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Mucoadhesive Floating Drug Delivery Systems: An Advanced Approach For Enhanced Gastroretention

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Abstract: Even though the oral route is the most popular way to administer drugs, many pharmaceuticals face difficulties such quick stomach emptying, brief stomach residence time, and poor intestine solubility. Gastro-retentive drug delivery systems (GRDDS) were created to overcome these restrictions by extending the amount of time dosage forms remain in the stomach, improving drug absorption and overall therapeutic efficacy. Because they offer prolonged medication release and stay buoyant on stomach contents, floating drug delivery systems (FDDS) are one of the most popular methods. However, differences in stomach physiology may have an impact on their performance. Mucoadhesive polymers are added to the system to improve stability and dependability by enabling the dosage form to stick to the stomach mucosa and stay there for extended periods of time. Mucoadhesive floating systems, which combine both buoyancy and mucosal adhesion, offer a more effective approach for prolonged gastric retention. Polymers such as HPMC, Carbopol, and chitosan are commonly used to enhance adhesion, improve bioavailability, ensure controlled drug release, and reduce the frequency of dosing. All things considered, these methods hold great promise for medications that require extended stomach retention or are mostly absorbed in the upper gastrointestinal tract.

Index Terms – Carbopol**,** Mucoadhesive, **,** floating drug delivery, buoyant

I. INTRODUCTION

Because it is easy to use, affordable, and provides significant flexibility in formulation design for single-dose systems, the oral route is typically regarded as the most practical and preferable means of giving drugs. An oral drug delivery system should ideally deliver the medication in a single dose, release it at the intended site of action, and sustain an efficient therapeutic concentration for a long time. [1][10].

However, there are several physiological obstacles to this strategy, including poor drug solubility in the intestinal environment, instability of some medications under intestinal or colonic circumstances, individual differences in stomach emptying, and the gastrointestinal tract's short transit time. [2]. Reduced intestinal absorption results from the high solubility of many weakly basic medications in acidic environments and their poor solubility in alkaline ones.

By increasing the bioavailability of medications that primarily function in the stomach, such as antibiotics and antacids, gastro-retentive drug delivery systems (GRDDS) provide a significant benefit. In order to improve absorption in the stomach and upper gastrointestinal tract, these systems are specifically made to stay in the stomach for long periods of time and release the medication gradually. [1].

Several methods, such as floating drug delivery systems, high-density systems, mucoadhesive formulations, expandable or swellable devices, modified-shape systems, and delayed-gastric-emptying devices, have been developed to extend the duration of stomach residence. [3]. GRDDS can help lessen the gastrointestinal distress brought on by some drugs by allowing for controlled and prolonged release. These systems' primary benefit is their capacity to deliver medications straight to particular gastric regions, which is especially helpful in treating gastrointestinal conditions like gastroesophageal reflux [1].

ADVANTAGES OF GASTRORETENTION SYSTEM:[3]

1. Gastro-retentive processes are advantageous for medications meant to work locally in the stomach. Antacids, for instance.

2.Aspirin and other acidic chemicals can irritate the stomach wall upon contact. GRDD formulation may be effective for administering Aspirin and other related medications

3.Because diarrhoea shortens transit time and increases intestinal motility, it frequently decreases medication absorption Therapeutic efficacy can be greatly increased in these circumstances by using a floating mechanism to maintain the dosage form buoyant in the stomach.

4 The absorption of medications that are mostly absorbed in the stomach is enhanced by gastro-retentive mechanisms. For example, longer gastric retention is beneficial when ferrous salts are used in conjunction with antacids.

DISADVANTAGES OF GASTRORETENTION SYSTEM [3]

1.These systems are not applicable to nonsteroidal anti-inflammatory medications like aspirin.

2.Gastric irritation or lesions may result from certain medications being unstable in the stomach's acidic environment. It is difficult to design systems that rely on gastric retention since variables like stomach pH, gastric motility, and the presence or absence of food affect how well they function.

Factors Affecting a Dosage Form's Gastric Retention Time [6]

- Density: The dosage form's density must be less than that of stomach fluid (about 1.004 g/mL) for efficient gastric retention.

- Size: Should have diameter more than 7.5mm

- The dosage form's shape:
  Gastric retention may be impacted by dosage form geometry. For instance, it has been demonstrated that tetrahedral devices stay in the stomach longer than other designs of comparable size.. In general, multi-unit formulations are less impacted by the failure of a single unit and provide more consistent drug-release characteristics. They also allow different units to carry varying release profiles or incompatible ingredients, and they provide a higher safety margin compared to single-unit systems.

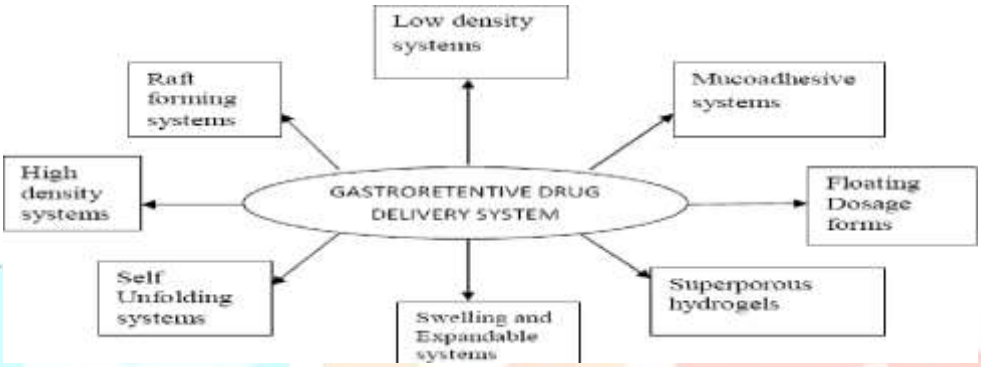
- Type of Meal:

  The type of food ingested can affect gastric retention. Meals containing indigestible polymers or fatty acids can affect gastric motility and limit the stomach's emptying capacity, hence prolonging the residence period of the dose form.

- Age: People beyond the age of 70 have considerably Longer GRT.

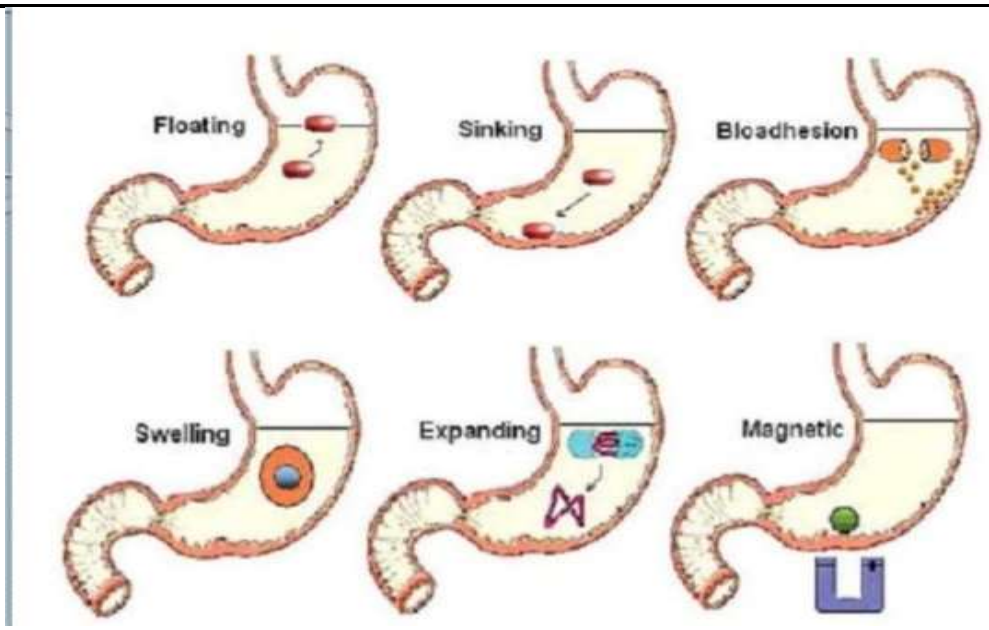
- Gender: Regardless of height, weight and body surface, GRT in male (3.4hrs) is less compared with female (4.6hrs)

Gastro retentive Drug Delivery System:



To create dose forms that can stay in the stomach for longer, several strategies have been devised. Low-density, high-density, swelling and expanding, super porous hydrogels, hydrodynamically balanced, gas-generating, raft-forming, floating, and ion-exchange resin systems are among them.
Floating drug delivery systems (FDDS) are one of the most widely used gastro-retentive drug delivery systems (GRDDS). Because of their low density, they stay buoyant on stomach contents for extended periods of time, guaranteeing localized and persistent medication release in the stomach. Because FDDS have little effect on gastrointestinal motility, they are frequently used. However, a major drawback is that adequate stomach fluid is necessary for their efficacy. When food or liquids enter the small intestine and the dose form settles close to the pylorus, rapid gastric emptying might lower the system's buoyancy.

This limitation can be addressed by incorporating mucoadhesive polymers, which enable the dosage form to adhere to the gastric mucosa. By combining the buoyancy of traditional FDDS with the capacity to keep intimate touch with the stomach lining, mucoadhesive floating drug delivery systems (MFDDS) improve drug retention and absorption. MFDDS provide better site-specific drug delivery and increased therapeutic efficacy as compared to other floating system types [1].



Floating drug delivery:
Floating systems, also known as hydrodynamically controlled systems [17], can stay buoyant in the stomach for extended periods of time without impeding gastric emptying because their density is lower than that of gastric fluids [14].

The medication is delivered gradually while the system is still floating on the stomach contents [3]. This leads to higher GRT [16] and improved control over changes in plasma medication concentration. Because of their buoyancy, they provide efficient stomach retention for medication release. "The remaining system is eventually emptied from the stomach after the drug is released in a slow and controlled manner"[4].

Three essential requirements must be met in order to create a floating dosage form that works:

(a) The system needs to have a specific gravity that is less than that of stomach contents, between 1.004 and 1.01 g/cm³.

b) The medication must be uniformly and carefully discharged from the dosage form in reservoir-type devices.

c) A cohesive gel-like barrier must be formed by floating systems. [4]
By avoiding direct contact with the stomach mucosa and allowing for regulated, sustained release of low doses, the floating drug delivery approach helps reduce the irritating effects of weakly acidic medicines [15].

In order to target drug release to particular parts of the gastrointestinal tract, particularly the stomach, polymers are frequently added to floating drug delivery systems. Because of their biocompatibility and capacity to hold medications in the stomach environment, natural polymers are very helpful. Chitosan, pectin, xanthan gum, guar gum, starch, husk, and alginates are a few examples [11].

Advantages

1.Tablets and capsules are examples of floating dose forms that can stay afloat for long periods of time at the alkaline pH of the colon [18].

2.Drugs that are largely absorbed in the stomach benefit from gastro-retentive systems. Examples include antacids and ferrous salts [18].

3. When an acidic substance, such as aspirin, comes into encounter with the stomach wall, it causes discomfort. As a result, HBS/FDDS formulations could be useful for administering aspirin and other comparable medications.[18]

4.Because FDDS dosage forms stay floating in the stomach and assist keep the medication at its site of action, they are particularly helpful during episodes of diarrhea or increased gastrointestinal motility, increasing the therapeutic response [18].

Disadvantages:

1. Variations in stomach motility, changes in gastric pH, and the presence or absence of food are some of the physiological factors that influence gastric retention. It is impossible to accurately calculate a dose form's buoyancy due to these unpredictable variables. [18]
2. "It is not appropriate to formulate drugs that irritate the gastrointestinal mucosa into floating drug delivery systems." [18].
3. Floating tablets may leave the stomach at random times in people who are sleeping. So, patients shouldn't take a floating-tablet dose right before bed. [18]

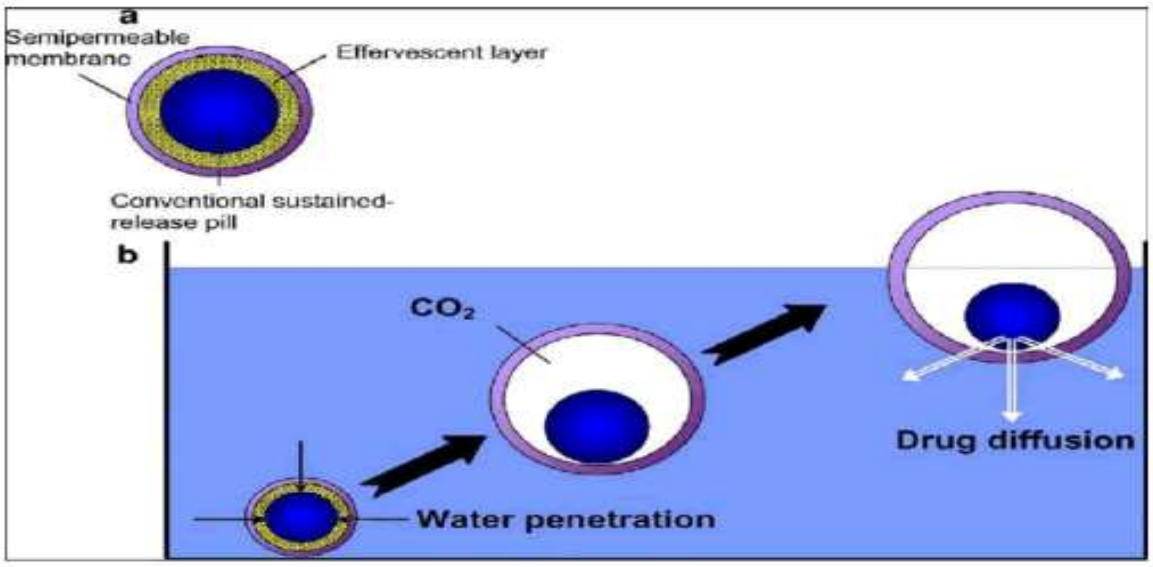
Technological developments in FDDS

Floating Drug Delivery Systems (FDDS) were initially discussed by Davis [20] in 1968.
He talked about a way to help people who gag or choke when they swallow medicines. He suggested that tablets with a density of less than 1.0 g/mL could float on stomach fluids, making this problem less of a problemSince then, numerous approaches to creating a safe and effective floating medication delivery system have been discovered. [7]

Mechanism

The polymer in these systems absorbs water and creates a gel-like barrier on the surface when it comes into touch with stomach fluids. Because it is small and low density, this structure helps the dosage form stay afloat in the stomach, which makes it stay there longer.

For around three to four hours, floating systems can remain buoyant in the stomach without affecting the rate at which the stomach empties. The most preferred polymer among cellulose ethyl polymers is hydroxypropyl methyl, a hydrocolloidal material that is recommended for controlled-release floating dose formulations.[4]



Mucoadhesive drug delivery systems:

Bio- or mucoadhesive systems adhere to the mucin layer or the stomach's epithelial surface. By improving the dosage form's interaction with the biological membrane, this prolongs its stay in the stomach.[8]

Bio adhesion is when two materials, at least one of which is biological, stay together for a long time because of interfacial forces. In the field of medicine, mucoadhesion refers to the ability of a substance to stick to mucus or a mucosal membrane.[9]"

"Mucoadhesion" refers to the binding between a mucous covering and an adhesive polymeric device, whereas "cytoadhering" refers to cell-specific bio adhesion.[13]

The gastrointestinal tract's natural defense mechanism serves as the foundation for this theory. Mucus, which is secreted by goblet cells, is essential for cytoprotectant. This thick, elastic, gel-like substance is mostly composed of glycoproteins. The mucus layer gradually thins from the epithelial surface to the GI lumen. Its primary purpose is to shield the underlying mucosal cells from acidic surroundings and digesting enzymes.

Additionally, it facilitates solid transit by acting as a lubricant and barrier against antigens, bacteria, and viruses. The mucin's adhesive qualities have been used to construct GRDDS using bio/mucoadhesive polymers. Adhesion to the stomach wall increases bioavailability by prolonging the delivery system's stay at the targeted site[8].

Mucoadhesive drug delivery methods use polymers that adhere to the stomach mucosa's surface, extending the period of gastric retention. These polymers are effective excipients for GRDDS because of their great affinity for the mucus gel layer. However, continuous mucus turnover may reduce the effectiveness of mucoadhesive drug delivery techniques [10].

These systems can employ semi-synthetic polymers like HPMC, Carbopol, and sodium carboxymethyl cellulose, or natural polymers such sodium alginate, gelatin, and guar gum.[6]

Also be synthetic include poly (acrylic acid) (Carbopol, polycarbophil), Chitosan, Gantries (Polymethyl vinyl ether/maleic anhydride copolymers), cholestyramine, tragacanthin, sodium alginate, sucralfate, polyethylene glycol, dextran and polylactic acid [8]

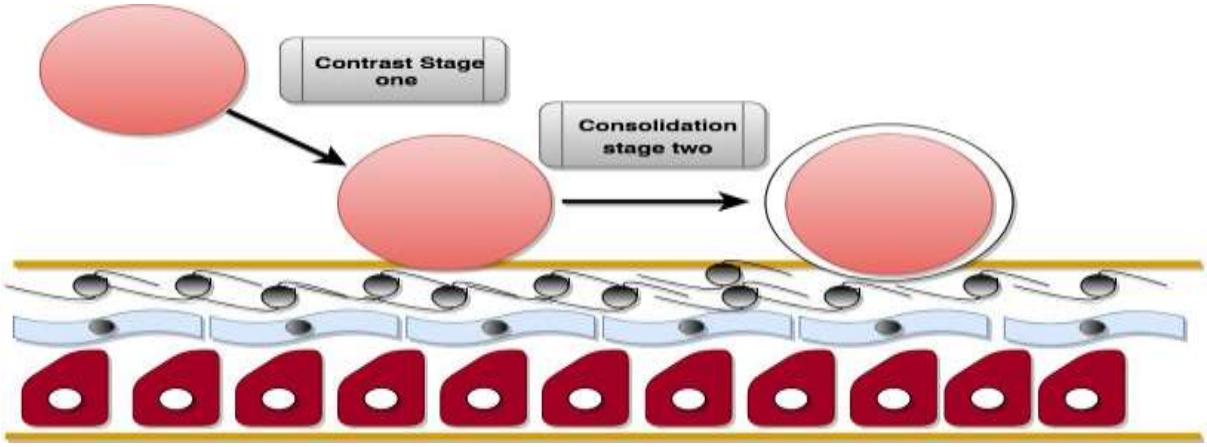
Chain length, molecular flexibility, hydrophilic functional groups, specific molecular weight, and structural conformation are some of the properties of these polymers.

The ideal medication delivery method ought to be non-toxic, non-absorbable, capable of forming non-covalent contacts with mucin and epithelial surfaces, quickly stick to moist tissues, facilitate effective drug release, target particular attachment sites, and continue to be economical.[8]

Mechanism of mucoadhesion:

The mucoadhesive substance must first disperse across the substrate in order for chain diffusion to occur effectively within the mucus. This ensures close contact and expands the surface area available for adhesion.

For a mucoadhesive to work effectively, attraction forces must take precedence over repulsion. Mucoadhesion typically occurs in two stages: contact and consolidation.[12]



Polymers can adhere to mucosal membranes through hydration, bonding, or receptor-mediated mechanisms.[6]

✧ **Hydration-mediated adhesion**

Significant water absorption causes hydrophilic polymers to swell and become sticky, giving them bio adhesive qualities. A bio- or mucoadhesive drug delivery system's capacity to sustain gastric retention is directly impacted by the polymer's rate of dissolution.[8]

✧ **Bonding-mediated adhesion**

Physical, mechanical, and chemical interactions cause polymers to adhere to mucus or epithelial surfaces. When the adhesive material gets within the mucosal layer's folds or cracks, physical-mechanical bonding occurs. Both main (covalent) and secondary bonds, such as ionic forces, can be involved in chemical interactions. Secondary interactions include weaker dispersive forces like Van der Waals attractions and stronger specific contacts like hydrogen bonds. The majority of these hydrogen bonds are created by hydrophilic functional groups like hydroxyl and carboxyl groups.[8]

✧ **Receptor-mediated adhesion**

By engaging with particular cell receptor locations, polymers can enhance the retention of dose forms in the stomach.[8] These polymers can be cationic, anionic, or neutral. Additionally, they may contain plant lectins, such as tomato lectins, which recognize and bind to sugar residues in the mucus layer or glycocalyx.

Advantages:

Mucoadhesive drug delivery techniques have a number of advantages over conventional oral controlled-release formulations because they prolong the medication's residence time in the gastrointestinal tract (GIT).

1.locating and directing the dose form to a certain location. [19]
2. Additionally, it is well known that mucoadhesive systems create close contact between the absorptive mucosa and the dose form, which increases drug flux at the absorbing tissue.[19]

Conclusion:

These systems provide a number of benefits over conventional drug delivery, including; low risk of toxicity,impoves patient compliance,no risk of dose dumping, release of predefined and rate-controlled medication.

The gastroretentive technique can effectively administer active drugs using biodegradable polymeric polymers, leading to improved treatment outcomes.

These devices release drugs in a regulated manner and offer them in absorbable form at optimal absorption sites.

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