

Review on Gastroretentive Drug Delivery System

¹Swapnil Bajirao Hole.
SPMs College Of Pharmacy, Akluj.

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ABSTRACT :- To overcome physiological challenges such short residence periods and unpredictably long stomach emptying times, rate-controlled drug delivery devices have been created. The intra- and inter-subject variability in stomach physiology, including variations in gastric pH and motility, has a major influence on gastric residence time and drug delivery behaviour. This sparked a rise in interest in the development of innovative delivery methods that could stay in the stomach for extended periods of time with predictable results. There are several methods that have been developed so far, including floating drug delivery systems (FDDS), swelling and expanding systems, bioadhesive systems, modified form systems, high density systems, and various delayed gastric emptying devices. Drugs that are locally active and have a limited window of absorption in the stomach or upper small intestine are of special relevance for FDDS.

KEYWORDS:- Gastric residence time, Buoyancy, Floating drug delivery system,

I. INTRODUCTION:-

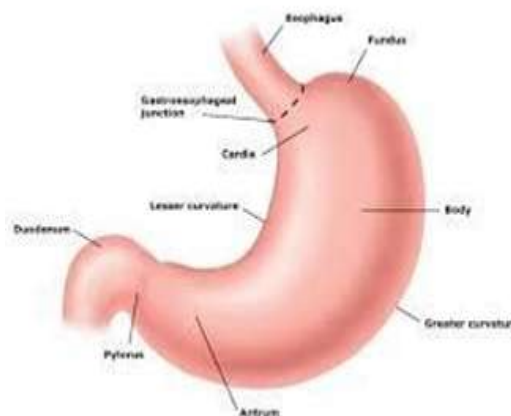
By focusing on site-specific medication release in the upper GIT for local or systemic action, gastro retentive drug delivery is a method to extend stomach residence duration. The most practical and often utilised mode of medication delivery is via the oral route. Unfortunately, there are a number of physiological issues with this method. Including a variable and unpredictable stomach emptying rate, a fast gastrointestinal transit time (80–12 hours), and the presence of a drug-specific absorption window in the upper small intestine. [1] Researchers have created a medicine delivery system that can stay in the stomach for a lengthy, predictable amount of time in response to these challenges. A medication delivery device that can produce therapeutically effective plasma drug concentration is currently being developed.

Physiology of stomach

The stomach has three sections according to its anatomy. An antrum, a body, and a fundus (pylorus) The proximal portion, which is composed

of the fundus and body, serves as a storage area for undigested materials, whereas the antrum is the primary location for mixing movements and serves as a pump for stomach emptying by sending out protons. Three regions, Fundus, Body, and Antrum, comprise the stomach anatomically (pylorus). The proximal portion, which is made up of the fundus and body, serves as a holding area for unprocessed materials, whereas the antrum is the primary location for mixing motions and serves as a pump for stomach emptying by propulsive activities. Both the fasted and fed states experience gastric emptying. An interdigestive series of electrical events that cycle through the stomach and small and large intestines occur when a person is fasting. The migrating myoelectric cycle (MMC) comprises four more stages. As follows:

1. Phase I (basal phase)
2. Phase II (preburst phase)
3. Phase III (burst phase)
4. Phase IV



Phase I It is quiescent period lasting from 30 – 60 minutes with no contractions.

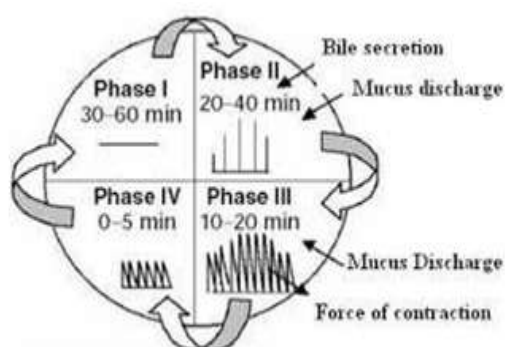
Phase II lasts between 20 and 40 minutes and is characterised by sporadic contractions that gradually get stronger as the period goes on. Later in this stage, gastric evacuation of liquid and extremely minute particles starts.

Phase III This lasts 10 to 20 minutes and is characterised by a brief period of powerful distal and proximal stomach contractions (4–5

contractions per minute). These contractions, often referred to as the "house-keeper wave," whisk gastric contents through the small intestine.

Stage IV The contractions stop during this brief transitional period of 0 to 5 minutes, which occurs between the quiescence of phase I and the latter portion of phase III.

After consuming a mixed meal, the pattern of contractions switches from that of a fasting state to that of a fed one. This pattern of continuous contractions, sometimes referred to as the digestive motility pattern, is similar to phase 2 of the fasting state. Food particles are shrunk down by these contractions (to less than 1 mm) and then sent in a suspension from the stomach towards the pylorus. The fed condition causes a delay in the beginning of MMC, which slows the pace at which the stomach empties. Orally administered controlled-release dosage forms are vulnerable to issues such as a short gastrointestinal residence duration and an unpredictably high gastric emptying rate, according to scintigraphic investigations on gastric emptying rate 13.



Illustrative representation of inter digestive motility

Advantages

1. Increased bioavailability As comparison to the administration of non-GRDF CR polymeric formulations, the bioavailability of riboflavin CR-GRDF is greatly increased. The amount of medication absorption is influenced by a number of interconnected mechanisms linked to drug absorption and transit in the gastrointestinal system.
2. Improved initial biotransformation The pre-systemic metabolism of the tested compound may be significantly increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner as opposed to by a bolus input, in a manner similar to the increased

efficacy of active transporters with capacity limited activity.

3. decreased dosage frequency and sustained medication delivery Sustained and slow input from CR-GRDF may cause a flip-flop pharmacokinetics and permit lower dose frequency for medications with a relatively short biological half-life. This quality is linked to better patient compliance, which enhances therapy.
4. targeted treatment for upper GIT conditions For local treatment in the stomach and small intestine, the extended and continuous delivery of the medication from GRDF to the stomach may be beneficial. Therapeutic drug concentrations can be reached locally by this form of administration, but systemic amounts after drug absorption and distribution are negligible.
5. less changes in drug concentration Compared to immediate release dosage forms, continuous input of the medication after CRGRDF administration results in blood drug concentrations within a tighter range. As a result, variations in medication effects are reduced, and undesirable effects that are concentration dependent and linked to peak concentrations can be avoided. This characteristic is especially crucial for medications with a limited therapeutic index. 24
6. minimization of medication concentration variations It enables the selective elicitation of pharmacological effects from medicines that activate various receptor types at various doses.
7. decreased body counteractivity In many instances, the pharmaceutical reaction that interferes with the body's normal physiological processes causes a rebound activity that reduces the effects of the medication. It has been demonstrated that introducing drugs slowly into the body reduces counteractivity, increasing medication effectiveness.
8. More time spent than necessary for effective focus The clinical response is not related to peak concentration for some medications having non-concentration dependent pharmacodynamics, such as beta lactam antibiotics, but rather to the amount of time spent over a crucial therapeutic concentration. The period above a critical concentration can be extended with the sustained method of administration, which amplifies the

pharmacological effects and improves clinical results.

9. reduced unfavourable colonic activity The quantity of medication that reaches the colon is reduced when it is retained in the GRDF in the stomach. As a result, the drug's negative effects in the colon may be avoided. The use of GRDF formulation for beta-lactam antibiotics, which are exclusively absorbed from the small intestine and whose presence in the colon results in the development of microorganism resistance, is justified by this pharmacodynamic factor.
10. localised medication delivery A floating dose form is a workable strategy, especially for medications with few upper small intestine absorption sites²⁵. The medication is delivered to the stomach in a regulated, gradual manner, resulting in adequate local therapeutic levels while limiting systemic exposure. This lessens the drug's adverse effects on the blood circulation. Moreover, a site-directed administration device may minimise the dose frequency because to the longer gastrointestinal availability.

Disadvantages

- a. Not suited for medications with a low acid solubility. Eg. phenytoin.
- b. Unsuitable for medications that lose their potency in an acidic environment. Example: erythromycin
- c. drugs with a delayed release that irritate or induce stomach lesions. Like aspirin and NSAIDs
- d. drugs that only selectively absorb in the colon. such as corticosteroids
- e. drugs with comparable GIT absorption. For instance, isosorbidedinitrate and nifedipine.
- f. For floating medicine delivery systems to work, the stomach must be filled with a lot of fluid.

Factors controlling gastric retention of dosage forms

The structure and physiology of the stomach contain variables that should be taken into account when creating gastro retentive dosage forms. The particle size should be between 1 and 2 mm in order to pass through the pyloric valve and enter the small intestine. Density, size, and shape of the dosage form, food intake and type, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity,

and diseased states of the individual are some of the most crucial factors influencing gastric retention time (GRT) of oral dosage forms (e.g. chronic metoclopramide, cisapride). Other crucial factors are the drug's ionisation state-dependent lipophilicity and molecular weight.

Drug dosage form density

The density of a dose form also influences the pace of gastric emptying and establishes where the system is located in the stomach. Whereas high density systems sink to the stomach's bottom, dosage forms with a density lower than the contents of the stomach might float to the surface. The dose system may be separated from the pylorus in either location. To demonstrate floating property, a density of less than 1.0 g/cm³ is needed.

The dose form's shape and size

Designing indigestible single unit solid dosage forms requires consideration of the shape and size of the dosage forms. Non-floating dose forms can be big, medium, or small units, and their size has a significant impact on their mean stomach residence periods. The gastric retention time (GRT) will often increase with dose form size since bigger dosage forms make it more difficult for them to move swiftly via the pyloric antrum and into the intestine.

Food consumption and its makeup

The amount of food consumed, its viscosity and volume, caloric content, and feeding frequency all have a significant impact on the retention of dosage forms in the stomach. The gastric retention time (GRT) of the dose form is influenced by the presence or absence of food in the gastrointestinal tract (GIT). The gastric retention time (GRT) of the dosage form is often improved by the presence of food in the gastrointestinal tract (GIT), and as a result, the medication absorption increases by allowing it to remain at the absorption site for a longer amount of time. Once more, a rise in acidity and caloric content results in a decrease in gastric emptying time (GET), which might enhance the retention of dose forms in the stomach.

Fed or not fed Fasting-related

GI motility is characterised by bursts of vigorous motar activity that happen every 1.5 to 2 hours. The MMC removes undigested matter from the stomach, and if the timing of the formulation

and the MMC are the same, the unit's GRT might be relatively brief. In contrast, when the MMC is delayed in the fast state, the GRT is longer.

Gender

Regardless of height, weight, or body surface, the mean ambulatory GRT for men (3.4 hours) is shorter than that of their age- and race-matched female counterparts (4.6 hours).

Age

Those older than 70 have GRTs that are noticeably longer. Anticholinergic medications like atropine and propetheline, as well as opiates like codeine, might prolong GRT when used concurrently.

Types of gastro retentive drug delivery system

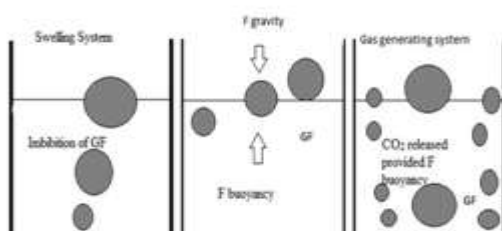
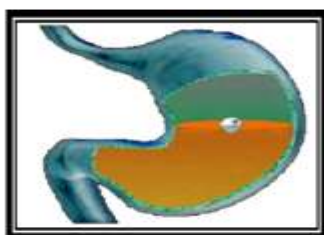
1. Floating systems

In 1968, Davis provided a description of floating systems. FDDS float in the stomach without slowing down the rate at which the stomach empties its contents since their bulk density is lower than that of gastric fluid. The medicine is slowly withdrawn from the system at the proper pace while the body is floating on the contents of the stomach. The stomach is emptied of the drug's residual system once it has been released. As a result, the GRT is elevated, and the oscillations in plasma drug concentration are better managed.

The floating system is divided in to two types

A) Non- effervescent systems

B) Effervescent systems



Mechanism of floating system, GF = Gastric fluid

The floating system's mechanism

A) Non- effervescent systems [13]

This type of system, after swallowing swells unrestrained via inhibition of gastric fluid to an extent that it prevents their exit from the stomach. Excipients used most commonly in these systems include Hydroxy propyl methyl cellulose (HPMC), Polyacrylate polymers, Polyvinyl acetate, Carbopol, agar, Sodium alginate, Polyethylene oxide and Polycarbonates.

This System can be further divided into four sub- types

a. Colloidal- gel barrier systems

Sheath and Tossounian first designated this "Hydro dynamically Balanced Systems". Such a system contain drug with gel forming hydrocolloids meant to remain buoyant the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel- forming highly soluble Cellulose type hydrocolloid.

These materials are commonly used as Hydroxy propyl methyl cellulose, Hydroxy propyl methyl cellulose, Hydroxyl ethyl cellulose, Hydroxy propyl cellulose, Polysaccharide and matrix forming Polymer, such as Polyacrylate and Polystyrene.

On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid- gel barrier around its surface.

b. Microporous compartment systems

A medication reservoir is enclosed inside a microporous compartment that has pores running the length of its top and bottom walls in order to implement this technique. To avoid any direct contact of the stomach surface with the dissolved medication, the outer walls of the drug reservoir compartment are entirely sealed. The delivery system floats above the gastric content in the stomach due to the flotation chamber's airtight seal. Via the opening, gastric fluid enters, dissolves the medication, and transports it continuously across the intestine for absorption.

c. Alginate beads

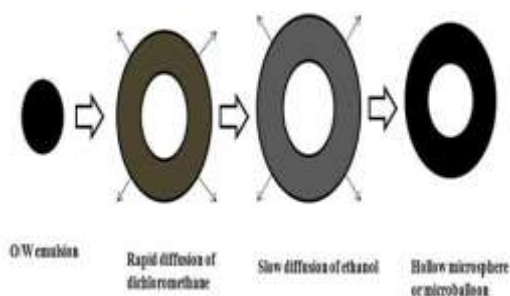
Calcium alginate that has been freeze-dried has been used to create multi-unit floating dosage forms. By adding sodium alginate solution to an aqueous solution of calcium chloride, calcium alginate will precipitate, resulting in spherical beads that are around 2.5 mm in diameter. After

being separated, the beads are quickly frozen in liquid nitrogen and freeze-dried at -40°C for 24 hours. This creates a porous structure that can sustain a floating force for more than 12 hours. The prolonged residency duration of these floating beads was more than 5.5 hours.

d. Micro balloons\ hallow microspheres

An innovative emulsion solvent diffusion technique was used to create hollow microspheres that contained medication in their outer polymer shelf. The drug's ethanol, dichloromethane, and enteric acrylic polymer solution was added to an agitated solution of polyvinyl alcohol that was heated to a constant 40°C .

The drug-coated polymer microsphere creates a cavity inside of which dichloromethane evaporates, creating the gas phase in the depressed polymer droplet. For more than 12 hours, the micro balloon floated continuously over the surfactant-containing surface of an acidic dissolving medium.



Hollow Microspheres

B) Effervescent systems [14]

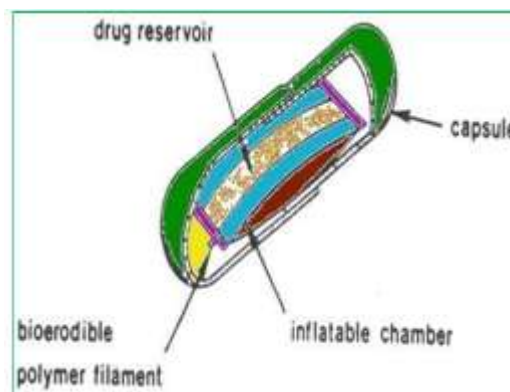
These buoyant systems make use of matrices made of effervescent components, polysaccharides (like chitosan), and swellable polymers like methocel (e.g., sodium bicarbonate, citric acid or tartaric acid).

The mechanism is so ready that when the formulation enters the stomach, carbon dioxide is produced, causing it to hover there. Others include floating systems based on ion exchange resin technology, floating minicapsules with a core of sodium bicarbonate, lactose, and polyvinyl pyrrolidone, and floating systems with a mixture of sodium alginate and sodium bicarbonate multiple unit floating pills that produce carbon dioxide when ingested, etc.

A] Systems for containing volatile liquids

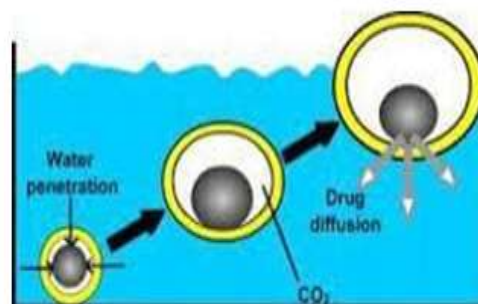
These kinds of systems have two chambers that are isolated from one another by a

moveable, pressure-responsive, impermeable bladder. The medicine is located in the first chamber, while the volatile liquid is located in the second chamber. As soon as the device is inflated, the medication is continually injected into the stomach fluid from the reservoir.



B]Methods for producing gas

The carbonate/bicarbonate salts and citric/tartaric acid in these buoyant delivery systems undergo an effervescent reaction to release CO_2 , which is then retained in the gellified hydrocolloid layer of the systems, reducing its specific gravity and causing it to float above chyme.



The fundamental workings of the CO_2 gas release technique for floating

2. Bio/muco-adhesive systems[15]

To improve medication absorption in a site-specific way, bio adhesive drug delivery systems (BDDS) are employed as a delivery device within the lumen. This method makes use of bioadhesive polymers, which may stick to the stomach's epithelial surface. The capacity of dose forms to resist the powerful propulsion forces of the stomach wall is often not imparted through the

gastric mucoadhesion. The capacity of muco-adhesion as a gastroretentive force also appears to be constrained by the constant generation of mucus by the gastric mucosa to replace the mucus lost during peristaltic contractions and the diluting of the stomach fluid. Excipients such polycarbophil, carbopol, lectins, chitosan, and carbopol, which have been utilised often in these systems, are some of the most promising.

Binding of polymers to the mucin/epithelial surface can be divided into three categories:

A] Hydration – mediated adhesion systems

Certain hydrophilic polymers have a propensity to absorb a lot of water, become sticky, and develop bio adhesive characteristics. The pace at which the polymer dissolves further regulates how long the bio/muco-adhesive delivery system remains in the gastro-intestinal tract.

B] Bonding –mediated adhesion systems

Polymers adhere to the surface of mucus or epithelial cells through a variety of bonding mechanisms. Deposition and inclusion of the adhesive substance in the mucosal fissures might lead to physical or mechanical connections. Dispersive interactions (also known as Vander Walls interactions) and stronger specific interactions, like as hydrogen bonds, make up secondary chemical bonds that contribute to the bio adhesive characteristics of materials. The hydroxyl ($-\text{OH}$) and carboxylic groups are the hydrophilic functional groups in charge of creating hydrogen bonding ($-\text{COOH}$).

C] Receptor – mediated adhesion systems

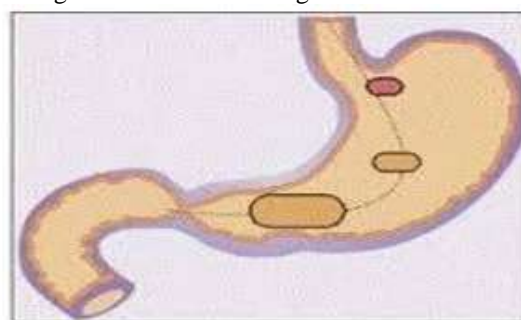
Certain polymers have the capacity to bind to particular receptor locations on the surface of cells. The receptor-mediated processes offer a viable strategy for improving bio/muco-adhesion and, consequently, the retention of dose forms in the stomach. The sugar groups found in mucus or on the glycocalyx are specifically interacting with certain plant lectins, such as tomato lectins.

3] Swelling systems[16,17]

These are the dose forms that, after being ingested, enlarge to the point that they cannot escape the pylorus. The dose form stays in the stomach for a very long time as a result. These systems may be referred to as "plug type systems" because of their propensity to remain ensconced at the pyloric sphincter. The medicine is delivered into the gastrointestinal cavity under controlled

circumstances and with gastric retention in mind. Even in fed state, such polymeric matrices persist in the gastrointestinal cavity for several hours. The right molecular weight polymer can be chosen to provide sustained and regulated medication release, and polymer swelling slows down drug release. The polymer absorbs gastric fluid when it comes into touch with it.

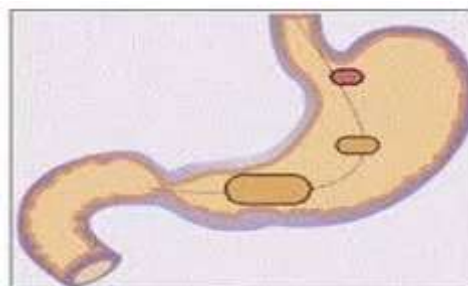
These cross connections keep the polymer from dissolving, maintaining the dosage form's physical integrity. It is important to maintain an ideal cross linking that balances swelling and breakdown.



Swellable tablet in stomach

4] High density system[18]

For pellets small enough to be held in the rugae or folds of the stomach body close to the pyloric region—the area of the organ with the lowest position when the body is upright—sedimentation has been used as a retention mechanism. Dense pellets (about $3\text{g}/\text{cm}^3$) caught in rugae also have a propensity to endure peristaltic motions of the stomach wall. Using pellets, the GI transit time can be prolonged from an average of 5.8 to 25 hours, with density having a greater impact than particle diameter²⁷. Excipients including barium sulphate, zinc oxide, titanium dioxide, and iron powder are frequently utilised. Some substances can raise density by $1.5\text{--}2.4\text{g}/\text{cm}^3$ or more.



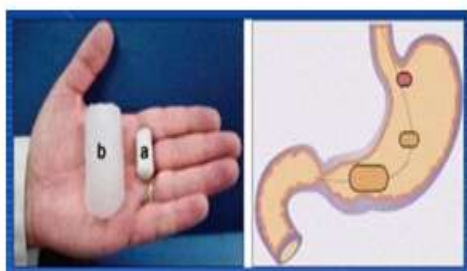
schematic localization off loading dosage forms in stomach

5] Magnetic system[19]

A tiny internal magnet is present in the dose form, and a magnet is also applied to the abdomen over the location of the stomach in this method to increase gastric retention time (GRT). Although the magnetic method appears to function, it requires precise positioning of the external magnet, which may reduce patient compliance.

6] Superporous hydrogels[20,21]

Extremely porous hydro gels are expandable, non-conventional systems. Conventional hydrogels absorb water relatively slowly, and it may take many hours to reach the equilibrium states at which the dosage form may prematurely evacuate. A super porous hydrogel with holes larger than 100 m swells to equilibrium size in a matter of minutes as a result of capillary wetting that occurs quickly through interconnected open pores. They enlarge and gain the mechanical strength needed to withstand the pressure from the contraction of the stomach. Co-forming a hydrophilic particle substance allows for this.



II. CONCLUSION

Longer GRT dosage formulations will result in new and significant treatment alternatives. They will greatly lengthen the window of opportunity for drug release, resulting in longer dosage intervals, and they will boost patient compliance above and beyond that of current CRDFs. Products having release and absorption phases of around 24 hours will replace many "Once-a-day" formulations. Moreover, GRDFs will significantly enhance the pharmacotherapy of the stomach by allowing for local drug release that results in high drug concentrations at the gastric mucosa that are maintained for a considerable amount of time. The "absorption window" will be employed with GRDFs as medication carriers. Notwithstanding the challenges that must be overcome to obtain sustained gastric retention, a significant.

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