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GASTRORETENTIVE DRUG DELIVERY SYSTEMS: AN INNOVATIVE APPROACH TO ENHANCE ORAL DRUG BIOAVAILABILITY

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ABSTRACT

An Dosage forms with controlled release have been widely utilised to enhance treatment with a number of significant medications. Nevertheless, a number of physiological challenges face the development processes, including the incapacity to confine and localise the system inside the intended gastrointestinal tract region and the extremely variable nature of the gastric emptying process. In considering the possibility that this variability could result in erratic bioavailability and durations to reach peak plasma levels, gastroretentive drug delivery systems (GRDDS) have become a ground-breaking innovation in the pharmaceutical sciences. By extending the period that medications taken orally dwell in the stomach, these systems allow for more controlled release and improved bioavailability. This article thoroughly examines the several kinds of gastroretentive drug delivery systems, as well as their benefits, drawbacks, and uses in enhancing the therapeutic efficiency of different medications.

KEYWORDS: GRDDS, Bioavilability, oral route, gastric residence.

1. INTRODUCTION

The most practical and recommended method of distribution to the systemic circulation is oral administration. The pharmaceutical industry has recently shown a growing interest in oral controlled release drug delivery as a means of achieving better therapeutic benefits,

including patient compliance, convenience of dosage administration, and formulation flexibility. Medications with a short half-life and easy absorption from the gastro intestinal tract (GIT) are rapidly removed from the systemic circulation. For these medications to have therapeutic effect, frequent administration is necessary. The creation of oral sustained controlled release formulations is an attempt to circumvent these restrictions by releasing the medicine gradually into the gastrointestinal tract and preserving an effective drug concentration in the systemic circulation for an extended period of time. In order to continually supply the medicine to its absorption location in the gastro intestinal tract after oral administration, such a drug delivery would be retained in the stomach and released in a regulated manner.[1] Drug administration methods that are gastroretentive have the ability to completely change how medications are given and absorbed by the body. By guaranteeing that medications stay in the stomach for a prolonged amount of time, These systems are intended to overcome the drawbacks of traditional oral drug administration. This article explores the several kinds of gastroretentive drug delivery systems, including their benefits, drawbacks, and uses. The gastric residence period of medications is further extended by gastro retentive devices, which can stay in the stomach area for several hours. Extended stomach retention increases the solubility of medications that are less soluble in high pH environments, decreases drug waste, and increases bioavailability. It can also be used to administer local medications to the stomach and the first segment of the small intestine.[5] Better accessibility to novel products with novel therapeutic potential and significant patient benefits is facilitated by gastro retention.

1.1 Adavntage of Gastroretentive drug delivery system[6,13]

1. **Better Absorption:** GRDDS helps keep medications in the stomach for a longer amount of time, improving bioavailability. This is especially beneficial for medications with limited upper gastrointestinal absorption windows. GRDDS improve drug absorption and bioavailability by lengthening the time the drug spends in the stomach, which produces more reliable and effective therapeutic results.
2. **Less Variability:** The variability in drug absorption across persons and within the same individual at different times is one of the problems with conventional drug delivery. By ensuring that the medicine is delivered and absorbed in a controlled manner, GRDDS minimise variability both within and between individuals. Because of this, drug levels in the bloodstream become more consistent, which is important for medications with limited therapeutic ranges. Controlled Drug Release: GRDDS enable controlled and sustained

drug release. This not only improves patient compliance by reducing the frequency of dosing but also minimizes potential side effects associated with rapid drug release. Controlled drug release ensures a more stable and prolonged therapeutic effect.

3. **Improved Local Drug Delivery:** Mucoadhesive GRDDS are especially useful for medications that target problems in the upper small intestine or stomach. Adhering to the gastrointestinal mucosa, these devices provide precise and long-lasting administration of medication to the intended site of action. This is advantageous for medications used to treat Helicobacter pylori infections and peptic ulcers.
4. **Decreased First-Pass Metabolism:** GRDDS can decrease first-pass metabolism by prolonging the stomach residence duration. This is particularly important for medications that need to be extensively metabolised in the liver in order to enter the bloodstream. Less first-pass metabolism means that more of the medication reaches the desired site of action.
5. **Enhanced Therapeutic Effect:** A more robust therapeutic effect is frequently the consequence of combining extended medication release with enhanced bioavailability. GRDDS has the potential to increase drug efficacy, which is especially beneficial for illnesses where treatment efficacy is crucial.
6. **Personalised Medicine Prospects:** Scientists are investigating the creation of intelligent, flexible GRDDS that can adjust to the specific requirements of each patient. This makes way for personalised medicine, in which the administration of medications is adjusted to meet the unique needs of each patient, thereby improving the course of treatment. Expanded Range of Drug Candidates: GRDDS can make drugs that were previously considered challenging for oral delivery more viable candidates. This includes drugs with poor solubility, low permeability, or those prone to degradation in the gastrointestinal environment.
7. **Improved Patient Compliance:** GRDDS's controlled and prolonged release of medications lowers dosage frequency, which makes it simpler for patients to follow their prescribed treatment plans. This may significantly affect how well pharmacological therapy work as a whole.
8. **Applications Specific to Diseases:** GRDDS can be modified to meet the needs of particular illnesses or ailments. This flexibility makes it possible to create customised medication delivery systems that maximise the effectiveness of treatment for a range of illnesses.

1.2. Disadvantage of Gastroretentive drug delivery system[6,13]

1. **Variability in Gastric Emptying:** Extended stays in the stomach are the nature of gastroretentive systems. However, diet, posture, and patient variability are just a few of the variables that affect the intricate process of stomach emptying. This can result in irregularities in the release and absorption of the medicine, which makes it difficult to guarantee steady therapeutic effects.
2. **Limited Usage for Drugs Absorbing Quickly:** GRDDS work best for medications whose absorption in the upper gastrointestinal tract is irregular or delayed. Retaining medications in the stomach for short periods of time may not be beneficial and may increase the risk of adverse effects and unwanted drug exposure.
3. **Bezoar Risk:** Bezoars are hard masses of undigested material that might clog the gastrointestinal tract. They can be formed by gastroretentive systems, especially those based on high-viscosity polymers or other materials. This may cause discomfort and necessitate medical attention.
4. **Gastric Irritation and Ulceration:** In sensitive people, certain gastric irritant drug delivery systems may cause discomfort or ulcers on the gastrointestinal mucosa. It's critical to take into account the materials' safety as well as any possible effects on the stomach lining while evaluating these systems.
5. **Patient Compliance:** GRDDS frequently call for patients to take bigger dosage forms, which can be difficult for some people to take, especially for those who have trouble swallowing pills or capsules. This may have an impact on the patient's compliance and adherence to the recommended drug schedule.
6. **Complexity of Development and Manufacturing:** Creating and producing gastroretentive medication delivery devices can be expensive and time-consuming. This could restrict their uptake, especially for generic medications or ones with little room for profit.
7. **Limited Applicability:** Not all medications or therapeutic applications are a good fit for gastro retentive systems. Their usefulness is mostly observed in medications with particular indications and absorption characteristics. Alternative drug delivery methods can be more suitable for some treatments.
8. **Potential for Incomplete Drug Release:** The medication may not always exit the gastroretentive system evenly, which could result in incomplete drug release and less than ideal treatment results.

1.3. Need for Gastroretentive drug delivery system

- The pharmaceutical industry frequently uses conventional oral administration to treat illnesses. However, there are a number of problems with traditional delivery, the main one being non-site specificity. Certain medications only absorb at a particular location. They demand a release at a specified location or one that ensures the maximum quantity of medicine reaches the designated location.[7]
- The pharmaceutical industry is currently concentrating on these medications that need to be site-specific.
- One site-specific method for delivering medications to the stomach or intestines is gastro-retentive delivery. It is achieved by keeping the dose form in the stomach, and the medication is then delivered gradually to a predetermined location in the stomach, duodenum, or intestine.[7,8]

2. Types of Gastro Retentive Drug Delivery System

1. High density systems
2. Floating systems

a. Depending upon the effervescence generation

i. Effervescent system
ii. Non effervescent system

b. Depending upon the system

i. Monolithic system
ii. Multiple unit system

c. Other

i. Low density system
ii. Raft forming system

3. Expandable systems
4. Superporous hydrogels
5. Mucoadhesive or bioadhesive systems
6. Magnetic systems
7. Dual working systems.

1. High density system

The stomach's rugae include these systems, which can endure the peristaltic movements of the stomach and have a density of about 3 g/cm3. Such systems can be held in the lower stomach region over a threshold density of 2.4–2.8 g/cm3. The idea behind the formulation of heavy pellets is that due to their larger density, the pellets may end up in the lower portion of the antrum. Usually, they are composed of steel or another dense substance. The primary drawbacks of this strategy are that the system's functionality depends on the condition of the stomach and that quite massive and hefty structures are required to achieve the intended result.[9]

2. Floating system

Low-density systems with enough buoyancy to float above the contents of the stomach and stay there for an extended amount of time are known as floating systems; Davis first characterised them in 1968. The medicine is given gradually at the correct rate while the apparatus hovers above the stomach contents, increasing GRT and minimising fluctuations in plasma drug concentration.

2.1. Classification of FDDS

Various categories can be used to group floating systems. They are divided into two categories: effervescent and non-effervescent systems based on gas generation, and single unit or monolithic systems and multiple unit systems based on the number of units in the system. Conversely, raft forming/in situ gelling systems and low density are two other FDDS classifications.

a. Depending upon the Effervescence Generation

i. Effervescent system

An inert gas can be introduced into the floating chamber by the volatilization of an organic solvent or by the CO2 produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts. This will allow a drug delivery system to float in the stomach. These devices have a hollow, malleable element that can be extended or deflated, and it can return to the collapsed state after a pre-set period of time, allowing the inflatable system to exit the stomach on its own.[10] The operation of an effervescent floating medication delivery system is explained and a multiple-unit oral floating drug delivery system is depicted in Figure 1.

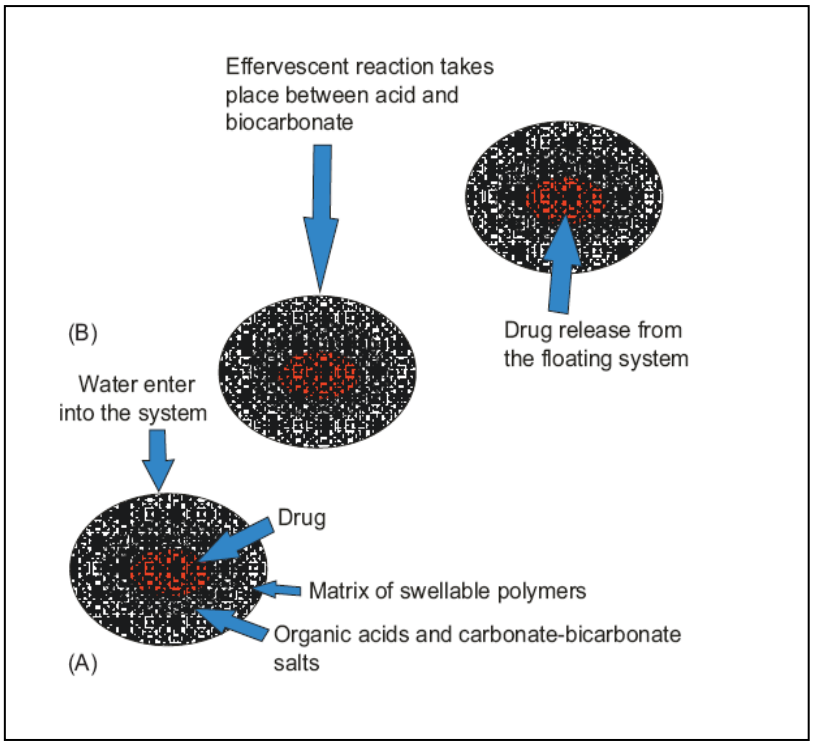

Fig. 1: (A) Multiple-unit oral floating drug delivery system. (B) Working principle of effervescent floating drug delivery system.

Utilising matrices made of swellable polymers (such as methocel), polysaccharides (such as chitosan), effervescent substances (such as sodium bicarbonate, citric acid, and tartaric acid), or chambers filled with a liquid that gasifies at body temperature are some examples of these buoyant structures. These systems are typically prepared using resin beads coated in ethyl cellulose and loaded with bicarbonate. Water is possible to permeate the insoluble but porous covering. Because of the release of carbon dioxide, the beads float in the stomach.

ii. Non Effervescent system

Hydrocolloids such as gel-forming or swellable cellulose, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene are used in non-effervescent floating dosage forms. The medicine and the hydrocolloid that forms gel are fully mixed as part of the straightforward formulation process. This dosage form swells in contact with gastric juices after oral administration, reaching a bulk density of less than 1. The dose form is buoyant due to the air trapped inside the inflated matrix. Through the gelatinous bulk, the resulting swelling gel-like structure serves as a reservoir for the drug's continuous release.[11]

b. Depending upon the Number of Units

i. Monolithic system

When effervescent materials are mixed with a hydrophilic polymer to create single unit systems like capsules or tablets, CO2 bubbles are retained within the swelling matrix. Single unit dose forms are another name for monolithic dosage forms. When creating indigestible solid dosage forms (single unit systems), size is particularly crucial. The diameter of the human pylorus is 12±7 mm. The stomach secretes solids gradually and on a regular basis. Interdigestive Migration Myoelectric Complex (IMMC) peristaltic waves are used to remove indigestible items, such as solid medicinal dosage forms. Particles less than 7 mm are effectively removed, and it is widely acknowledged that a diameter larger than 15 mm is required for a meaningful extension of retention, particularly when fasting.[12,13]

ii. Multiple unit floating system

Among the many floating systems are microsphers, microbeads, microballoons, and so on. When using dose forms with multiple units, gastric emptying usually occurs at a pulsatile rate as well as a steady rate of passage, provided the units are smaller than the pyloric sphincter (i.e., less than 1 mm in diameter). Because particles act somewhat independently, it is hypothesised that in the event of floating multiple-unit dose forms, the bulk of particles will stay above stomach contents for an extended period of time. The statistical repartition of several unit systems, like those based on microparticles, prevents the gastrointestinal tract from emptying completely or nothing at all. But it's crucial that the units don't combine into a mass that floats at the top of the stomach, but rather stay scattered and suspended separately in the gastric fluid.[13]

c. Other classification

i. Low density system

The lag period that low density systems invariably experience before floating on the contents of the stomach can cause the dose form to prematurely pass through the pyloric sphincter. Thus, devices with instantaneous buoyancy and low density (< 1 g/cm3) have been produced. Because of their low density construction, they can trap air or oil.[14]

ii. Raft-forming systems

In this case, when coming into contact with gastric juice, a gel-forming solution (such as a sodium alginate solution containing carbonates or bicarbonates) swells and produces a thick cohesive gel containing entrapped CO2 bubbles. Antibiotics and antacids, such as calcium

carbonate or aluminium hydroxide, are frequently added to formulations to lessen stomach acidity. Raft-forming systems are frequently used to treat gastroesophageal reflux disease because they create a layer on top of gastric fluid. Raft forming systems have drawn a lot of interest in the administration of medications for gastrointestinal infections and other conditions, as well as antacids. The mechanism underlying the creation of the raft involves the formation of a cohesive gel that is viscous when it comes into contact with stomach fluids. Each part of the liquid expands to form a continuous layer known as a raft. Because CO2 production results in a low bulk density, this raft floats on gastric fluid. To make the system less dense and more able to float on the stomach juices, the system typically consists of an alkaline bicarbonate or carbonate responsible for the generation of CO2 and a gel-forming agent.[14,15]

3. Expandable system

Expandable dosage forms offer a way to create a drug delivery system that is both too big to be eaten and small enough to go past the pylorus. According to reports, the pylorus has a wide range of diameters in individuals, ranging from 12.8 to 7.0 mm. However, because the pylorus is a sphincter muscle, it can expand in response to pressure applied to it. The end effect is that under powerful migrating myoelectric complex contractions, even huge dosage forms can pass from the stomach. The dosage form needs to be strong in at least two dimensions and large (larger than roughly 20 mm) in order to prevent this. Among the difficulties with this strategy are the dangers of releasing anything too quickly or slowly. Severe difficulties may arise if the dose form becomes lodged in the oesophagus while swallowing. A medication may be incorporated as an independent part of the gastroretentive system or it may be enclosed in its polymeric composition.[16,34] A number of techniques were proposed to enable the self-unfolding effect:

1. Hydrogels that expand when in contact with gastric juice are one method
2. Osmotic systems consisting of an osmotic medium within a semipermeable membrane.
3. Systems utilising low-boiling liquids that turn into gases at body temperature, giving the system the desired volume and facilitating drug release.

4. Superporous hydrogels

These systems are swellable, yet they differ enough from the traditional varieties to be classified differently. Because the pore size of traditional hydrogels ranges from 10 nm to 10 μm, the process of absorbing water is very sluggish. It may take several hours to reach an

equilibrium condition, during which the dosage form may evacuate prematurely. With an average pore size of more than 100 μm, superporous hydrogels expand to equilibrium in less than a minute as a result of fast water absorption through capillary wetting through several connected open pores. Additionally, they grow to a huge size and are designed to be strong enough to endure the pressure caused by the contraction of the stomach.[17,18]

5. Mucoadhesive system

Mucoadhesive systems are designed to adhere to the gastric mucous membrane with the goal of extending the GRT. Certain natural or synthetic polymers' bioadhesion on soft tissues has been used to regulate and extend the delivery systems' stomach retention. The polymers' adherence to the mucosal membrane can be facilitated by receptor-mediated adhesion, bonding, or hydration. The hydrophilic polymers in hydration-mediated adhesion hydrate and become mucoadhesive and sticky. Chemical or mechanical bonding may be involved in bonding-mediated adhesion. Van der Waals forces, covalent bonds, or ionic bonds between the polymer molecules and the mucous membrane are examples of chemical bonding. Certain polymers and particular receptors produced on stomach cells bind together through a process known as receptor-mediated adhesion. It's possible that the polymers are anionic, catonic and neutral.[26,27,35]

6. Magnetic system

These devices resemble tiny, gastroretentive capsules that contain a magnetic substance that, when in contact with a powerful enough magnet applied to the stomach's surface, prevents the substance from being eliminated from the stomach. The true usefulness of such systems is questionable despite multiple reports of successful tests, as the necessary effects can only be obtained if the magnet position is selected with extremely high precision. The magnetic dosage forms have an extra-corporal magnet that regulates the dosage form's gastrointestinal transit in addition to a tiny internal magnet. These devices appear to function, however patient compliance may be jeopardised by the need for precise positioning of the external magnet.[28,29,36]

7. Dual working system

The two operating principles of these systems are either swelling and bioadhesion or floating and bioadhesion. FDDS are designed to stay afloat in the gastric fluid after a meal when the stomach is full. Nevertheless, the dosage form's buoyancy may decrease when the stomach empties and the tablet enters the pylorus. It's possible that the dose form will enter the small

intestine after passing via the pylorus. As a result, an FDDS's buoyancy in the stomach might only last for three to four hours. Moreover, medication is not always released by floating devices at the desired location.[31] When a bioadhesive drug delivery system is full and its semiliquid contents are swirling about because of peristalsis, it is quite likely that the system may come loose from the stomach mucosa wall. The disadvantages of bioadhesive, swelling, and floating systems would be eliminated by a dual functioning system, which would also significantly enhance the therapeutic efficacy of the relevant medication.[19,20,21,36]

3. Applications of Gastroretentive Drug Delivery Systems

- Anti-ulcer Drugs: GRDDS work well with medications such proton pump inhibitors that treat peptic ulcers.
- Antiretroviral Drugs: By increasing the bioavailability of these medications, their therapeutic impact is enhanced.[32]
- Controlled Release Formulations: GRDDS is advantageous for extended-release formulations of several therapeutic classes, including opioids for pain relief.[33]
- Local Drug Delivery: Antibiotics for H. pylori infections, for example, can be specifically delivered to the upper gastrointestinal tract using mucoadhesive GRDDS.[21,22,23]

4. Future Perspectives

The subject of gastroretentive treatment delivery systems is always changing due to ongoing research and improvements in technology. Future directions involve investigating applications in personalised medicine and creating intelligent, responsive systems that can adjust to the specific needs of each patient.

5. CONCLUSION

One intriguing method to get around the drawbacks of traditional oral medicine delivery is the use of gastroretentive drug delivery devices. For a variety of medications, these systems provide increased therapeutic efficacy, regulated release, and higher bioavailability. Despite obstacles, further study and innovation in this area should lead to more efficient treatments and improved patient results.

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