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History, Factors, Mechanism, Formulation, Evaluation, Application, And Advancement Of Gastro Retentive Drug Delivery System

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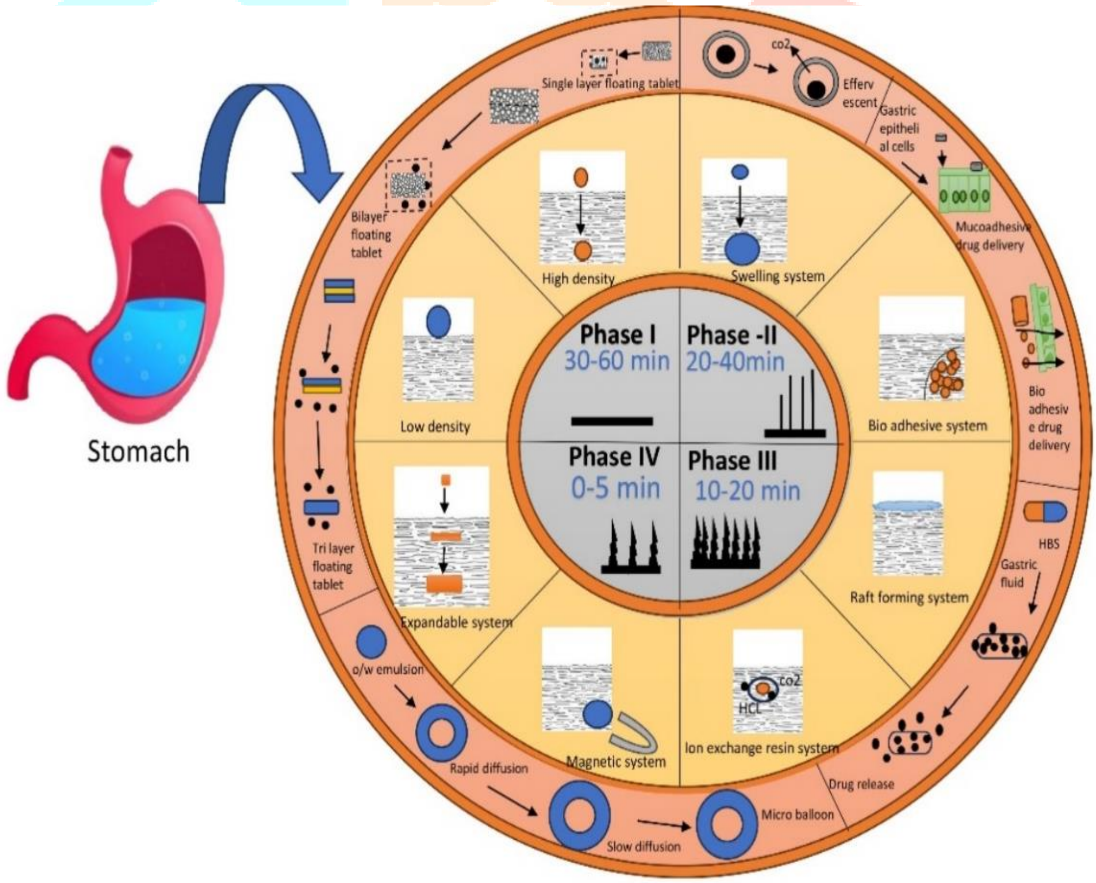
Graphical abstract:



Abstract: -

Pharmacokinetic properties are widely connected in the form of oral dose, to treat different kind of disease. This type of formulation is very quickly eliminated through the body so it became very challenging work to maintain the therapeutic effect. Some of medication work locally in gastric problem but it last very few times in the stomach. Now a days very different studies have been done to point out the formulation which can increase the drug lasting time in stomach.

More increase stomach retention time of the dosage form, different kind of approaches are done, one such approach is the development of gastro retentive controlled drug delivery. It useful for many more drugs that are orally administered. GRDDS is a type of novel drug delivery system it increases the gastric residence time of the formulation, increase the bioavailability of the drug and used different kind of gastric related disease. GRDDS approaches, the factors affecting the gastric retention, advantages, and disadvantages are briefly discussed. Method for development of the Gastro-retentive Multi particulate System, Comparison of conventional and gastro retentive drug delivery systems, assessment of gastro retentive dose forms, use of polymeric material in gastro retentive formulations.

Key Word: History, Factors effecting, classification of mechanism, formulation, evaluation, application, advancement, gastro retentive drug delivery system, GRDDS

Introduction

Oral drug delivery systems have overlooked other drug delivery systems because of their wide range of advantages such as formulation flexibility, accessible transport, storage, high patient compliance, ease of administration, and cost effectiveness. However, due to factors such as the pH of commensal flora, surface region, enzymatic activity, gastro retention period of dosage type, and poor bioavailability, the existing oral drug delivery systems have faced numerous challenges. Some other prominent factors of conventional drug delivery systems, such as improper drug release and reduced efficacy of doses, render this system less susceptible to the delivery of drug formulations[1]. Researchers have developed a novel system for delivering drugs at controlled and predetermined rates to overlook these limitations. The gastroretentive drug delivery systems (GRDDS) are formulated to achieve enhanced gastric retention time and controlled drug release. The drug bioavailability of these systems increases with their high intimacy with the mucous membrane. Decreased drug loss, local action in the stomach and duodenum, increased drug efficacy, and enhanced drug solubility are some of the benefits of these systems over the conventional systems[2]. There are many approaches like super porous hydrogel, magnetic system, low density system, mucoadhesive systems, expandable systems, and high-density systems to deliver the medicament in a controlled manner for a prolong period of time. Mentioned drugs delivery systems are supposed to enhance the gastric residence time of the dosage formulation in stomach region[2]. GRDDS now a day is an efficient drug delivery system to eradicate the *H. pylori*[3]. Gastro-retention techniques are also useful for medications exhibiting reduced gastric absorption in lower GIT, unstable drug candidates which have very little solubility in basic pH, exhibiting local effect in upper GIT, or possessing shorter half-lives[4]. In gastro retentive dosage formulations, the excipients' physicochemical properties are also crucial. The ratio of effervescence-producing chemicals and the excipient density are essential elements for developing effervescent floating DDS. Strong swelling properties of sodium carboxymethyl cellulose and crospovidone are essential for the production of porous hydrogels[5].

Back ground Gastro retentive drug delivery system: -

GRDDS serves to increase the residence time of the dosage form in the stomach for more effective drug release in upper GI tract. This plainly helps in delivering those drugs that are better absorbed at acidic pH, show instability in the intestinal region, or have a narrow window of absorption in upper GI tract[7].

With delayed gastric emptying and CR principles as a foundation, the GRDDS should be concentrated on limiting and localizing the drug delivery device in the stomach or upper portion of the small intestine until full release of the medication. The processes or approaches for getting the stomach retention vary and include: sedimentation, in high-density systems; muco adhesion, by practicing bioadhesive systems; expansion, in swelling and expanding systems; geometry, in modified shaped systems; and floatation or buoyancy, which is seen in floating systems. Other strategies include giving drug at the same time as fatty acid salts or sham feeding hydrogels that change the stomach's motility pattern to a fed state and are either indigestible like polycarbophil or enzyme-digestible[6].

Historical Background

Initial Concepts (1960s-1970s):

It was in the late 1960s and early 1970s that the concept of extending the duration of stomach residence time for oral drugs started to gain momentum. Scientists realized that in order to improve a medication's bioavailability and therapeutic effectiveness, it was necessary to keep it in the stomach for a maximum time. Large, single-unit dosage forms meant to remain in the stomach due to their low weight were one of the early methods, although these were frequently inconvenient and uncomfortable for patients [8].

Floating Systems (1970s-1980s):

One of the first notable developments was floating medication delivery systems. Because of their lower density than gastric fluids, these systems are able to float on the gastric fluid of the stomach and release the medication gradually. Among the examples are tablets that produce gas and release carbon dioxide to produce a buoyant system [9].

Expanding Systems (1980s-1990s):

Hydrogels and other polymer-based materials were extensively utilized to create expandable systems that inflate or unfold in the stomach, increasing their size to impede transit through the pylorus. Overall, the evolution of gastro retentive drug delivery system reflects a continuous effort to optimize oral drug delivery, increase the therapeutic outcomes, and improve patient experiences[10].

Physiology of Stomach- A thorough study of the architecture and physiology of the stomach is necessary for the effective creation of the gastroretentive dosage form since the stomach plays a significant role in the GRDDS. Git is always showing a state of continuous motility. The motility pattern are a. the digestive mode and b. inter digestive mode. Both while feeding and when fasting, gastric emptying takes place. An interdigestive sequence of electrical events cycles through the small intestine and stomach every two to three hours when a person is fasting. The terms migrating myoelectric complex and, inter-digestive myoelectric cycle describe this electrical activity [11].

Phase I - It is a period of quiescence that lasts for 30 to 60 minutes and occasionally contracts.
Phase II - It is made up of sporadic contractions and action potentials that get stronger and more frequent as the phase goes on. The duration is between 20 -40 minutes.
Phase III- It moves the undigested food from the stomach to the small intestine for 10 to 20 minutes during a brief, strong, consistent contraction. Because Phase III makes it possible to remove all undigested contents from the stomach and down to the small intestine, it is often referred to as the "housekeeper wave." A brief transitional phase IV takes place in between phases III and I of two successive cycles.
Phase IV- Transitional period lasting between 0 and 5 minutes.

MECHANISM OF DRUG DELIVERY WITH DIAGRAM

Dosage form with a limited window for absorption in the upper gastrointestinal tract can benefit from the longer stomach retention period offered by gastro retentive drug delivery systems. For better retention of oral dosage form in the stomach many approaches are done, including floating system and non-floating system. One of the has lees density than gastric fluid and it can float on the gastric media and release drug for long time. Others are high density system, mucoadhesive and more. GRDDS accomplishes gastric retention by a number of methods including-

1.High density system.
2.Low density system.
3.Swelling system.
4.Mucoadhesive system.
5.Super porous Hydrogel system.
6.Magnetic system.
7.Raft forming system.

FACTORS INFLUENCING DRUG DELIVERY SYSTEM: -

The effectiveness of Gastro retentive Drug Delivery Systems (GRDDS) is influenced by a variety of factors that can affect the retention time in the stomach and the overall drug release profile. These factors include physiological, formulation, and physicochemical properties. Here are the key factors:

1. Gastric Motility: Gastric emptying time varies between the fasted and fed states. In the fed state, the gastric retention time is generally longer due to delayed gastric emptying. The presence of food can significantly affect the performance of GRDDS[11].

2. Gastric Transit Time: Individual differences in gastric transit time can impact the effectiveness of GRDDS. Conditions like gastroparesis or use of prokinetic agents can alter transit time.

3.Size of the dosage form: Forms of dosage that are larger in diameter than the pyloric sphincter's diameter stays in the stomach area because they cannot be impacted by the gastric emptying process or go away with the contents of the stomach into the intestine.The GRT of dosage form units larger than 7.5 mm is said to be higher than those of units 9.9 mm in diameter. Larger dose forms often have a longer gastric retention period than smaller ones because they are emptied during the digesting phase (weaker MMC) and because the pyloric sphincter hinders their transit into the small intestine[12].

4. Posture and Activity Level: The posture of the patient (e.g., lying down vs. upright) can influence the gastric retention time. Physical activity can also impact gastric motility and, consequently, the performance of GR. Patients' GRT might change while they are ambulating upright or in a supine position.

Upright Position: Regardless of size, the floating shape stays above the stomach contents when in an upright position, protecting it from postprandial emptying. The traditional dose forms sink to the lower section of the distal stomach, where they are evacuated through the pylorus by astral peristaltic movements, whereas floating dosage forms exhibit longer and more reproducible GRTs[12].

Supine Position: There is no consistent defense against inconsistent and early emptying at this position. Large dose forms—both floating and conventional—have longer retention times in supine patients. Anywhere in the range between the stomach's lesser and larger curvatures appears to be where the gastric retention of floating forms stays buoyant[12].

5. Shape of dosage form: It is generally accepted that dose forms with a round, spherical, or ring shape are superior to those with other shapes. It has been found that devices shaped like rings and tetrahedrons, having a flexural modulus of 48 and 22.5 kilopounds/inch2, respectively, have a superior GRT (90% - 100% at 24 hours) than other shapes[13][14].

6. Concomitant drug administration: When some medications are taken with gastric motility enhancers or depressants, the gastric retention time and, consequently, the absorption of pharmaceuticals that are unique to the stomach are significantly impacted. Opioids such as codeine and atropine, which are anticholinergic, can extend GRT[15].

7.Density: The dosage form's density (1.004 g/ml) should be lower than the contents of the stomach. It needs to fall between 1 and 2.5 grams per cubic centimeter[13]. Dosage form buoyancy determines GRT, which is a density dependent function. Additionally influencing the velocity of stomach emptying is a dose form's density. With a density lower than the stomach juices, a buoyant dose form floats. The dose unit is held in the stomach for a long time since it is not in the way of the pyloric sphincter. Until hydrodynamic equilibrium is reached, drug flotation is dependent on time. At the bottom of the atrium, dosage forms with a density greater than the stomach content sink and settle, releasing the active ingredient gradually over an extended period of time[12].

8.Gender: Gastric retention time for male 3 to 4 hours and for female 4 to 6 hours. Male have lees retention time than female[15].

9. State of disease: The gastric retention time is altered by disorders involving the stomach, such as diabetes, Crohn's disease, etc[16].

10. Age: In comparison with normal adulthood, gastric retention duration is shorter in newborns and youngsters and longer in elderly people. Older adults, particularly those over 70, have noticeably longer GRTs[13][14].

11.Nature of meal: The amount of fatty acids and other indigestible polymers present decreases the duration of gastric retention because to alteration in gastric motility[16].

12. Frequency of feed: when successive meals are given the GRT can increase by over 400 minutes and it compared with a single meal due to the low frequency of MMC[13][14].

13. Caloric Content: GRT get increased 4 to 10 hours having high in proteins and fats meals [13].

14. Fed or unfed state: The gastric motility during a fast is typified by bursts of intense motor activity that happen every 1.5 to 2 hours. The unit's GRT can be extremely short if the MMC and the stomach empty the undigested material at the same time. In a fast state, on the other hand, the GRT is prolonged and the MMC is delayed[6].

15. Viscosity of the Formulation: High-viscosity formulations can slow gastric emptying and enhance retention time. The choice of excipients that increase viscosity can be beneficial. Polymer viscosity and interaction have a significant impact on drug release and the floating characteristics of GRFDDS. The study revealed that low viscosity polymers, such HPMC K100 LV, yielded better floating qualities compared to high viscosity polymers, like HPMC K4M. Increases in polymer viscosity were also shown to be accompanied by a decrease in release rate[12].

CLASSIFICATION OF FORMULATION: -

Gastro retentive Drug Delivery Systems (GRDDS) can be classified based on the various mechanisms they use to extend the retention time of drugs in the stomach. The main categories include:

1. Floating Drug Delivery Systems

A. Effervescent Systems
- i. volatile liquid containing system.
- ii. gas generating system.

B. Non-effervescent Systems
- i. hydro dynamically balanced system.
- ii. microballons.
- iii. swollen beads
- iv. matrix layered tablets
- v. raft forming system

2.Non floating drug delivery -
- i. Bio adhesive or Mucoadhesive Systems
- ii. Swelling and Expanding Systems
- iii. High-Density Systems
- iv. Magnetic Systems
- v. expandable system.

Floating Drug Delivery Systems (FDDS)- These low-density systems maintain their buoyancy in the stomach without influencing the rate at which the stomach empties itself, thanks to their bulk density being lower than that of gastric fluids. They also provide improved control over fluctuations in the drug's concentration in the plasma. It is classified as

A. Effervescent systems

B. Non effervescent system

A. Effervescent Systems

These dosage forms are made in such a way that when they come into contact with the stomach's digestive fluids, the sodium bicarbonate, citric acid, and tartaric acid interaction produces carbon dioxide gas, which is then trapped in the swollen hydrocolloids. This causes the dose form to float on the stomach juices, giving it buoyancy. These systems might also include liquids that, when heated to body temperature, gasify and evaporate, lowering the specific gravity and causing the dosage form to float [6].

This also classified as-

I. Volatile liquid containing systems -it also classified as-

a. Intragastric floating gastrointestinal drug delivery systems: The floating chamber in these devices, which can be filled with air, vacuum, or innocuous gas, and the microporous compartment that encloses the medication reservoir are what allow them to float in the stomach[13] .

b. Inflatable gastrointestinal drug delivery system: These devices are made up of an inflatable chamber that inflate in the stomach when liquid ether gasifies to body temperature. The medication reservoir within this inflated chamber is enclosed in a gelatin capsule. Following oral administration, the capsule dissolves and releases the inflating balloon and medication reservoir [13].

c. Intragastric osmotically controlled drug delivery system: It is made comprised of an inflated support inside a biodegradable capsule and a drug delivery system with osmotic pressure control. The inflated capsule releases the osmotically regulated medication administration upon dissolving in the stomach. The inflated support inside creates a deformable hollow polymeric bag with a liquid within that gasifies at body temperature to inflate the bag.

The drug reservoir and the osmotically active compartment make up the two parts of the osmotic pressure-controlled medication delivery device. The pressure-responsive collapsible bag that encloses the drug reservoir compartment is impermeable to liquid and vapor. has a delivery opening. The semipermeable membrane that encloses the osmotically active salt makes up the osmotically active compartment. When the device reaches the stomach, it dissolves the osmotically active salt and produces the osmotic pressure by absorbing water from the gastro intestinal fluids via the semipermeable barrier into the osmotically active compartment. The drug reservoir compartment is forced to initiate the discharge of the medicine in solution form through the delivery aperture by the pressure that builds up on the collapsible bag. The floating support is discharged from the stomach after the prescribed amount of time because the biodegradable plug in the support erodes and deflates[13] [6] .

ii. Gas generating systems-The creation of gas bubbles in these systems allows for floatability. When carbonates or bicarbonates are added, they react with acid—either the stomach's natural acid or an acid mixture such as citric or tartaric acid—to produce carbon dioxide in the process. The medicine is released at a predetermined rate by the gas produced, which causes the systems to float on the stomach juices. These come in several varieties[13] [17].

a. Floating capsules-An acidic environment causes the formation of carbon dioxide, which becomes trapped in the hydrating gel network, causing floating capsules. These are made by filling a mixture of sodium alginate and sodium bicarbonate [6].

b. Floating pills- These systems consist of an effervescent layer within that contains sodium bicarbonate and tartaric acid, as well as an outside swellable polymeric membrane. The inner layer is divided into two sublayers in order to keep sodium bicarbonate and tartaric acid from coming into physical contact. This tablet sinks to the bottom of the buffer solution at 37 °C, allowing the buffer solution to enter the effervescent layer and pass through the outer swelling membrane. Carbon dioxide is produced when tartaric acid and sodium bicarbonate combine, which is what produces bloated tablets or balloons. Because the generated carbon dioxide is contained within the delivery mechanism, the device floats. These systems exhibit good buoyancy independent of pH or medium viscosity, can float entirely in less than ten minutes, and release the medicine in a controlled way[17].

c. Floating systems with ion exchange resins:
These systems are made by mixing the beads with a sodium bicarbonate solution to produce bicarbonate-loaded ion exchange resin. These loaded beads were surrounded by a semi-permeable barrier to stop the sudden loss of carbon dioxide. The beads rise to the top of the contents and form a floating layer of resin beads that releases the medication at a predefined period due to the exchange of chloride and bicarbonate ions that takes place when the beads come into contact with stomach contents[13].

B. Non-effervescent Systems- Drug delivery systems that grow through the imbibition of gastric fluids to the point that it hinders the fluids' ability to leave the stomach are known as non-effervescent delivery systems. Because of their propensity to remain lodged close to the pyloric sphincter, these systems are also known as "plug-type systems." There exist various kinds of non-effervescent systems, including

i. Hydro dynamically balanced systems (HBS)- Hydrogel-forming hydrocolloid systems, or HBS for short, are systems that combine a medication and gel-forming hydrocolloid. The capsules containing the drug hydro colloid mixture dissolve in contact with the gastric fluids, causing the mixture to swell and form a gelatinous barrier. As a result of the surface's constant erosion, this barrier provides the stomach contents with buoyancy for a considerable amount of time. This allows water to permeate into the inner layers, maintaining the buoyancy of the dose form and surface hydration. The pace at which fluid enters the device and the medicine is subsequently released from the system is regulated by this gel barrier[18] .

ii. Micro balloons / hollow microspheres- Hollow microspheres, often known as micro balloons, are low density systems with sufficient buoyancy to float above the contents of the stomach and remain there for a considerable length of time. Drug-loaded polymer shells on the outside make up these systems. When the gel formers and polymers hydrate in the presence of stomach fluid, a colloidal gel barrier is created that controls the pace of fluid penetration into the device and the subsequent release of the drug. By hydrating the nearby hydrocolloid layer, the gel layer is preserved when the dosage form's outer surface dissolves. The air that the expanded polymer traps reduce density and gives the microspheres buoyancy. These are regarded as one of the most promising buoyant systems due to their center hollow area inside the microspheres, which gives them the special advantage of having numerous unit systems and improved floating qualities[13][17] .

iii. Alginate beads: These are the approximately 2.5 mm diameter freeze-dried calcium alginate beads. They were made by dissolving sodium alginate solution into an aqueous calcium chloride solution, which precipitated calcium alginate and created a porous system that allowed the system to float on the stomach contents. These have a floating force that lasts for more than 12 hours because of their porous nature. Comparing these floating beads to solid beads, which had a one-hour residence duration, It exhibits a longer residency duration of over 5.5 hours[6]

iv. Matrix layered tablets- These dose forms have hydrocolloids that create gels, allowing the delivery mechanism to float on the contents of the stomach. These could consist of one, two, or three layers.
a. To create single layered matrix tablets, the medicine is intimately mixed with gel-forming hydrocolloids, which expand when in contact with stomach secretions and retain a bulk density lower than that of the secretions[15] .

b. One rapid release layer and one sustained release layer are present in bi-layered tablets The sustained release layer absorbs gastric fluids and creates a bulk density lower than that of GI fluids, allowing the medicine to remain in the stomach for a longer amount of time. The immediate release layer releases the first dose of the drug[6] .

c. Tri-layered tablets have three layers: one for continuous release, one for quick release, and one for gas generation, which aids in system flotation[15].

v. Raft forming systems- These systems include an agent that forms gels as well as alkaline bicarbonates, or carbonates that produce carbon dioxide and help the system become less thick and float on the stomach fluid. When stomach fluids come into touch with the material, raft formation is initiated by the development of a cohesive, viscous gel. Every area of the liquid swells to create a continuous layer called a raft. These systems have received a lot of interest for the administration of antacids and drugs for gastrointestinal infections and illnesses because the raft floats on stomach contents and functions as a barrier between the stomach and the esophagus to prevent reflux[6].

2. Non-Floating drug delivery systems- These are the medication delivery methods that stay in the stomach for an extended amount of time rather than floating. Various methods have been employed to hold the device in the stomach, such as

i. Bio adhesive systems: Adhesion of the delivery system to a biological surface, such as mucus or the mucosal surface, is referred to as bio adhesion. Bio adhesive systems stick to the stomach's mucosa, stay in close proximity to the membrane for an extended amount of time, and stay in the stomach throughout the duration of their release. These systems are made with bio adhesive polymers[6] .

ii. Swelling system- Expanding the dose form's size above the pylorus's diameter can improve its gastro-retentiveness. This means that the delivery systems are made of polymers that swell when they come into contact with the stomach. As a result, the device is retained in the stomach and is unable to move past the pyloric sphincter[6].

iii. High density systems: - the density of gastric content is comparable to that water. when the patient takes high density pellets, they sink to the stomach bottom where they become caught in the antrum folds and are unable to pass through the stomach walls peristaltic waves[19]. The stomach antrum contain these system ,which have density of roughly 3g\cm3 and can survive the peristaltic motions of the stomach the technical difficulty of producing formulations with high drug content and achieving a density of roughly 2.8g/cm3 is the sole significant disadvantages of such system[15].
These systems sink to the bottom of the stomach and stay there for an extended amount of time because their density is higher than that of the gastric juices. Usually, the medication is coated on heavy inert materials such as iron powder, zinc oxide, or titanium dioxide to create these[6] .

iv. Expandable / unfolded systems- The gastro retentivity of the dose form is obtained in these systems by expanding the delivery system's size beyond the pylorus's diameter. This led to the development of expanded or unfolded drug delivery devices. These dose forms are typically easily absorbed due to their small size. After coming into touch with the gastric fluids in the stomach, they enlarge to a bigger size in order to facilitate gastric retention. Under these systems, compressed systems are encapsulated in capsules and delivered; upon coming into touch with stomach fluid, the systems expand into forms that are longer-lasting in the stomach[6] .

v. Magnetic systems: The dose form of these is made with a tiny inside magnet thanks to clever design. Following the dosage administration, a tiny magnet is applied to the abdomen, covering the stomach's location. The dose form with an internal magnet is held in the stomach area using this technique till the external magnet is still there. Each dose form has a tiny internal magnet, and to keep the dosage form in the stomach area, a magnet is positioned in the abdomen above the stomach This technique uses a small magnet in the dose form, and another magnet is applied to the abdomen, above the location of the stomach. It's important to precisely adjust the external magnet, which could make patients less compliant [15].

PREPARATION METHOD WITH FORMULA TABLE -

The preparation methods of Gastro retentive Drug Delivery Systems (GRDDS) vary depending on the type of system being developed. Below are the preparation methods for different types of GRDDS along with example formulations for each.

1. Floating Drug Delivery Systems (FDDS)
Materials: Hydroxypropyl methyl cellulose K4M, Clarithromycin, Potassium chloride, Hydrochloric acid, Sodium bicarbonate, Citric acid, Magnesium stearate, Talc[20] .

Preparation Method:
- Wet granulation technology was used to create floating matrix tablets containing clarithromycin.
- Different grades of polymers were combined with sodium bicarbonate at variable amounts.
- Using a glass crusher and pestle, polymers and clarithromycin were combined uniformly. As a granulating agent, isopropyl alcohol was utilized.
- The wet coherent mass was passed through a # 16 filter to create the granules. At 60ºC the granules are dried in a hot air oven.

- Before compression, 4-5 minutes' prior, dried granules were sifted through #20/44 sieves, combined with sodium bicarbonate and lubricated with talc and magnesium stearate.

Example formula: -

Ingredient	Function	Quantity (mg/tablet)
Clarithromycin	Active ingredients	250
HPMC K4M	Swellable Polymer	50
Sodium bicarbonate	Gas forming agent	100
Citric acid	Gas forming agent	25
Magnesium stearate	Lubricant	2
Talc	Glidant	4

B. Bio adhesive or Mucoadhesive Systems

Materials: Ofloxacin, psyllium husk, HPMC K100M, VP K30, Cross povidone, Talc, Magnesium stearate[21]

Preparation Method:

- wet granulation was used.
- A list of the different excipients utilized, All the excipients were passed through sieve no. 40, mixed and granulated with PVP K30.
- The granules that had dried mixed with talc and magnesium stearate.

Example Formula: -

Ingredient	Function	Quantity(mg/tablet)
Ofloxacin	Therapeutic Agent	400
Psyllium husk	Therapeutic Agent	100
Sodium bicarbonate	Gas generating Agent	20
Betacyclodextrin	Therapeutic Agent	100
Cross Povidone	Polymer	200
HPMC K 100	Swellable polymer	40
Magnesium Stearate	Lubricant	5
Talc	Glidant	5

D. Swelling and Expanding Systems

Materials- Levofloxacin hemihydrate antibiotic, gellan gum, Sodium alginate, Pectin, Xanthan gum, Calcium chloride dihydrate, Aluminum chloride hexahydrate, Magnesium stearate[22] .

Preparation Method:

- Each component was weighed precisely
- Using a 45-mesh sieve, every component was sieved.
- 6.25 mg of 1% w/w magnesium stearate was added and blended as a glidant.
- The powder combination was manually fed into a die of a single punch machine with a 12-mm punch diameter.

Example Formula: -

Ingredient	Function	Quantity(mg/tablet)
Levofloxacin hemihydrate	Therapeutic agent	250
Gellan gum	Swellable Polymer	375
Sodium alginate	Swellable polymer	375
Calcium chloride dihydrate		125
Aluminum chloride hexahydrate		125
Pectin	Swellable polymer	375
Xanthan gum	Swellable polymer	375

E.High-Density Systems

Materials- alcohol, 0.1 N HCl, Solution, Lactose, Sodium Alginate, Sodium bicarbonate, Magnesium Stearate, Talc, Theophylline and Polyvinylpyrrolidone[23].

Preparation Method:

- Using heat and a wet granulation process tablets are made.
- Theophylline is placed in a mortar, followed by the addition of polymer, lactose, sodium bicarbonate, and mixing until everything is well combined.
- mixture's sieving through a sieve with a mesh number of 60, aquadest was gradually added until a wet mass was created.
- The wet mixture was then dried in an oven at 500C for 12 hours after being sieved through a sieve with mesh number 10.
- After drying, the granules were sieved through a 16-mesh sieve. The sifted granules were then combined with the lubricant and crushed using a tablet press.

Example Formula: -

Ingredient	Function	Quantity(mg/tablet)
Theophylline (mg)	High density materials	109,37
Sodium Alginate (mg)	Swellable polymer	46,87
Polyvinylpyrrolidone (mg)	High density materials	1250
Sodium Bicarbonate (%)	Gas generating agent	1
Talc	Lubricant	2
Lactose	Filler	7126
Magnesium stearate	Glidant	1

EVALUATION OF GASTRORETENTIVE DOSAGE FORM-

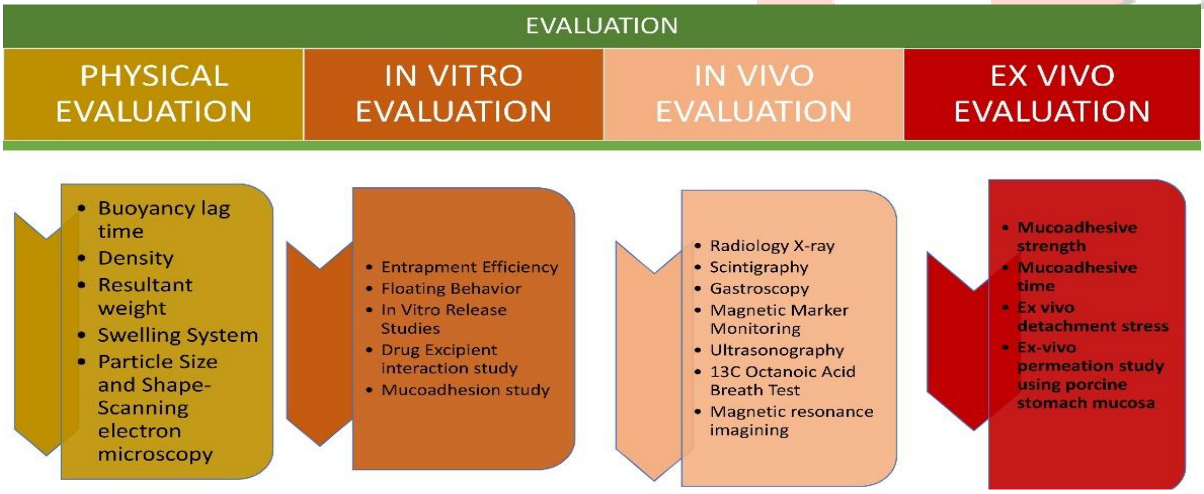


Figure 1 : Classification of evaluation of gastroretentive dosageform

PHYSICAL EVALUATION -

1.Buoyancy Lag Time- It is computed to determine the amount of time required for the dosage form to float at the top of the medium following insertion. The dissolving test may include measurements of these factors of the medium of dissolution. It's expressed in either minutes or seconds[6].

2.Density: - Density can be calculated by applying the displacement method with benzene as the displacement medium. Density can be measured by mass to volume ratio. The density is calculated putting the weight, radius and side length of the tablet[6].

3. Resultant Weight- Floating time and bulk density are the two main components that determine buoyancy. But because density varies over time as a function of variations in the resultant weight, a single density measurement is insufficient to accurately capture buoyancy. For instance, a matrix tablet comprising bicarbonate and a matrixing polymer first float because of gas production and entrapment.

However, after a while, a particular drug is released, and concurrently, part of the outer layer of the matrixing polymer may erode away, resulting in a change in the dosage form's final weight[15] [6] .

4. Swelling systems-
Swelling Index: After submerging the dosage form in a swelling solution at 37°C, it is removed from the SGF on a regular basis. Dimensional changes are quantified as a rise in tablet diameter or thickness over time[6] .

Water Uptake: It is an indirect method of measuring the swellable matrix's swelling property. The dose form is removed in this instance at regular intervals, and weight fluctuations are tracked over time [15].

5. Particle Size and Shape-Scanning electron microscopy (SEM) improves resolution over light microscopy (LM). SEM and light microscopy (LM) are the most widely used techniques for observing microparticles.
The form and external structure of a multi particulate can be ascertained by both. LM provides control over coating parameters in the context of double-walled microspheres.
The Multi particulate forms are visible and measurable under a microscope both before and after coating.
After particles are cross-sectioned, SEM can examine double-walled systems in addition to multi particular surfaces.
Multiple walled microsphere structure is characterized via conflocal fluorescence microscopy. In addition to instrumental methods, the size, shape, and morphology of the Multiarticulate can be characterized using laser light scattering and multisize Coulter counter [6].

IN VITRO EVALUATION-

1.Entrapment Efficiency -Calculating the multi particulates capture efficacy or entrapment percentage requires letting the washed multi particulate lyse. Then, the active components of the lysate are identified in compliance with the monograph's specifications[6] .

2.Floating Behavior- A magnetic stirrer is used to mix the floating microparticulate in the proper amount into 100 milliliters of the simulated gastric fluid (SGF, pH 2.0).
After pipetting, filtration is utilized to get rid of the buoyant microparticulate layer. Filtration is used to separate the particles in the sinking particulate layer. In a desiccator, the two kinds of particles are dried until their weight doesn't change. The weight ratio of the floating particles to the sum of the floating and sinking particles is used to compute buoyancy after both microsphere fractions have been weighed[18].

3. In Vitro Release Studies-The floating microparticulate release rate is measured in a dissolution instrument. Filling the basket of the dissolving rate equipment with a weighted quantity of floating microspheres equal to the dosage of medication. A sink condition is created by rotating the dissolving fluid at a pace that keeps it at 37 ± 0.5°C during the drug release investigation[6].

4. Drug Excipient interaction study- FT-IR spectroscopy, differential scanning calorimetry, and high-performance liquid chromatography may all be used to look into it. There is a drug-excipient interaction when a new peak appears and/or the previous drug or excipient peaks vanish[6] .

5.Mucoadhesion study-The mucoadhesive property of gastroretentive formulation are cheeked by measuring the strength, with which the formulation is attached to the mucus lining of the biological tissue. And measure the amount of force to detach the formulation from the mucus lining and measure the mucoadhesion strength[18] .

IN VIVO EVALUATION TEST –

1.Radiology X-ray- For the evaluation of internal body systems, radiology X-rays are frequently employed. X-ray These days, a highly common assessment criterion for floating dose forms is scintigraphy. By locating the dose form in the gastrointestinal tract (GIT), one may more accurately estimate and establish a correlation between the dosage form's transit through the GIT and the gastric emptying time. Radio Opaque Marker made of barium sulphate is commonly used. The interior bodily systems are examined using X-rays. Therefore, X-ray pictures are collected at different intervals to observe stomach retention and $BaSO_4$ is inserted inside the dose form[18] .

2. Scintigraphy- Similar to X-rays, scintigraphy emitting materials are added to dosage forms and then used to take pictures. 99Tc is a common emission material. A tiny quantity of stable isotope is mixed into the dosage forms for γ-scintigraphy during preparation. A γ-emitting radionuclide can be added to a formulation to enable indirect external observation with a scinti scanner or γ-camera[6] .

3. Gastroscopy- Gastroscopy is the per-oral endoscopy with fiber optics or video technology. The consequences of stomach expansion can be visually examined with the use of gastroscopy. Because there is no need for an incision, this surgery is regarded as minimally invasive. With this method, the stomach's GRDF is visually inspected. In essence, it's a kind of peroral endoscopy that uses a video camera together with optic fibers. The examined system might be taken out of the stomach for more thorough information. On the other hand, the endoscopist's level of experience has a significant impact on both the study's quality and interpretation. An insufficient study may also result from persistent uncontrolled bleeding, blood that remains in the stomach, and food or antacid retention.

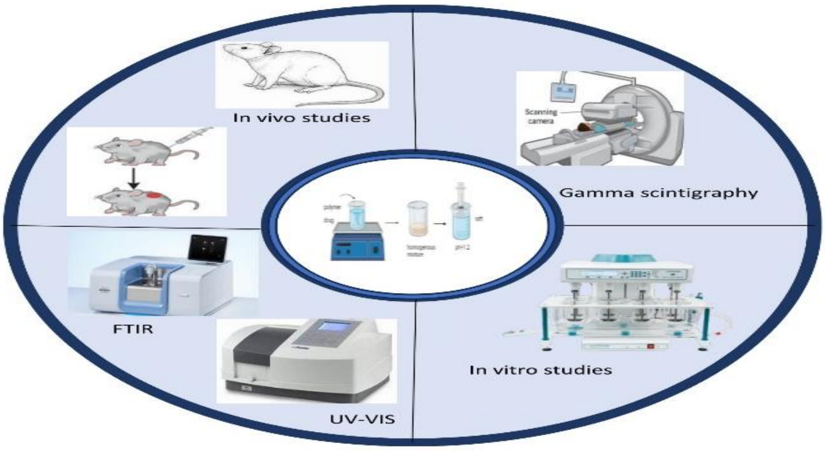


Figure 2: Invivo evaluation of gastroretentive dosageform

4. Magnetic Marker Monitoring- Magnetometric Marker Observation This technique makes use of a magnetically tagged dosage form loaded with iron powder to enable extremely sensitive biomagnetic measurement equipment to acquire photos. This method's benefit is that it uses less radiation, for that it can be used more safely and making life safer.

5. Ultrasonography-Images of the architecture of the body are created using ultrasonic waves. Wherever there is a change in density, the waves are reflected back after passing through tissues. The reflected echoes are received by an electronic equipment that assesses their intensity level and the position of the tissue reflecting them. The output might be shown as a moving image of the inside of the body or as static photos. The majority of dosage formulations don't possess distinct auditory inconsistencies throughout their contact with the body. Thus, ultrasonography is not utilized frequently for the FDDS assessment. Sometimes used, but not frequently because ultrasonography cannot be traced to the gut. Ultrasonography is not frequently employed in GRDDS evaluations. An in vivo plasma profile can also be acquired by conducting the investigation on an appropriate animal model[24].

6. 13C Octanoic Acid Breath Test- 13°C GRDDs include octanoic acid. Octanoic acid in the stomach releases CO_2 gas through a chemical process that causes the gas to escape through breath. The substantial Carbon atom that will be present in CO_2 is replaced by the 13C isotope.
Consequently, the stomach retention period of the dose form can be defined as the amount of time that 13 CO_2 gas is retained in the breath. As the dosage form moves toward the colon, no reaction occurs and no CO_2 is emitted. As such, this method is less costly than other[15].

7.Magnetic resonance imagining- MRI is a non-invasive method of diagnosis. An intense magnetic field, radio frequency pulses, and a computer are used in magnetic resonance imaging (MRI) to provide detailed images of bone, soft tissues, organs, and almost all other interior body components. After that, the pictures may be seen on a computer screen, sent via email, printed, or duplicated on a CD. Ionizing radiation is not used in MRIs (x-rays). Over the past several years, it has been clear that MRI is a useful tool in gastrointestinal research for studying pharmacological models and the intra-gastric distribution of macronutrients as well as motility and stomach emptying. great soft tissue contrast, great temporal and spatial resolution, and the absence of ionizing radiation are some of the benefits of magnetic resonance imaging (MRI). Additionally, innocuous paramagnetic and supra-magnetic MR imaging contrast chemicals can be used to selectively increase or decrease the signal of fluids and tissues of interest, enabling improved organ delineation and analysis.

EX VIVO EVALUATION-

Mucoadhesive strength- Tablet ex-vivo mucoadhesive strength was determined using a texture profile analyzer. The experiment was carried out within three hours of the local butcher providing fresh goat stomach mucosa membrane, which was preserved in phosphate buffer at pH 7.4. After the underlying connective tissue was cut away, the mucosal membrane was removed and put on the Texture Analyzer's base. With the use of double-sided tape, a tablet was fastened to the stainless-steel probe on the texture analyzer's moveable arm. One hundred and fifty microliters of gastric simulated fluid were applied to the mucosal contact region. Up to a collision, the moveable arm was lowered at a pace of 0.5 mm/s.

Mucoadhesive time-The pill was moistened with 1 drop of 0.1 M HCl (pH 1.2) and pasted to the fresh goat stomach mucosa by using a mild touch with a fingertip for 30 seconds. The fresh goat stomach mucosa was secured to the glass slide using double-sided tape. The glass slide was positioned beneath the vessel paddle type USP Type-II apparatus. 900 milliliters of 0.1 N HCl were used for the test, which was conducted at 37 ± 100C. The pill adhesion was observed for 24 hours after 2 minutes, during which a 50-rpm swirling rate was used to mimic the conditions of the stomach. The mucoadhesion time was defined as the amount of time it took for the pill to separate from the goat's stomach mucosa.

Ex vivo detachment stress- The ex vivo detachment stress was assessed using the modified balance method on freshly cut goat stomach mucosa. Using a beaker on the right pan and a five-gram weight on the left, the two sides of the balance were maintained in equilibrium. An area of 3 by 3 cm, with the mucosal side facing upwards, was adhered to an inverted beaker coated in an inert aluminum surface using cyanoacrylate adhesive. In order to maintain the mucosa's moisture content, the beaker was next lowered into a glass container that had phosphate buffer (pH 4.5) and set beneath the balance's left-hand pan. After being hydrated for 30 minutes at pH 4.5 in phosphate buffer, FCS (fanicular cylindrical system) was slightly swelled. It became lodged on the left-hand pan's lower surface of the balance. When the beaker was taken out of the right pan, the FCS and the left pan both lowered. For a duration of two minutes, the balance remained in this position. After replacing the beaker over the right-hand pan, water was gradually poured to the beaker over the right-hand pan at a rate of 2 milliliters per minute until the mucosal membrane separated from the gel surface. Based on the lowest weight required to separate the mucosal tissue from each formulation's surface, the detachment stress—expressed as mucoadhesive force in dynes/cm2—was calculated. For every measurement, the stomach mucosa was replaced[25] .

Ex-vivo permeation study using porcine stomach mucosa-To enable the penetration of pure FAM and optimized FAMRFT, the swine stomach mucosa was employed as a transport barrier. PBS (phosphate buffer saline) pH 7.4 at room temperature was used to transport a pig stomach from a local butcher to the lab. A surgical knife was used to cut through the mucosal membrane to expose the stomach's muscle and connective structures, including the submucosal layer. Following a one-minute immersion in PBS pH 7.4 at 60–65 °C, the mucosal layer was cut free from the submucosa using a surgical knife. After being checked for integrity visually and measured to have a thickness of 0.5–0.8 mm, the mucosa was cleansed with deionized water, cut into circular pieces (2.0 cm in diameter), and frozen at 20 °C. On the day of the experiment, frozen tissues were used after 15 minutes of room temperature immersion in PBS pH 7.4. For permeation investigations, Franz-diffusion cells with a 30-32 mL vertical capacity and a 2.8 cm2 permeation area were employed. The stomach membrane was oriented with its mucosal side facing the donor compartment. The PBS (pH 7.4), which was thermostated at 37 ◦C and magnetically stirred, was utilized as the receiving phase in order to prevent boundary layer effects. PBS was first heated at 37 °C and then put inside the donor compartment to make sure there was no membrane leakage. A volume of 2 mL of pH 1.2 simulated gastric fluid (SGF) was introduced into the compartment. The moistened 10 mg (5 mm) minitablet was added to the optimal Following that, 1 mL of PBS was taken from the receptor phase on a regular basis and replaced with brand-new PBS. To recover the concentration, the donor was dissolved in a pH 11 borate buffer following the experiment. 20 milliliters of methanol were used to extract stomach mucosa slices, and HPLC was used to measure the drug concentration. Plots showing the quantity of FAM carried into the receptor compartment were created as a function of time. The linear portion of the curves used to determine the average flux's slopePU-1580 Intelligent HPLC pump and UV-1575 Intelligent UV/VISIBLE detector were installed in the Jasco HPLC system, which was used to perform HPLC analysis. Using the Jasco Borwin LC-Net II/ADC system, version 1.5, the data were merged. A mixture of water, methanol, and acetonitrile in a 70:20:10% v/v/v ratio was injected at a flow rate of 1.0 mL/min as the mobile phase. A membrane filter with a 0.45 µ opening was used to filter the mobile phase. Chromatopak Peerless Basic C-18 column paired with guard column was utilized for the chromatographic separation, which was carried out at room temperature [26].

Application of GRDDS: -

Reduced Fluctuations-Blood drug concentrations are produced by the medication being continuously added after CRGRDF delivery. among a more limited selection as opposed to the instantaneous release limitless quantity types. As a result, pharmacological impact variations are reduced, and concentration-dependent side effects that are connected to peak concentrations are avoided. This characteristic is especially crucial for medications with a low therapeutic index.

Decreased adverse activity at the colon-The amount of medication that enters the colon is reduced when it is retained in the HBS systems of the belly. Consequently, the drug's unwanted effects on the colon are likewise avoided. The basis for GRDF formulation for beta lactam antibiotics, which are only absorbed from the small amount of viscosity and whose presence in the colon leads to the emergence of microbial resistance, is provided by this side of pharmacodynamics.

Absorption enhancement- Pharmaceuticals with low bioavailability due to site-specific absorption from the upper portion of the stick are good candidates to be designed as floating drug delivery devices, which would maximize their absorption. Riboflavin used for Essential nutrients, mouth ulcer and sore throat, Cilostazol Inhibits platelet aggregation, Pregabalin Fibromyalgia, diabetic peripheral neuropathy, post-herpetic neuralgia, and adjunctive therapy for partial onset seizures [27].

Site specific drug delivery systems- For medications that are selectively absorbed from the belly or the proximal portion of the small intestine, these devices are quite beneficial. The medication is delivered to the abdomen gradually and under supervision, limiting overall exposure to the drug while delivering sufficient native therapeutic levels. This lessens the negative impact that the medication has on the blood circulation. Furthermore, a web-directed delivery system's extended internal organ convenience may reduce the frequency of dosage as well. For instance, B2 and Lasix [10].

Sustained drug delivery- Sustained and delayed input from CR-GRDF may cause a flip-flop in the pharmacokinetics of medicines with relatively short biological half-lives, allowing for lower dose frequency. Therapy is enhanced by this characteristic, which is linked to increased patient compliance[27].

Enhanced Bioavailability- Compared to the administration of non-GRDF CR polymeric formulations, the bioavailability of riboflavin CR-GRDF is markedly increased. Numerous mechanisms that are connected to the medication's transit and absorption in the gastrointestinal system work in tandem to affect the amount of drug absorption [27].

Potential drug candidate for GRDDS –

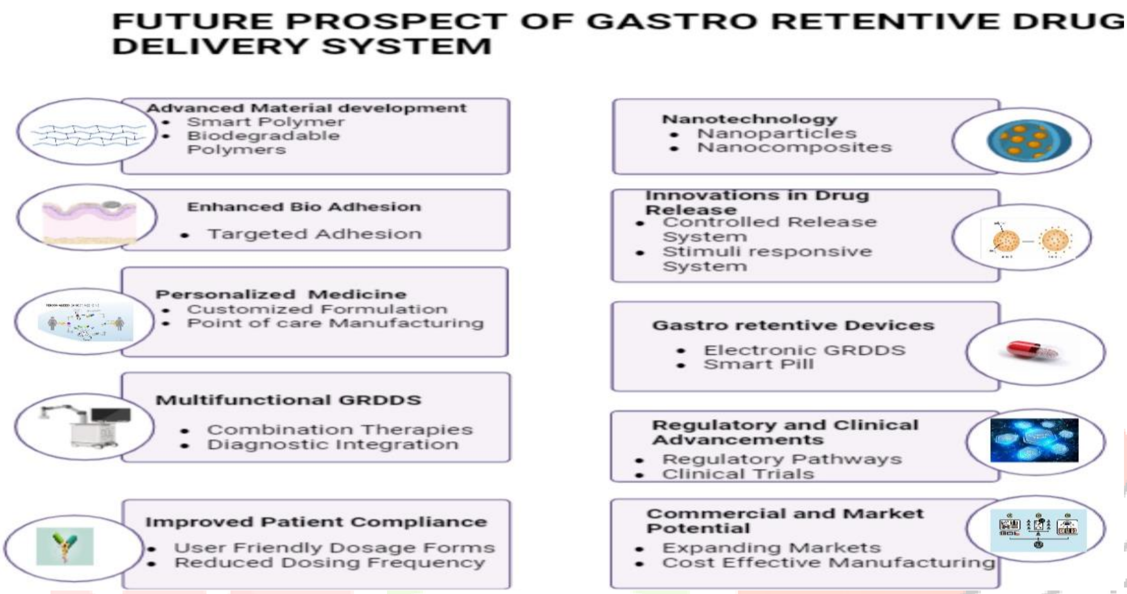
1. Drugs that have narrow absorption window in GIT are L-DOPA, p-aminobenzoic acid, furosemide, riboflavin.
2. Drugs those are locally active in the stomach are misoprostol, antacids.
3. Drugs those are unstable in the intestinal or colonic environment captopril, ranitidine HCl, metronidazole [36]
4. Drugs that disturb normal colonic microbes are antibiotics used for the eradication of Helicobacter pylori, such as tetracycline, clarithromycin, amoxicillin.

5. Drugs that exhibit low solubility at high pH values are diazepam, chlordiazepoxide, verapamil.

6. For gastro irritant drugs are Diclofenac sodium, Ibuprofen, Acetylsalicylic acid, etc[27].
7. For acid labile drugs that are stable at gastric pH are Macrolide antibiotics.
8. Drugs which are local activity and used for Peptic ulcer and reflux esophagitis, eradication of H. pylori are Ranitidine, Amoxicillin, Levofloxacin, Metronidazole.
9. Drugs that have poor absorption window in GIT are Atenolol, Lafutidine. used in hypertension, gastric and duodenal ulcer [28].

Future Prospect of GRDDS: -

The future prospects of Gastro retentive Drug Delivery Systems (GRDDS) are promising, driven by advancements in pharmaceutical technology, materials science, and a deeper understanding of gastrointestinal physiology. Here are some key areas where GRDDS are expected to evolve and make significant impacts:



1. Advanced Material Development

Smart Polymers: Development of pH-sensitive, temperature-sensitive, and bio-responsive polymers that can further improve the precision and efficacy of drug delivery[29].

Biodegradable Polymers: Use of biodegradable and biocompatible materials to enhance safety and reduce the environmental impact of GRDDS[29].

2. Nanotechnology

Nanoparticles: Utilization of nanoparticles for improved drug solubility, stability, and targeted delivery.

Nanocomposites: Integration of nanocomposites that can enhance the mechanical strength and functional properties of GRDDS.

3. Personalized Medicine

Customized Formulations: Tailoring GRDDS formulations to individual patient needs based on genetic, metabolic, and microbiome profiles to maximize therapeutic outcomes[30] .

Point-of-Care Manufacturing: Development of portable manufacturing devices that can produce personalized GRDDS on-site in healthcare settings[30].

4. Multifunctional GRDDS

Combination Therapies: Incorporating multiple drugs within a single GRDDS to provide synergistic effects, reduce side effects, and improve patient compliance.

Diagnostic Integration: Embedding diagnostic sensors within GRDDS to monitor gastric environment and drug release in real-time[31].

5. Enhanced Bio adhesion and Muco adhesion

Targeted Adhesion: Developing GRDDS that can selectively adhere to specific regions of the stomach for localized drug delivery.

6. Innovations in Drug Release Mechanisms

Controlled Release Systems: Refining controlled release mechanisms to provide more precise drug release profiles over extended periods[32] .

Stimuli-Responsive Systems: Creating GRDDS that respond to external stimuli such as magnetic fields, ultrasound, or light to trigger drug release.

7. Gastro retentive Devices

Electronic GRDDS: Development of electronic devices that can be ingested and controlled externally to modulate drug release.

Smart Pills: Use of smart pills with sensors and microprocessors to monitor and adjust drug delivery based on real-time data[33].

8. Improved Patient Compliance

User-Friendly Dosage Forms: Designing GRDDS in forms that are more acceptable to patients, such as chewable tablets, orally disintegrating tablets, and flavored formulations.

Reduced Dosing Frequency: Formulating GRDDS that provide therapeutic effects with less frequent dosing to improve adherence to treatment regimens[34].

9. Regulatory and Clinical Advancements

Regulatory Pathways: Streamlining regulatory pathways to accelerate the approval of innovative GRDDS[35] .

Clinical Trials: Conducting robust clinical trials to establish the safety, efficacy, and benefits of GRDDS in various therapeutic areas[35].

10. Commercial and Market Potential

Expanding Markets: Increasing the market penetration of GRDDS in emerging economies and addressing unmet medical needs in chronic diseases.

Cost-Effective Manufacturing: Developing cost-effective manufacturing processes to make GRDDS more accessible and affordable.

CONCLUSION –

Most medications are mostly absorbed in the stomach; but, because of variations in the rate of gastric emptying, certain medications pass through the stomach unabsorbed, leading to a variety of absorption patterns.

Several delivery systems that keep the delivery system in the stomach for a predefined amount of time have been developed as a result of advancements in pharmaceutical technology, which improves medication absorption. Pharmacies with limited absorption windows and low solubility can be optimally delivered by using gastro-retentive drug delivery systems, which have proven to be an effective strategy in increasing bioavailability of pharmaceuticals. It seems that the most successful method for regulating controlled oral medication distribution is to use delayed stomach emptying rates and buoyancy concepts.

Oral drugs are mostly absorbed in the stomach and intestines. It is thus essential to use a drug delivery system called a gastro-retentive drug delivery system, which can extend the time that the drug is in touch with the stomach. The GRDDS is a long-term drug delivery system that has the capacity to hold medications in the stomach for protracted amounts of time.

Gastro retentive drug delivery system has the ability to increase bioavailability, make medications more soluble in alkaline solutions, control therapeutic levels to avoid fluctuations, and extend the half-life to lessen the need for repeated dosages. Oral drugs are mostly absorbed in the stomach and intestines. It is thus essential to use a drug delivery system called a gastro-retentive drug delivery system which can extend the time that the drug is in touch with the stomach.

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Reference:

[1] S. Dhiman *et al.*, "An Insight on Novel Approaches & Perspectives for Gastro-Retentive Drug Delivery Systems," *Curr. Drug Deliv.*, vol. 20, no. 6, pp. 708–729, 2022, doi: 10.2174/1567201819666220819200236.

[2] K. M. Hwang, C. H. Cho, N. T. Tung, J. Y. Kim, Y. S. Rhee, and E. S. Park, "Release kinetics of highly porous floating tablets containing cilostazol," *Eur. J. Pharm. Biopharm.*, vol. 115, pp. 39–51, 2017, doi: 10.1016/j.ejpb.2017.01.027.

[3] S. K. Dey *et al.*, "Floating mucoadhesive alginate beads of amoxicillin trihydrate: A facile approach for H. pylori eradication," *Int. J. Biol. Macromol.*, vol. 89, pp. 622–631, 2016, doi: 10.1016/j.ijbiomac.2016.05.027.

[4] S. A. El-Zahaby, A. A. Kassem, and A. H. El-Kamel, "Design and evaluation of gastroretentive levofloxacin floating mini-tablets-in-capsule system for eradication of Helicobacter pylori," *Saudi Pharm. J.*, vol. 22, no. 6, pp. 570–579, 2014, doi: 10.1016/j.jsps.2014.02.009.

[5] S. Cvijic, S. Ibric, J. Parojcic, and J. Djuris, "An in vitro - in silico approach for the formulation and characterization of ranitidine gastroretentive delivery systems," *J. Drug Deliv. Sci. Technol.*, vol. 45, no. February, pp. 1–10, 2018, doi: 10.1016/j.jddst.2018.02.013.

[6] B. V. Reddy, K. Navaneetha, and P. S. A. Deepthi, "Journal of Global Trends in Pharmaceutical Sciences Volume . 4 , Issue 1 , pp -1018-1033 , January – March 2013 GASTRORETENTIVE DRUG DELIVERY SYSTEM- A REVIEW," vol. 4, no. 1, pp. 1018–1033, 2013.

[7] H. P. Chhetri and P. Thapa, "An Overview on Gastroretentive Drug Delivery System," *Kathmandu Univ. J. Sci. Eng. Technol.*, vol. 10, no. 1, pp. 90–103, 2014, doi: 10.3126/kuset.v10i1.63690.

[8] A. Hooda, A. Nanda, M. Jain, V. Kumar, and P. Rathee, "Optimization and evaluation of gastroretentive ranitidine HCl microspheres by using design expert software," *Int. J. Biol. Macromol.*, vol. 51, no. 5, pp. 691–700, 2012, doi: 10.1016/j.ijbiomac.2012.07.030.

[9] O. A. Odeku, A. A. Aderogba, T. O. Ajala, O. D. Akin-Ajani, and A. Okunlola, "Formulation of floating metronidazole microspheres using cassava starch (Manihot esculenta) as polymer," *J. Pharm. Investig.*, vol. 47, no. 5, pp. 445–451, 2017, doi: 10.1007/s40005-017-0319-7.

[10] P. Diós *et al.*, "Preformulation studies and optimization of sodium alginate based floating drug delivery system for eradication of Helicobacter pylori," *Eur. J. Pharm. Biopharm.*, vol. 96, pp. 196–206, 2015, doi: 10.1016/j.ejpb.2015.07.020.

[11] U. K. Mandal, B. Chatterjee, and F. G. Senjoti, "Gastro-retentive drug delivery systems and their in vivo success: A recent update," *Asian J. Pharm. Sci.*, vol. 11, no. 5, pp. 575–584, 2016, doi: 10.1016/j.ajps.2016.04.007.

[12] G. R.K., "Formulation development and evaluation of gastro retentive drug delivery systems- A review," *J. Pharm. Res.*, vol. 11, no. 2, pp. 167–178, 2017.

[13] M. Jhansee and D. A. Kumar, "Recent Advances in Gastro Retentive Drug Delivery System : a Review," no. July 2013, pp. 26–28, 2013.

[14] Nayak A. K., Malakar J., and Sen K. K., "Gastroretentive_drug_delivery_technologi (2)," *J Pharm Educ Res Vol. 1, Issue No. 2, December 2010*, vol. 1, no. 2, 2010.

[15] M. Jassal, U. Nautiyal, J. Kundlas, and D. Singh, "A review: Gastroretentive drug delivery system (grdds)," *Indian J. Pharm. Biol. Res.*, vol. 3, no. 01, 2015, doi: 10.30750/ijpbr.3.1.13.

[16] K. Chaturvedi *et al.*, *Sodium alginate in drug delivery and biomedical areas*. Elsevier Inc., 2019. doi: 10.1016/B978-0-12-817055-7.00003-0.

[17] P. Landge, J. Lavande, A. Swami, and V. Dharashive, "A Review on Gastroretentive Drug Delivery System," *Res. J. Pharm. Dos. Forms Technol.*, vol. 13, no. 12, pp. 62–68, 2023, doi: 10.52711/0975-4377.2023.00011.

[18] K. Koch, B. Dew, T. E. Corcoran, T. M. Przybycien, R. D. Tilton, and S. Garoff, "Surface tension gradient driven spreading on aqueous mucin solutions: A possible route to enhanced pulmonary drug delivery," *Mol. Pharm.*, vol. 8, no. 2, pp. 387–394, 2011, doi: 10.1021/mp1002448.

[19] S. K. Savale, "Formulation and evaluation of Metformin HCl micro beads by ionotropic gelation method," *Der Pharm. Lett.*, vol. 8, no. 3, pp. 189–196, 2016.

[20] R. B. Mistry and N. S. Sheth, "International Journal of Pharma and Bio Sciences FORMULATION AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM Corresponding Author," pp. 571–580, 2011, [Online]. Available: www.ijpbs.net

[21] M. D. Chavanpatil, P. Jain, S. Chaudhari, R. Shear, and P. R. Vavia, "Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin," *Int. J. Pharm.*, vol. 316, no. 1–2, pp. 86–92, 2006, doi: 10.1016/j.ijpharm.2006.02.038.

[22] S. A. El-Zahaby, A. A. Kassem, and A. H. El-Kamel, "Formulation and in vitro evaluation of size expanding gastro-retentive systems of levofloxacin hemihydrate," *Int. J. Pharm.*, vol. 464, no. 1–2, pp. 10–18, 2014, doi: 10.1016/j.ijpharm.2014.01.024.

[23] A. Nur, E. Fiskia, and B. Tjiroso, "Evaluation Profile In Vitro Release Gastroretentive High Density Tablet Theophylline Using Sodium Alginate and PVP," *E3S Web Conf.*, vol. 328, pp. 0–3, 2021, doi: 10.1051/e3sconf/202132801001.

[24] K. Patel and R. Chouksey, “A Recent Advantage on Gastroretentive Drug Delivery System: An Overview,” *Res. J. Pharm. Dos. Forms Technol.*, vol. 13, no. 10, pp. 36–44, 2023, doi: 10.52711/0975-4377.2023.00007.
[25] P. Rajput, D. Singh, and K. Pathak, “Bifunctional capsular dosage form: Novel fanicular cylindrical gastroretentive system of clarithromycin and immediate release granules of ranitidine HCl for simultaneous delivery,” *Int. J. Pharm.*, vol. 461, no. 1–2, pp. 310–321, 2014, doi: 10.1016/j.ijpharm.2013.11.053.
[26] S. Bharati, V. Gaikwad, A. Pawar, and B. Chellampillai, “Investigation of a biopolymer-based pH-responsive and sustained release raft-gel-forming tablet of famotidine: In-vitro, ex-vivo, bioavailability and anti-ulcer evaluation in New Zealand albino rabbit,” *J. Drug Deliv. Sci. Technol.*, vol. 86, no. June, p. 104649, 2023, doi: 10.1016/j.jddst.2023.104649.
[27] J. Tripathi, P. Thapa, R. Maharjan, and S. H. Jeong, “Current state and future perspectives on gastroretentive drug delivery systems,” *Pharmaceutics*, vol. 11, no. 4, 2019, doi: 10.3390/pharmaceutics11040193.
[28] S. Basak, S. Mandal, and M. Chattopadhyay, “Simultaneous spectrophotometric assay for estimation of norfloxacin and metronidazole in tablets,” *Asian J. Chem.*, vol. 22, no. 8, pp. 5971–5975, 2010.
[29] K. Vinchurkar, J. Sainy, M. A. Khan, S. Mane, D. K. Mishra, and P. Dixit, “Features and Facts of a Gastroretentive Drug Delivery System-A Review,” *Turkish J. Pharm. Sci.*, vol. 19, no. 4, pp. 476–487, 2022, doi: 10.4274/tjps.galenos.2021.44959.
[30] S. Biller, D. Baumgarten, and J. Haueisen, “Magnetic marker monitoring: A novel approach for magnetic marker design,” *IFMBE Proc.*, vol. 29, pp. 260–263, 2010, doi: 10.1007/978-3-642-13039-7_65.
[31] A. Bathool, D. V. Gowda, M. S. Khan, A. Ahmed, S. L. Vasudha, and K. Rohitash, “Development and evaluation of microporous osmotic tablets of diltiazem hydrochloride,” *J. Adv. Pharm. Technol. Res.*, vol. 3, no. 2, pp. 124–129, 2012, doi: 10.4103/2231-4040.97292.
[32] S. Bhise and N. Aloorkar, “Formulation and in vitro evaluation of floating capsules of theophylline,” *Indian J. Pharm. Sci.*, vol. 70, no. 2, pp. 224–227, 2008, doi: 10.4103/0250-474X.41460.
[33] R. A. K. Arza, C. S. R. Gonugunta, and P. R. Veerareddy, “Formulation and evaluation of swellable and floating gastroretentive ciprofloxacin hydrochloride tablets,” *AAPS PharmSciTech*, vol. 10, no. 1, pp. 220–226, 2009, doi: 10.1208/s12249-009-9200-y.
[34] I. V. Evaluation, “Sustained Release Floating Microspheres Of Acyclovir : Formulation , International Journal of Drug Development & Research Available online http://www.ijddr.in Covered in Official Product of Elsevier , The Netherlands Sustained Release Floating Microspheres Of Acyclovir : Formulation , Optimization , Characterization And In Vitro Evaluation,” no. March 2011, 2016.
[35] L. Yin *et al.*, “Gastro-floating tablets of cephalexin: Preparation and in vitro/in vivo evaluation,” *Int. J. Pharm.*, vol. 452, no. 1–2, pp. 241–248, 2013, doi: 10.1016/j.ijpharm.2013.05.011.