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An Overview on Floating Drug Delivery System: A Review

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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, bio-adhesive systems, modified form systems, high density systems, and various delayed gastric emptying devices. Drugs that are locally active, have a short window for absorption in the stomach or upper small intestine, are unstable in the intestinal or colonic environment, and have low solubility at high pH levels are particularly interested in FDDS. The goal of this review article is to provide comprehensive information on the pharmacological foundation of their design, categorization, benefits, and various forms of FDDS, as well as the potential of FDDS in the future.

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. However, there are a number of physiological issues with this route. including a variable and unpredictable gastric 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. An effort is being made to create a drug delivery system that can deliver therapeutically effective plasma drug concentration for a longer period of time, reducing the frequency of dosing and minimising fluctuation in plasma drug concentration at steady state.

GRDDSs (gastro retentive drug delivery system) are one innovative method in this field. GRDDs are dosage forms that can be retained in the stomach. By constantly releasing the drug for a lengthy time before it reaches its absorption site, GRDDSs can enhance the controlled administration of medications with an absorption window. For medications that are absorbed from the proximal region of the GIT (gastro intestinal tract), those that are less soluble in alkaline pH or are destroyed by alkaline pH, or those that come into contact at the lower section of the GIT, prolonging the stomach retention of the pharmaceuticals may occasionally be beneficial to achieve therapeutic effects. [2]

Drugs with short half-lives and easy GIT absorption are swiftly removed from the systemic circulation. These medications must be dosed often to get the desired therapeutic effect. The development of oral sustained controlled release formulations is an effort to bypass this restriction by slowly releasing the medication into the GIT and maintaining an effective drug concentration in the systemic circulation for an extended period of time. Such a drug delivery would be kept in the stomach after oral administration and release the medication in a regulated way, allowing the drug to be constantly given to its GIT absorption sites. [3]

Physiology of Stomach:

The stomach is separated into three parts anatomically. Fundus, Antrum (pylorus), and Body While the antrum is the primary location for mixing motions and serves as a pump for gastric emptying by propelling food into the stomach, the proximal portion made of the fundus and

body serves as a reservoir for undigested materials. The stomach is anatomically split into three sections: the Fundus, the Body, and the Antrum (pylorus). The body and fundus-made proximal portion serve as a holding area for undigested materials, while the antrum serves as the primary location for mixing movements and a pump for stomach emptying by propulsive activities. Both when one is fasting and when one is eaten, the stomach empties. The term "inter digestive myloelectric cycle" or "migrating myoelectric cycle" (MMC) refers to a sequence of electrical events that occur during the fasting condition and cycle through the stomach and intestine every 2-3 hours.

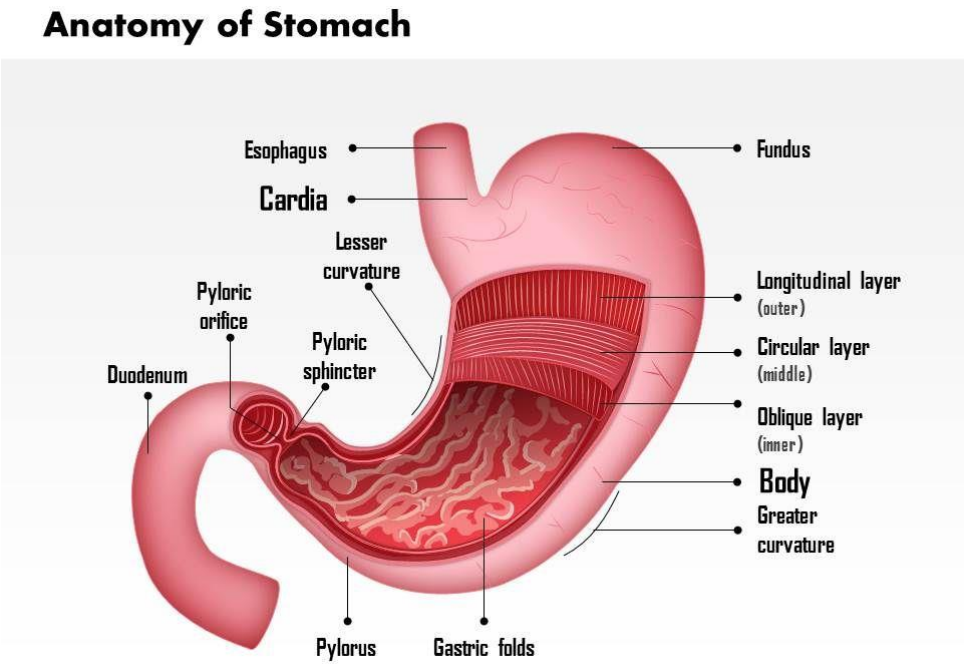

Fig.1: Anatomy of Stomach

Migrating myoelectric cycle (MMC) is further divided in to four phases.

They are:

1. Phase I (basal phase)

2. Phase II (preburst phase)

3. Phase III (burst phase)

4. Phase IV

Phase I: It is a quiet time of between 30 and 60 minutes without contractions.

Phase II: It lasts for 20 to 40 minutes and comprises of irregular contractions that gradually get stronger as the phase goes on. Later in this phase, gastric ejection of liquids and tiny particles starts.

Phase III: The "house-keeper wave" is a brief period of severe distal and proximal stomach contractions that lasts for 10 to 20 minutes. These contractions push gastric contents down the small intestine.

Phase 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.

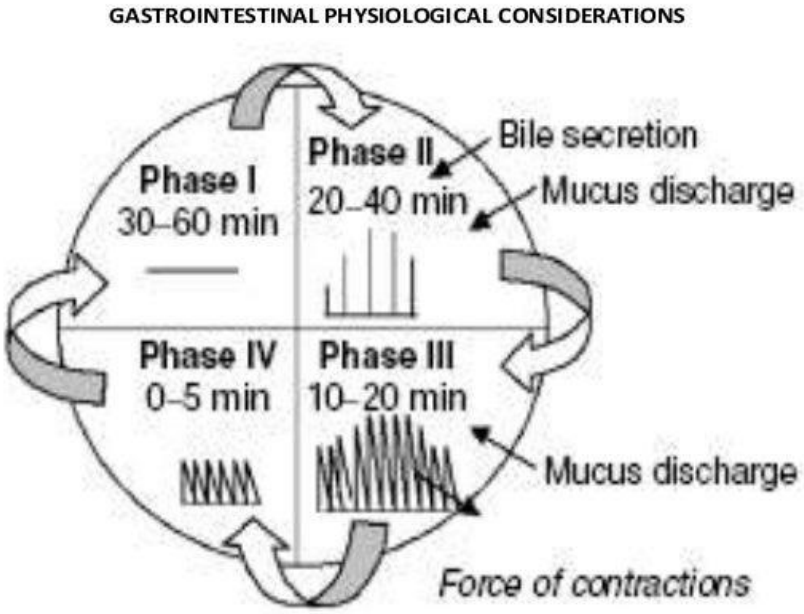

Fig.2: Schematic representation of inter digestive motility

The pattern of contractions switches from that of a fasting state to that of a fed state following the consumption of a mixed meal. In phase 2 of the fasting state, constant contractions are seen in this pattern, which is also known as the digestive motility pattern. These contractions reduce the size of the food particles (to less than 1 mm), which are then pushed in a suspension towards the pylorus. The fed condition causes MMC to start later, which slows down the pace at which the stomach empties. Orally administered controlled-release dosage forms are vulnerable to problems due to a short stomach residence time and an unpredictably high gastric emptying rate, according to scantigraphic investigations.[2]

Advantages of FDDS:

1. Enhanced bioavailability

When compared to the administration of riboflavin CR polymeric formulations without GRDF, the bioavailability of riboflavin CR-GRDF is significantly 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. Enhanced first-pass biotransformation

When the drug is given to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner rather than by a bolus input, the pre-systemic metabolism of the tested compound may be significantly increased, similar to the increased efficacy of active transporters with capacity limited activity.

3. Reduced fluctuations of 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.

4. Minimization of fluctuations in drug concentration

It enables the selective elicitation of pharmacological effects from medicines that activate various receptor types at various doses.

5. Reduced counter-activity of the body

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.

6. Extended time over critical (effective) concentration

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.

7. Minimized adverse activity at the colon

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 feature.

8. Site specific drug 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. Additionally, a site-directed delivery system may reduce the frequency of dosing by extending gastric availability.

Disadvantages:

1. Ineffective for medications with a low acid solubility. Eg. phenytoin.

2. Not appropriate for medications that are unstable in an acidic environment. Example: erythromycin

3. Drugs with a delayed release that irritate or lead to stomach sores. Like aspirin and NSAIDs

4. Drugs that only selectively absorb in the colon, such as corticosteroids

5. Medicines that are equally well absorbed by the GIT. For instance, isosorbide-dinitrate and nifedipine.

6. Floating medication delivery methods need a lot of fluid in the stomach to work.

Factors controlling gastric-retention of dosage forms [9,10]

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 (such as chronic metclopramide, cisapride) are some of the most crucial factors affecting the gastric retention time (GRT) of oral dosage forms. Other crucial factors include the drug's ionisation state, molecular weight, and lipophilicity.

Density of dosage forms:

The density of a dose form also influences the pace of gastric emptying and establishes where the system is located in the stomach. While high density systems sink to the stomach's bottom, dosage forms with a density lower than the contents of the stomach can 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 gm/cm must be present.

Shape and size of the dosage form:

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) is often inversely correlated with the size of the dose form since bigger dosage forms make it more difficult for them to move swiftly via the pyloric antrum and into the intestine.

Food intake and its nature:

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.

Shape of the dosage form:

Compared to other devices of the same size, the tetrahedron stayed in the stomach for a longer time. (Multiple unit formulations demonstrate more predictable diseases, such as diabetes, than single unit formulations.) and administration of medications that have an effect on gastrointestinal transit time, such as atropine, propantheline, opiates (codeine, for example), prokinetic agents (e.g. release profile and minimal performance impairment brought on by unit failure. When compared to single unit dosage forms, allow co-administration of units with different release profiles or containing incompatible substances, as well as a larger margin of safety against dosage form failure.

Fed or unfed state:

Fasting-related GI motility is characterised by bursts of vigorous motor activity that happen every 1.5 to 2 hours. The GRT of the unit can be relatively short if the time of the formulation and the MMC are the same, but in the fast state, the MMC is delayed and the GRT is prolonged because it sweeps undigested material from the stomach.

Nature of meal:

Feeding the stomach with indigestible polymers or fatty acids can cause the stomach's motility pattern to transition to a fed state, slowing down gastric emptying and extending the time that drugs are released. A meal heavy in protein and fat might boost the calorie content and GRT by 4–10%.

Frequency of feed:

Due to the low frequency of MMC, the GRT can increase by more than 400 minutes when compared to a single meal.

Gender:

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

Age:

Ages greater than 70 are associated with noticeably longer GRT. Anticholinergic medications like atropine and propetheline, as well as opiates like codeine, might prolong GRT when used concurrently.[3]

Types of gastro retentive drug delivery system [11,12]

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.

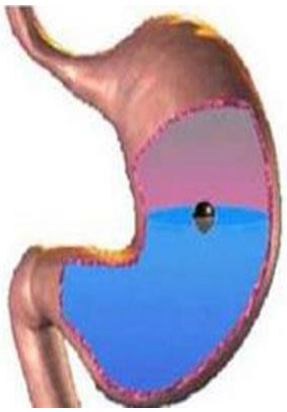

Fig.3: Floating System

The floating system is divided in to two types.

A) Non- effervescent systems

B) Effervescent systems

A) Non- effervescent systems [13]

After swallowing, this sort of system grows uncontrolled by inhibition of gastric fluid to the point where it hinders their escape from the stomach. Excipients such Polyacrylate polymers, Polyvinyl acetate, Carbopol, agar, Sodium alginate, Polyethylene oxide, and Polycarbonates are most frequently utilised in these systems.

This System can be further divided into four sub- types.

a. Colloidal- gel barrier systems

This was originally referred to as "Hydro dynamically Balanced Systems" by Sheath and Tossounian. Such a system contains medication that has hydrocolloids that produce gels and are intended to keep the stomach content buoyant. This extends GRT and increases the quantity of medication that arrives at the absorption sites in solution form for immediate absorption. This system contains a significant amount of one or more hydrocolloids of the cellulose type that form gels and are very soluble.

The hydrocolloid in the system hydrates and forms a colloid-gel barrier around its surface when it comes into touch with stomach fluid.

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. Through the aperture, 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 lengthy residence period of more than 5.5 hours was provided by these floating beads.

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. A solution of polyvinyl alcohol that

had been stirred and had been thermally regulated at 40°C was added together with a drug's ethanol dichloromethane solution and an enteric acrylic polymer.

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

B) Effervescent systems [14]

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

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

a. Volatile liquid containing systems

These kinds of systems have two chambers that are separated 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. The apparatus inflates, releasing the medication constantly into the stomach fluid from the reservoir.

b. Gas–generating systems

These buoyant delivery systems release CO2 by an effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid. The CO2 is then trapped in the systems' gellified hydrocolloid layer, which lowers its specific gravity and causes it to float atop chyme.

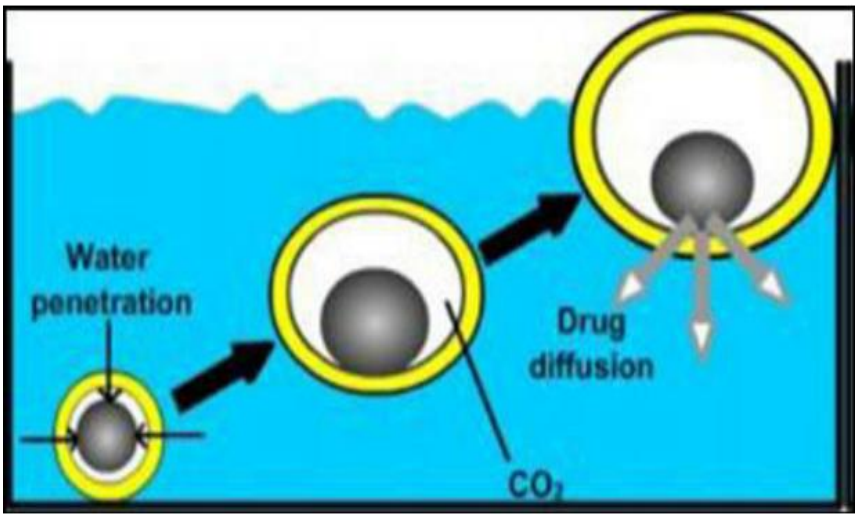

Fig.4: Principle mechanism of floating by CO2 gas releasing method

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. Muco-adhesion's potential as a gastro-retentive force appears to be constrained by the gastric mucosa's ongoing synthesis of mucus to replace the mucus lost during peristaltic contractions and the dilution of the stomach's contents.

There are three types of binding of polymers to the mucin/epithelial surface:

a. Hydration – mediated adhesion systems

Some hydrophilic polymers have a propensity to absorb a lot of water, become sticky, and develop bio adhesive properties. The pace at which the polymer dissolves further regulates the bio/muco-adhesive delivery system's longer gastro-retention.

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 (--OH) and carboxylic groups (--COOH) are the hydrophilic functional groups that produce hydrogen bonding.

c. Receptor – mediated adhesion systems

Some 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 the particular targets of interaction for some 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 the 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 water when in contact with stomach fluid and expands. These polymers are more extensive because the network of hydrophilic polymers contains physical/chemical cross-links.

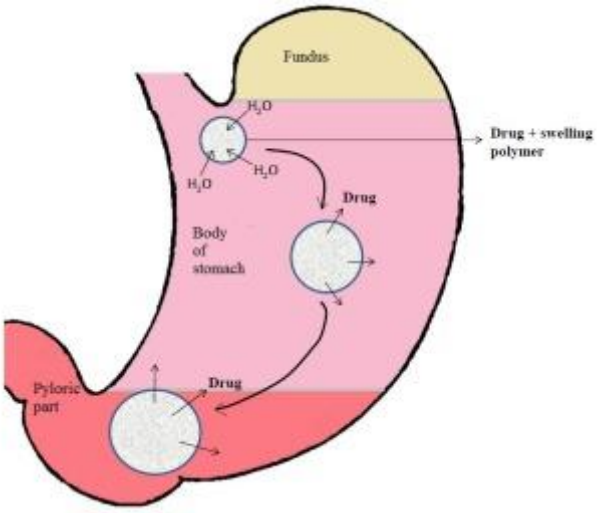

Fig.5: Swellable tablet In Stomach

These cross linkages keep the polymer from dissolving and so preserve the dosage form's physical integrity. It is important to maintain an ideal cross linking that balances swelling and breakdown.[5]

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 3g/cm-3) caught in rugae also have a propensity to endure peristaltic motions of the stomach wall. With pellets, the GI transit time can be prolonged from an average of 5.8 to 25 hours, with density having a greater impact than pellet diameter27. Excipients including barium sulphate, zinc oxide, titanium dioxide, and iron powder are frequently utilised. These substances raise density by 1.5–2.4g/cm3 or more.

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 system appears to work, it requires precise positioning of the external magnet, which may reduce patient compliance.

6. Super-porous hydrogels [20,21]

Super-porous hydrogels are expandable, non-conventional structures. 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. This is accomplished by combining a hydrophilic particle material with the formulation.[4]

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. Additionally, GRDFs will significantly enhance the pharmacotherapy of the stomach by causing local drug release that results in high drug concentrations at the gastric mucosa that are maintained for a long time. The "absorption window" will be employed with GRDFs as medication carriers. Numerous businesses are working to commercialise this technique despite the fact that there are a number of challenges to overcome in order to achieve prolonged gastric retention.

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