads to a higher level of patient compliance. More than 50% of the drug delivery systems available are to be administered through the oral route. Reasons behind using the oral route are that it is the most promising route of drug delivery and effective oral drug delivery may depend upon many factors such as gastric emptying process, gastrointestinal transit time of the dosage form, drug release from the dosage form, and site of absorption of drug. A high level of patient compliance is the major advantage of using the oral route. Modifying the GI transit time is one of the main challenges in the development of an oral controlled drug delivery system. Gastric emptying of pharmaceuticals is highly variable and dependent on the dosage form and the fed/fasted state of the stomach[1].

For oral administration, controlled-release medication administration devices have been developed. The medication is dispersed via these drug delivery systems in a specified, predictable, and regulated manner. Due to stability or absorption difficulties, they are not appropriate for medications with low bioavailability[2]. The development of concepts for the prolongation of the gastric residence time of dosage forms has been the focus of pharmaceutical scientists for more than half a century. The prolonged residence of dosage forms in the stomach, so-called gastro retention, can have various therapeutic and biopharmaceutical benefits. These include improved local drug activity in the stomach, decreased fluctuations of drug concentration in the plasma, improved patient compliance due to the reduced dosing frequency, or improved bioavailability for certain drugs with absorption windows in the upper small intestine[3]. Modern methods, which are intended to increase the residence of such pharmaceuticals in the stomach for an extended period of time, can help with those problems. Such drug delivery systems are called Gastroretentive Drug Delivery Systems (GRDDS)[2].

GRDDS is a mechanism that keeps substances in the stomach for a long enough time, releases the active portion in a regulated way, and then eventually metabolizes them throughout the body. Gastro retentive drug delivery is an approach to prolong gastric

residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including high-density (sinking) systems that are retained in the bottom of the stomach, low-density (floating) systems that cause buoyancy in gastric fluid, mucoadhesive systems that cause bio adhesion to stomach mucosa, unfold able, extendible, or swellable systems which limit emptying of the dosage forms through the pyloric sphincter of stomach, super porous hydrogel systems, magnetic systems etc[4].

GRDDS can improve the regulated delivery of medications with an absorption window by constantly releasing the drug before it reaches its absorption site. Prolonging the gastric retention of drugs is sometimes desirable for achieving therapeutic benefits of drugs that are absorbed from the proximal part of the GIT (gastrointestinal tract), are less soluble in alkaline pH, or encounter at the lower part of the GIT.

GRDDS is advantageous for such medications by enhancing their:

1. Bioavailability

2. The effectiveness of treatments

3. A possible dosage decrease.

4. Constant therapeutic level maintenance for an extended period of time, resulting in less therapeutic level fluctuation

5. Reduce unused medication.

6. Makes less soluble medications more soluble at low temperatures

7. High pH environment (e.g., papaverine, domperidone, or other weakly basic drugs)[5]

Gastric retentive devices can help some medications work better. These consist of [6]:

- gastrointestinal drugs have a local effect

E.g. antacids with misoprostol, a medication for H. Pylori

- the majority of a drug's absorption occurs in the stomach

E.g. Amoxicillin

- Drugs with low solubility at alkaline pH

E.g. Furosemide, zolpidem, verapamil, etc.

- medications having a constrained window of absorption

E.g. Levodopa, methotrexate

- Drugs that are quickly absorbed from the GI tract.

E.g. tetracycline and metronidazole.

- Medications that break down in the gut.

E.g. ranitidine and metformin HCl.

- drugs that interfere with healthy colonic bacteria

E.g. Medications for Helicobacter pylori

Apart from these advantages, these systems offer various pharmacokinetic advantages, maintenance of constant therapeutic levels over a prolonged period, and thus a reduction in fluctuation in the therapeutic levels. Drugs that are easily absorbed from GIT and have short half-lives are eliminated quickly from the systemic circulation. Frequently dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained controlled release formulations is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and released the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the GIT.

DISCUSSION

Anatomy of GI Tract

The gastrointestinal (GI) tract stretches from the mouth to the anus and is made up of organs that each serve a specific purpose. It includes the esophagus, stomach, small intestine, large intestine, colon, rectum, biliary tract, gallbladder, liver, and pancreas. The GI tract serves two main functions—assimilating nutrients and eliminating waste[7].

In the mouth, food is processed, mixed with salivary amylase, and delivered to the gut lumen. The esophagus propels the bolus into the stomach; the lower esophageal sphincter prevents oral reflux of gastric contents. The squamous esophageal mucosa protects against significant diffusion or absorption. Aboral esophageal contractions coordinate with the relaxation of the upper and lower esophageal sphincters on swallowing. The stomach triturates and mixes the food bolus with pepsin and acid. Gastric acid also sterilizes the upper gut. The proximal stomach serves a storage function by relaxing to accommodate the meal. Phasic contractions in the distal stomach propel food residue against the pylorus, where it is ground and thrust proximally for further mixing before it is emptied into the duodenum. The stomach secretes intrinsic factors for vitamin B12 absorption[7].

Anatomy of the Stomach

The stomach is a sac-like enlargement of the digestive system positioned between the esophagus and the small intestine in most vertebrates. Before food is transferred into the intestine, the stomach functions as an interim structure for storage and mechanical distribution. Although a minimal amount of digestion occurs in the mouth, chemical digestion really gets underway in the stomach, primarily as the initial site of protein digestion[8]. It may, nonetheless, be a very dynamic structure that is constantly expanding and shifting in size and position. These contractions help the digestive process mechanically. The stomach is only slightly larger than a fist when empty, but it can expand to hold up to 4 Litres of food and liquid, or more than 75 times its empty volume, before contracting back to its resting size.

The stomach is mainly divided into the cardia, fundus, body, and pylorus. Food enters the stomach through the cardia (also known as the cardiac area), which connects the esophagus to the stomach. The dome-shaped fundus is situated above and to the left of the cardia, inferior to the diaphragm. The body, the largest portion of the stomach, lies beneath the fundus. The duodenum and stomach are linked by the pylorus, which resembles a funnel. The funnel's widest end, the pyloric antrum, joins the stomach's main body. The pyloric canal, which joins the duodenum to the narrower end, is known. This latter point of attachment houses the pyloric sphincter, a smooth muscle that regulates stomach emptying. The convex lateral surface of the stomach is called the greater curvature; the concave medial border is the lesser curvature. The stomach is held in place by the lesser omentum, which extends from the liver to the lesser curvature, and the greater omentum, which runs from the greater curvature to the posterior abdominal wall[9].

Depending on the amount of food in the stomach, it has the potential to expand or constrict. When the internal walls are contracted, they generate numerous folds (rugae), which disappear when the walls are distended. The walls' thick mucous membrane lining is densely packed with small gastric glands, which release a mixture of enzymes and hydrochloric acid that partially digests proteins and lipids[8]. The stomach's wall is composed of the same four layers as the majority of the alimentary canal, but the mucosa and muscularis have been modified in order to enhance the functions of this particular organ. The muscular has an inner oblique smooth muscle layer in addition to the conventional circular and longitudinal smooth muscle layers. As a result, the stomach has the ability to vigorously churn food, mechanically breaking it down into smaller particles, in addition to pushing it through the canal. The gastric glands contain a variety of cell types, despite the fact that mucus cells make up the majority of the walls of the gastric pits. Mucus-secreting cells make up most of the cells of the cardia and pylorus glands. The pyloric antrum is made up of cells that release mucus as well as several hormones, primarily gastrin, a stimulatory hormone. Most gastric secretions are produced by the stomach's fundus and body, which have significantly larger glands and are where most chemical digestion takes place. Numerous secretory cells make up these glands. These consist of enteroendocrine cells, chief cells, mucous neck cells, and parietal cells[9].

Functions of stomach

The functions of the stomach include the following:

- Convenient holding allows the pepsins, which are digesting enzymes, to act
- Chemical digestion –pepsins break proteins into polypeptides.
- Mechanical breakdown- the three smooth muscle layers enable the stomach to act as a churn, gastric juice is added and the contents are liquified to chime. Gastric motility and secretion have increased by parasympathetic nerve stimulation.
- Limits absorption- water, alcohol, and some lipid-soluble drugs.
- Non-specific defense against microbes- provided by hydrolytic acid in gastric juice. Vomiting may occur in response to the ingestion of gastric irritants, E.g., microbes or chemicals.

- Preparation of iron for absorption- the acid environment of the stomach solubilizes iron salts, essential for iron absorption in the small intestine.

- Production and secretion of intrinsic factors needed for absorption of vitamin B12 in the terminal ileum.

- Regulation of the passage of gastric contents into the duodenum. When the chyme is sufficiently acidified and liquefied, the pylorus forces small jets of gastric contents through the pyloric sphincter in the duodenum. The sphincter is normally closed, preventing, the backflow of chime into the stomach[10].

Gastrointestinal transit time and motility:

There are two different patterns of gastrointestinal motility based on the fasting and fed states of the stomach. Some cyclic contractile events, also known as Migrating Myoelectric Complex (MMC), are linked to the fasting condition.

The slightly constricted sphincter is readily passed through by liquid components. An "antral-sieving" procedure, on the other hand, keeps the bulky undigested debris. Usually, the stomach experiences a number of inter-digestive events. It has been said that the Migrating Myoelectric Complex (MMC), which controls the pattern of gastrointestinal motility, goes through alternating periods of activity and quiescence. There appear to be four periods of activity in MMC that follow one another[11].

➢ Phase I: This is a quiescent, 30- to 60-minute phase during which there are no contractions.
➢ Phase II: This phase lasts between 20 and 40 minutes and consists of sporadic contractions that gradually get stronger as the phase goes on.
➢ Phase III: Known as the "housekeeper wave," this phase is characterized by brief bursts of severe distal and proximal stomach contractions (4–5 contractions per minute), which persist for around 10–20 minutes.
➢ Phase IV: This is a brief transitional phase lasting 0 to 5 minutes during which the contractions cease between the last stages of phase III and phase I's quiescence

There are no requirements for any indigestible solids to be present in the stomach for the fasted-state emptying pattern to exist. The stomach contracts in a pattern that reduces solid

food to suspension-like particles smaller than 1 mm in diameter that pass into the pylorus. The physiochemical properties of the consumed food affect how long the contractions last[12].

A meal of roughly 450 calories will often cause the fasting state motility to be interrupted for three to four hours. According to reports, antral contractions shrink food particles to a diameter of around 1 mm and force them through the pylorus[13].

Gastric retention requirements

It is feasible for gastric retention to be successful when the dose form complies with the following conditions[14]:

1. The dosage form needs to be strong enough to survive the pressures generated by the stomach's peristaltic waves, as well as its ongoing contractions, grinding, and churning processes.

2. It must prevent early stomach emptying in order to work as a gastric retention device.

3. The gadget should be easy to remove from the stomach after its goal has been fulfilled.

Drugs that are inappropriate for GRRDS

Drugs that are unstable in acidic environments, have very little acid solubility, undergo significant first-pass metabolism, are intended for selective release in the colon, and non-steroidal anti-inflammatory drugs that harm the stomach are some examples of situations where gastric retention is not a desirable option and will not benefit from incorporation into gastric retention systems.

The types of medications that need meals and stomach fluid levels that are high enough to extend their gastric emptying period are another setback for GRDDS[15].

Advantages of gastro retentive drug delivery systems

1. More favourable bioavailability profile

GRRDS offers a way to improve the bioavailability profile. The bioavailability of riboflavin has been markedly enhanced in CR-GRDF compared to non-GRDF CR polymeric formulations following oral administration, for example. Many variables affect medication absorption through the digestive system[16].

2. Medication delivery with precision

A possible method to produce a targeted effect is gastric retention through a floating device, especially for medications with low proximal small intestine absorption.

Due to limited absorption, systemic effects of the medication are avoided by the gradual and controlled administration of the pharmaceuticals to the stomach, which permits sufficient amounts of the drug to generate local effects[17].

3. Patient Compliance Has Improved

GRDDS may extend the effects of medications, and this characteristic is especially important for treatments with short half-lives since it lowers the frequency of doses, which improves patient compliance[18].

4. Avoiding the huge bowl's activities

GRDDS allows for gastric retention, which reduces the amount of drug that reaches the colon and prevents drug action at the large bowl. This may be extremely important in some situations, such as when beta-lactam antibiotics are given to the colon and cause the emergence of microbial resistance. By using beta-lactam antibiotics in gastroretentive formulations, resistance in microorganisms is prevented from developing[18].

5. Enhances clinical results

Sometimes, rather than the peak concentration, the length of time the medication remains above the critical concentration determines the pharmacodynamics of the agent.

The purpose of GRDDS is to produce sustained mode concentration, extending the amount of time that the drug is kept above the critical concentration. This characteristic significantly affects the pharmacological effects and improves the therapeutic results[18].

Disadvantages of gastro retentive drug delivery systems

- Not appropriate for medications that could lead to stomach lesions, such as non-steroidal anti-inflammatory medicines.
- Inappropriate medicines that become unstable in a very acidic or basic environment.

- More predictable and reproducible floating qualities should be attained under all extreme gastric situations.
- For intestinal retention, the dosage form needs to transit intact through the gastric environment, which is difficult to accomplish.
- Not ideal for medications that become unstable in a highly acidic or basic environment.
- When contrasted with conventional dosage forms for medications that are absorbed through the gastrointestinal tract, these systems do not provide any appreciable advantages[19-20].

Factors affecting gastric retention

Density

- Lower-density dosage forms float and remain in the stomach for longer than higher-density dosage forms.

Size of dosage form

- Larger dosage forms cannot pass through the pyloric sphincter rapidly to reach the intestine, which results in an increased gastric residence time in the majority of cases[19].

Shape of dosage form

- Tetrahedron and ring-shaped devices are reported to have better GRT and ~ 90% to 100% retention at 24 hours compared with other shapes[21].

Single or multiple-unit formulation

- Formulations with multiple ingredients exhibit a more controlled release profile, co-admiration of various units, and a higher safety margin[21].

Fed or unfed state

- Usually, the presence of food in the stomach increases the GRT of the dosage form and increases drug absorption by allowing it to stay at the absorption site for a longer time.

Nature of meal

- By altering the stomach's motility pattern to a fed state through the feeding of indigestible polymers or fatty acid salts, the rate at which the stomach empties its contents can be slowed down, extending the time that drugs remain active in the body.

Calorie content and frequency of food intake

- A high-protein, high-fat meal can raise GRT by 4 to 10 hours. Because of the low frequency of MMC, the GRT can increase by almost 400 minutes when successive meals are given instead of a single meal.

Posture

- The floating medication will be directed toward the pyloric antrum while the patient is lying on their left side. If the patient lies on its right side, it will face the other way. GRT can vary between the supine and upright ambulatory states of the patient.

Age and gender

- Elderly persons and females have a slow gastric emptying rate. It was found that gastric emptying in women is slower than in men regardless of height, weight, and body surface area. Regardless of weight, height, or body surface, the mean ambulatory GRT in males (3.4 plus or minus 0.6 hours) is lower than that in their age and race-matched female counterparts (4.6 plus or minus 1.2 hours).

Concomitant drug administration

- Anticholinergic like atropine and propantheline opiates like codeine and prokinetic agents like metoclopramide and cisapride[19].

Approaches of gastro retentive drug delivery system:

Floating drug delivery systems:

The objective of the floating system is to lengthen gastric retention time (GRT) by floating in and above the stomach content. It is a low-density method, and because its bulk density is lower than that of gastric fluids, it floats in the stomach, gently releasing the medicine without slowing down the rate at which the stomach empties. The delivery mechanism is discharged when the medicine leaves the stomach.

It is mainly classified into two types:

1. Effervescent System
2. Non-Effervescent System

Effervescent system

These systems are of the matrix form prepared with the use of several effervescent substances and swellable polymers, including methylcellulose and chitosan.

For example, sodium bicarbonate, tartaric acid, and citric acid. These are designed in such a way that when they come into contact with gastric contents, CO2 is released and captured in swelling hydrocolloids, providing buoyancy to the dosage form.

Swellable, asymmetric triple-layer tablets served as the foundation for the delivery system's design[22].

a) Volatile liquid systems

These have an inflatable chamber that contains a liquid, such as ether or cyclopentane That vaporizes at body temperature to produce the inflation of the chamber in the stomach. These systems are osmotically controlled floating systems with a hollow deformable unit. The system has two chambers, the first of which holds the medicine and the second of which holds the volatile system.

b) Gas generating systems

This system's primary mechanism involves the reaction between sodium bicarbonate, citric acid, and tartaric acid, which results in the formation of CO2 gas. The gas created causes the system's density to decrease, causing it to become less dense and float on the stomach contents. Salts and citric/tartaric acid emit CO2, which gets trapped in the system's jellified hydrocolloid layer and lowers its specific gravity, causing it to float over the chime. The system consists of a sustained-release pill acting as the seed and being encircled by two layers. The inner layer is an effervescent layer made of tartaric acid and sodium bicarbonate. A swellable membrane layer with PVA, shellac, and other materials makes up the outer layer[23-25].

c) Matrix tablets

They are available in two different forms: single-layer and bilayer matrix tablets. A medication and a hydrocolloid-forming gel are used to create single-layer matrix tablets, while bilayer matrix tablets have two layers: an immediate-release layer and a sustained-release layer. Using various ratios of HPMC-K4M and karaya gum as retarding polymers and sodium bicarbonate as an effervescent agent by direct compression technique, Saisivam et

al.[26] created single-layer floating matrix tablets containing losartan potassium. Results of an in vivo investigation of an optimized formulation showed that the tablet floated in stomach content and that the GRT was extended to about 12 hours. An X-ray imaging investigation on albino rabbits revealed that the tablet continued to dwell in the stomach even after 12 hours had passed.

Non-effervescent system

a) Hydrodynamically balancing systems

These systems contain medications with hydrocolloids that form a gel and are designed to float on stomach contents. One or more hydrophilic polymers that form gels are present in this single-unit dosing form. To create these systems, excipients including hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans, or alginic acid are frequently used[27].

b) Microballoons

These systems have a drug-loaded outer polymer shell. Polymers including polycarbonate, cellulose acetate, calcium alginate, agar, etc. make up the exterior polymer shell. The number of polymers employed in the formulation determines the buoyancy lag time and the rate at which the medicine is released from the system. The emulsion-solvent diffusion process is used to make this formulation[28].

c) Alginate beads

Multi-unit floating dosage forms have been developed from frozen calcium alginate[29]. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into an aqueous solution of calcium chloride. Causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen and freeze-dried at 400C for 24 h, leading to the formation of a porous system, which can maintain a floating force for over 12 h. These floating beads gave a prolonged residence time of more than 5.5 h[21].

d) Layered tablets

Layered tablets are more popular due to the ease of their preparation, low cost, and high stability. These are of two types:

- **Single-layered floating tablets:**

These tablets were made by combining narcotics and gases in the matrix tablet. Due to the formulations' lower bulk density than that of gastric fluid, they maintain their buoyancy in the stomach by raising GRT[30]. Wet granulation and compaction were used by Kim et al[31]. To create non-effervescent gastroretentive pregabalin tablets that are taken once daily. The concentrations of HPMC and crospovidone were discovered to be important variables impacting the produced tablets' in vitro dissolving and floating characteristics[2].

- **Double-layered floating tablets:**

It consists of two formulations with two different release profiles that are layered one on top of the other and separated by stacking[32]. By using the direct compression approach, Kuldeep et al[33]. Created a bilayer floating tablet with metoprolol succinate (sustained-release layer) and rosuvastatin calcium (immediate-release layer). As gel-forming agents, HPMC K100, K4M, and K15M were employed. As a super disintegrant, cross-carmellose sodium, sodium starch glycolate, and crospovidone were employed. The effervescent agent used in beverages is sodium bicarbonate. The in vitro buoyancy study revealed that floating lag time decreases as gas-generating agent concentration rises. Additionally, it was shown that the floating lag time and overall floating duration were influenced by the ratio of polymer gas-producing agents[30].

Non-floating drug delivery systems

a) Bio-adhesive tablets

The development of bio-adhesive or muco-adhesive formulations was initially done to improve GRT and regulate drug distribution for all sorts of pharmaceuticals. The process involves covering microcapsules with a bio-adhesive polymer, allowing them to stick to the intestinal mucosa and stay in the GI tract for a longer period of time while the active medication is released from the device matrix. Because of their well-known propensity to

bind to gastric mucosa, cationic chitosan polymers can be employed to develop bio-adhesive formulations that are pharmaceutically acceptable[13].

The basis of adhesion is that a dosage form can stick to the mucosal surface by different mechanisms. These mechanisms are:

- The wetting theory, is based on the ability of bio adhesive polymers to spread and develop intimate contact with the mucous layers.
- The diffusion theory, which proposes physical entanglement of mucin, strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.
- The absorption theory, suggests that bio adhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.
- The electron theory, proposes attractive electrostatic forces between the glycoprotein mucin network and the bioadhesive material[34].

b) Swelling systems

Swelling systems are a type of gastroretentive system which after contact with gastric content swells to large size and pylorus sphincter prevents the passage of swelled dosage form due to large size[35]. Because of the swelling of the dosage form, these dosage forms are kept in the stomach for an extended amount of time. Because of their proclivity to become trapped in the pyloric sphincter, these gastric retentive dosage forms are sometimes referred to as plug type dosage forms[36]. The use of polymeric materials with swelling properties in the presence of gastric fluids increases the size of the dosage form and prevents pyloric sphincter access. Controlling swelling rate and polymer erosion is critical for maintaining optimum therapeutic efficacy while minimizing undesired side effects[37].

c) High-density system

These systems can endure peristaltic motions of the stomach by storing active medication molecules in the rugae of the stomach. The density of the gastric content is 1.004 gm/cm3, which is close to water. Because these dosage forms are high-density pellets, they can endure peristaltic motions of the stomach wall. If the patient remains upright, the pellets sink to the bottom of the stomach and become imprisoned in the folds of the antrum. A

gastric content density of roughly 2.5 gm/cm3 is effective enough to extend the gastric residence time. The incorporation of drug-coated heavy core with inert components such as barium sulfate, iron powder, zinc oxide, and titanium oxide is an effective development technique for the manufacture of these formulations. Following this stage, the density of the dose form increases to 1.5-2.4 gm/cm3, which is near to the density of stomach content 38-42.

d) Expandable systems

If the size of the dosage form is greater than the pyloric sphincter of the stomach, then this type of dosage form is suitable to resist the stomach's gastric transit property. With regard to gastric transit, the size of the dosage form must be small enough so that it may be easily ingested by the patient without causing any type of obstruction in the stomach either used alone or in combination[37]. These systems can expand and remain in the stomach for a longer period of time. These are typically formulated as a capsule containing a folded and compressed dose form. When exposed to stomach environment, the capsule shell disintegrates and the dosage form swells, preventing it from passing through the stomach. An appropriate polymer can be used to enable continuous and regulated medication delivery[21].

Ingredients used for the preparation of GRDDS:

GRDDS uses a number of different substances. The following polymers have been frequently used for preparation of floating drugs: HPMC K4 M, HPMC K15, HPMC K4, HPMC 4000, HPMC 100, calcium alginate, sodium alginate, Eudragit S100 Eudragit RL, Eudragit S, Eudragit RS, propylene foam, ethyl cellulose, poly methyl methacrylate, methodical K4M, polyethylene oxide, cyclodextrin, CMC, HPC, metolose, PVP, PVA, HPCH, HPC-M, acrylic polymer E4 M, polyethylene glycol, polycarbonate, and carbopol. Synthetic, anionic or nonionic hydrocolloids such hydrophilic gums, acacia, pectin, agar, alginates, gelatin, casein, bentonite, and veegum, as well as modified cellulose derivatives like MC, HPC, HEC, and NaCMC, are suitable hydrocolloids that may be employed in GRDDS[15].

Effervescent substances such sodium bicarbonate, citric acid, tartaric acid, di-sodium glycine carbonate (DiSGC), and citroglycine (CG) are additional compounds utilised in GRDDS. Lactose and mannitol are release rate promoters. Release rate inhibitors such as

talc, magnesium stearate, and dicalcium phosphate. Low-density materials such as Acurel MP 1000® polypropylene foam powder. Tween 80, span 80, and SLS are examples of surfactants that are employed as stabilizers or emulsifiers and also serve as microsphere hardeners. Formaldehyde, glutaraldehyde, or diacid chlorides like terephthaloyl chloride are employed as cross-linking agents to create microspheres, as are hardening agents to aid the microspheres generated in the processing media hardening. for instance, petroleum ether and n-hexane[43].

Recent combinational approaches for gastro retention:

Currently following combination approaches used in GRDDS[44]:

a. Swellable and floating

b. Bioadhesive and floating

c. Bio adhesion and swelling

d. Bio adhesion and High-density

e. Floating pulsatile system

CONCLUSION:

In recent years, gastrointestinal medication delivery systems have been intensively researched. Gastroretentive drug delivery systems are the best choice for delivering medications with a small absorption window near the stomach. Based on recent advances, it has been concluded that a gastroretentive drug delivery system is a promising approach for drugs with low bioavailability prior to their absorption being restricted, particularly in the upper gastrointestinal tract, thereby maximizing absorption and enhancing bioavailability[10]. Drugs with limited absorption windows, high acid solubility, and instability at alkaline pH have a lot of room for improvement in terms of therapeutic efficacy with GRDDS. The successful design of GRDDS requires an in-depth knowledge of the anatomy and physiological state of the stomach, as well as research into the effects of formulation and process variables on dosage form quality. Although a variety of GRDDS, including magnetic, low- and high-density systems, bio/mucoadhesive, and low-density systems, have been reported in the literature, their therapeutic value has not yet been fully explored.

Future GRDDS initiatives may need to concentrate on a combination strategy in order to improve product quality, considering the pharmaceutical industry.

ACKNOWLEDGEMENT

"Devoting the necessary time and effort is a crucial element on the path to achieving success". I am profoundly thankful to the Almighty and my parents for providing me with the support needed to meticulously complete this comprehensive analysis. My heartfelt appreciation goes out to the numerous individuals who contributed their time and encouragement during this extensive review.

I am grateful to all those with whom I had the privilege of collaborating during this analytical review. My special thanks go to the computer operators and other professionals who provided technical assistance and ensured the timely preparation of this manuscript.

Last but not least, I want to express my extensive appreciation to everyone who has been directly or indirectly connected to my research.

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