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AN OVERVIEW ON GASTRORETENTIVE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The development of oral controlled release and site-specific drug delivery systems has attracted considerable attention in the pharmaceutical industry to provide enhanced therapeutic benefits. The process of drug absorption within the gastrointestinal tract is highly unpredictable, and extending the gastric retention time of the dosage form increases the duration for drug absorption. A gastro retentive drug delivery system represents one of the innovative strategies aimed at prolonging the time a drug remains in the stomach, thus facilitating targeted drug release for both local and systemic effects. This strategy is particularly advantageous for medications that have a limited absorption window in the upper portion of the gastrointestinal tract. Various methods for gastro retentive drug delivery systems, including both floating and non-floating approaches, are explored in this review. Additionally, this review outlines the advantages, disadvantages, and evaluation criteria associated with gastro retentive systems.

KEYWORDS: Gastro retentive drug delivery system, non-floating system, floating system, evaluation parameters.

INTRODUCTION

In spite of significant progress in drug delivery technologies, the oral route remains the most favored method for achieving systemic circulation because of its ease of use, low cost, patient adherence, and formulation adaptability. Approximately 90% of all medications intended for systemic effects are delivered orally. Among orally administered medications, solid oral dosage forms are the most commonly utilized category of products. Tablets are the

predominant form of solid dosage used today, categorized based on their drug release mechanisms, specifically into conventional immediate release and modified release types. The conventional immediate release tablets possess various limitations, including non-specific drug release sites. However, numerous drugs are absorbed at specific locations within the gastrointestinal tract and necessitate localized release to enhance absorption.

Drug absorption within the gastrointestinal tract is a highly unpredictable process influenced by various factors such as the rate of gastric emptying, gastrointestinal transit duration of dosage forms, the release of the drug from its formulation, and the sites within the GIT where drugs are absorbed. Medications that are readily absorbed in the gastrointestinal tract and have short half-lives are quickly eliminated from systemic circulation, requiring frequent dosing to maintain effective therapeutic levels. Additionally, drugs with a narrow absorption window in the upper sections of the GIT are ill-suited for oral sustained release drug delivery systems due to their short duration of action.

The time it takes for gastric emptying of tablets is approximately 2.7 ± 1.5 hours (h) for stomach transit and 3.1 ± 0.4 h for intestinal transit.[6] hence the bioavailability of drugs that primarily absorb in the stomach is often limited. A gastro-retentive drug delivery system is one strategy to extend the time drugs spend in the stomach, thereby allowing for targeted drug release that can have local or systemic effects. These dosage forms can stay in the stomach for extended durations, significantly increasing the retention time of drugs in this area. They deliver the drug in a controlled manner within the stomach, ensuring a continuous supply to the absorption site in the gastrointestinal tract (GIT), specifically the stomach.[7]

In 1968, Davis first introduced the idea of a floating drug delivery system after noticing that some individuals had difficulty swallowing pills. To resolve this issue, he created pills with a density lower than 1 gm/ml, allowing them to float on the surface of water. Since then, various methods have been proposed for creating optimal floating delivery systems.[8] Scientific literature indicates that there is a growing interest in innovative dosage forms that can remain in the stomach for an extended and reliable duration in both industrial and academic settings.[9]

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM (GRDDS)

1. The GRDDS offers several benefits.
2. Increased bioavailability: The drugs that absorb in the upper section of the gastrointestinal

tract, such as riboflavin and levodopa, have shown significant improvements in bioavailability compared to traditional dosage forms.[10, 11]

3. Prolonged drug delivery and fewer dosages, which enhances patient adherence to treatment.

4. Targeted drug delivery at the upper gastrointestinal tract, making it effective for local treatments of various conditions in that area, such as antacids, anti-ulcer medications, and antibiotics for H. pylori infections.[5,12]

5. Suitable for drugs that have pH-dependent absorption from the stomach, like Furosemide.[13] Captopril.[14] Diazepam, Verapamil, and Cefpodoxime proxetil.[15] Also suitable for drugs that degrade in the intestine or colon.[16] such as Ranitidine hydrochloride.

6. Minimal drug level variations are observed, helping to maintain optimal therapeutic plasma and tissue concentrations over an extended period. This helps avoid sub-therapeutic doses and toxic levels, thus reducing the risk of medical treatment failures and undesirable side effects.

Other drawbacks associated with specific types of GRDDS are given the table below [17]:

Technology	Drawbacks
High density system	Very difficult to incorporate large amount of drugs. No such systems are available in the market till date
Floating system	Floating highly depends on the fed state of the stomach and higher level of fluid is required in gastric region
Expandable system	Chocking problem; storage problem due to hydrolysable and biodegradable polymers; difficult to manufacture and not economical
Mucoadhesive system	Can be detached from gastric mucosa due to rapid turnover of mucus and peristaltic wave of stomach. It may also attach to the mucus of oesophagus
Magnetic system	Problem with patient compliance

ELEMENTS INFLUENCING GASTRIC DRUG DELIVERY SYSTEMS

1. Numerous elements can impact the gastric emptying process, which can significantly influence the release and absorption of a drug, making it essential to create a drug delivery system that maintains prolonged gastric retention and a drug release profile that is not influenced by patient-specific factors.[18]

2. The elements that influence gastric emptying and subsequently the retention of drugs in the stomach include:

3. The state of the stomach—whether fasting or fed: In a fasting state, a series of inter-digestive electrical events occur, cycling through both the stomach and intestines every two to three hours. Conversely, in a fed state, this cycle is prolonged, resulting in a slower gastric emptying rate.[19]

4. The density, size, and shape of the drug formulation.[20, 21, 22]

5. The interaction of food intake with drugs: The type of food, its caloric value, and the frequency of consumption significantly affect how long drugs remain in the stomach.[23, 24]

6. The simultaneous administration of certain medications, such as anticholinergic drugs (e.g., atropine, propantheline) and opiates, tends to delay gastric emptying, while prokinetic agents like metoclopramide and cisapride promote faster gastric emptying.[25, 26]

7. Biological factors including gender, body position, age, sleep patterns, body mass index, levels of physical activity, and medical conditions such as diabetes and Crohn's disease.[27,20,28]

VARIOUS METHODS OF GRDDS

Various methods have been employed to enhance the retention of oral dosage forms within the stomach. Some are designed as single-component formulations, while others consist of multiple components. GRDDS can be generally classified into floating and non-floating systems.

A. Non-floating system: These gastro-retentive drug delivery systems do not float in the stomach; instead, they remain there through various mechanisms. The non-floating system can be further categorized into:

a. High-density (sinking) drug delivery system

b. Bioadhesive or mucoadhesive system

c. Magnetic system

d. Unfoldable system

B. Floating drug delivery system (FDDS): Unlike high-density drug delivery systems, floating systems have a density that is lower than that of gastric contents, allowing them to remain buoyant in the stomach for an extended duration without influencing the gastric contents. Floating drug delivery systems are also referred to as low-density systems. Figure 1 illustrates the mechanism by which this system achieves buoyancy.

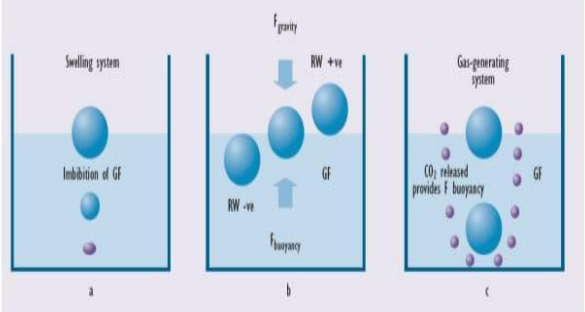

Figure: The mechanism of floating system.[9]

A floating drug delivery system can be categorized into

a. Effervescent system.

b. Noneffervescent system

i. Hydrodynamically balanced system

ii. Microbaloons or hollow microspheres

iii. Alginate beads

iv. Microporous compartment

A. Non-floating system

a. High Density (Sinking) Drug Delivery System

In this method, formulations are designed by coating the drug onto a dense core or mixing it with substances like iron powder, barium sulfate, zinc oxide, and titanium oxide so that the formulation's density exceeds that of standard gastric contents.[29] These components can increase density up to 1.5-2.4 gm/cm³. Based on density, the gastrointestinal transit duration of pellets can range from an average of 5.8 to 25 hours. However, the effectiveness of this system in humans has not been demonstrated.[30] and no products have been commercially available.

b. Bioadhesive or mucoadhesive system

The residence time in the stomach is enhanced by attaching the bioadhesive system to the gastric mucosal membrane (Fig. 2). The adhesion of the delivery system to the stomach wall extends its residence time and thereby enhances bioavailability. Substances used for mucoadhesion include polycarbophil, carbopol, lectin, chitosan, carboxy methyl cellulose, and gliadin, among others.[31] Innovative adhesive materials derived from bacterial fimbriae or their synthetic equivalents have also been explored for attaching to the gut.

Nonetheless, the mucoadhesive force in the stomach is typically insufficient to withstand the propulsion force of the stomach wall. The ongoing production of mucus and the dilution of gastric contents pose additional challenges for this type of system. Many researchers have attempted to combine floating and bioadhesion systems for synergistic effects.

c. Magnetic system

This system incorporates a small magnet within the dosage form, while an additional magnet is placed externally on the abdomen over the stomach area. Precise placement of the external magnet is crucial, which may reduce patient compliance.

d. Unfoldable system

The drug delivery mechanism expands and increases in size, remaining lodged at the sphincter to prevent its exit from the stomach (Fig. 3 and 4). The system must be small enough to be ingested but should unfurl upon contact with gastric fluid, then revert to a smaller size after a set duration to facilitate easy evacuation. Unfoldable systems are composed of various biodegradable polymers.

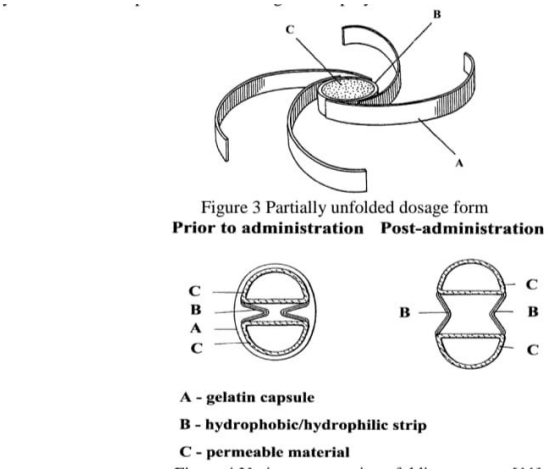

Figure: Various geometric unfolding systems.[11]

B. Buoyant Drug Delivery System

a. Effervescent System

This system incorporates swellable polymers such as chitosan and effervescent agents like sodium bicarbonate, disodium glycine carbonate, cytroglycine, citric acid, and tartaric acid. Upon contact with gastric fluids, the system generates carbon dioxide, which enables the formulation to remain buoyant in the stomach.[32] The ideal ratio of citric acid to sodium bicarbonate for optimal gas production is reported to be 0.76:1.[9] This system is further

categorized into single unit matrix tablets or multiple unit capsules. A single unit matrix tablet may be either of single layer or multilayer design. There are also reports of floating systems using ion exchange resins. Figures 5 and 6 illustrate the effervescent system and the drug release from such a system, respectively.

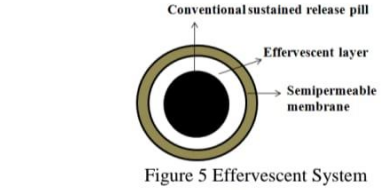

Figure 5 Effervescent System

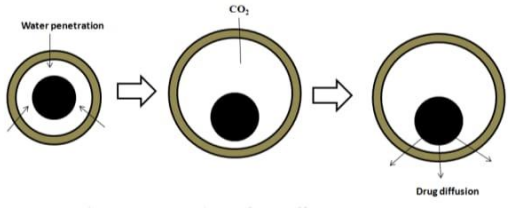

Figure: Drug release from effervescent system.

b. Non-effervescent system

This system utilizes gel-forming or highly swellable hydrocolloids made from cellulose, polysaccharides, and polymers that form matrices, including polycarbonate, polyacrylate, polymethacrylate, and polystyrene. Upon oral intake, this dosage form expands upon encountering gastric fluids and achieves a bulk density of less than 1. The air trapped within the expanded matrix provides buoyancy to the dosage form. The resultant swollen gel-like structure serves as a reservoir and facilitates the sustained release of the drug through the gelatinous mass. An excellent illustration of this approach is superporous hydrogels. The dosage form swells dramatically to several times its initial volume when it comes into contact with gastric fluid, and the contractions of the stomach propel the dosage form towards the pylorus. However, due to the larger size of the dosage form, these contractions glide over its surface, causing the dosage form to be pushed back into the stomach.[33]

Figure: Gastric retention of highly swellable gastro retentive drug delivery system.[34]

The non-effervescent system can be further categorized into hydrodynamically balanced systems, microballoons, alginate beads, and microporous compartments.

i. Hydrodynamically balanced system: The hydrodynamically balanced system (HBS) was initially developed by Sheth and Tossounian.[35] HBS comprises the drug along with gel-forming hydrocolloids that are designed to stay buoyant on the contents of the stomach. This system incorporates one or more gel-forming cellulose-based hydrocolloids, such as hydroxypropyl methyl.

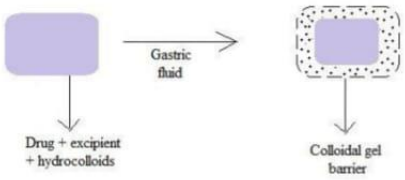

Figure: Hydrodynamically balanced system.

ii. Microballoons or hollow microspheres: Hollow microspheres (microballoons), which contain a drug within their outer polymer shells, are created using the emulsion-solvent diffusion technique. The procedure for this technique is summarized in figure 9. A solution of ethanol and dichloromethane in a 1:1 ratio, along with an acrylic polymer, is added to an agitated aqueous solution of polyvinyl alcohol at a temperature of 40°C. The gas phase produced within the dispersed polymer droplet as the dichloromethane evaporates leads to the formation of an internal cavity in the polymer microsphere, which encapsulates the drug. The microballoons remain buoyant on the surface of acidic dissolution media containing surfactant for over 12 hours.[36]

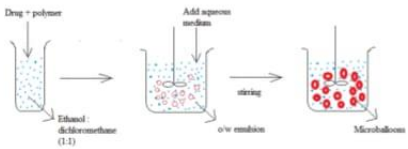

Figure: Preparation of microballoons.

iii. Alginate beads: Freeze-dried calcium alginates have been utilized to create multi-unit floating dosage forms. By introducing a sodium alginate solution into a calcium chloride aqueous solution, spherical beads approximately 2.5 mm in diameter can be formed. These beads are then separated and air-dried, resulting in a porous structure that remains buoyant in the stomach.

iv. Microporous chamber: In this system, a drug reservoir is enclosed within a microporous compartment that has pores on both its top and bottom surfaces. The air trapped within the

floatation chamber allows the delivery system to remain afloat above the gastric contents. Gastric fluid passes through the openings, dissolves the drug, and facilitates the transport of the dissolved drug to the stomach and the early part of the small intestine for absorption.

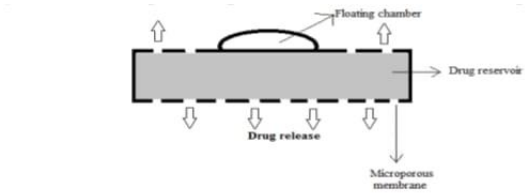

Figure: Microporous compartment.

POTENTIAL CANDIDATES FOR GASTRO RETENTIVE DRUG DELIVERY SYSTEMS

1. Below are potential candidates, though not exhaustive, for gastro retentive drug delivery systems:
2. Medications needed for local therapeutic effects in the stomach include antacids, agents targeting H. pylori, and misoprostol.[24]
3. Medicines with a narrow absorption window in the stomach or upper sections of the small intestine include furosemide.[38] riboflavin-5-phosphate.[39] metformin hydrochloride.[40] ciprofloxacin.[41] alfuzosin hydrochloride.[42] ofloxacin.[43] norfloxacin.[44] and domperidone.[45] among others.
4. Drugs that disrupt normal colonic flora include amoxicillin trihydrate.[46]
5. Medications that are unstable in the lower gastrointestinal tract include captopril.[47]
6. Drugs that are insoluble in intestinal fluids consist of quinidine and diazepam.[48]
7. Medications that degrade in the colon include ranitidine hydrochloride.[49] and metronidazole.[50]

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Medications needed to provide localized therapeutic effects in the stomach include antacids, anti-H. pylori agents, and misoprostol.[24]

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EVALUATION PARAMETERS OF GRDDS

The evaluation parameters for GRDDS typically encompass

1. Interaction between drug and excipient

This is assessed using FTIR and HPLC. The emergence of a new peak or the disappearance of initial drug or excipient peaks indicates interaction between the drug and excipient.

2. Floating lag time

This refers to the duration taken for the tablet to float to the surface after being placed in the dissolution medium. It is measured in either minutes or seconds.

3. In vitro drug release and duration of floating

This is evaluated utilizing the USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at 37±2°C in simulated gastric fluid with a pH of 1.2. Samples are withdrawn for analysis of drug content. The time the drug stays afloat on the surface of the medium represents its floating duration.

4. In vivo evaluation of gastric retention

The evaluation of the location of the dosage form within the gastrointestinal tract involves imaging techniques like γ-scintigraphy and X-ray.

For γ-scintigraphy, a small quantity of stable isotope is integrated into the dosage forms during preparation. The incorporation of a γ-emitting radio-nuclide in a formulation permits indirect external observation utilizing a γ-camera or scintillation scanner.

In the case of X-ray, barium sulfate serves as a contrast agent. It aids in identifying the dosage form in the gastrointestinal tract, facilitating predictions and correlations regarding

gastric emptying time and dosage form transit.

Moreover, gastroscopy and ultrasonography studies may be included in the in vivo assessment of GRDDS. Gastroscopy involves per-oral endoscopy, employing fiber optics and video systems. Ultrasonography is not commonly employed in GRDDS evaluation. In vivo plasma profiles can.

5. Water uptake study

This is performed by submerging the dosage form in simulated gastric fluid at 37°C and measuring dimensional changes, such as diameter and thickness, at regular intervals. After the designated time, the swollen tablets are weighed, and water uptake is expressed as a percentage weight gain, calculated as:

WU = (Wt - Wo) × 100/Wo; where Wt refers to the weight of the tablet after time t and Wo represents the initial weight.

Additionally, tablets are assessed for hardness, friability, and weight variation, which are relevant for standard immediate-release tablets. For multiple-unit dosage forms like microspheres, several tests are essential alongside the above assessments:

1. Morphological and dimensional analysis: This is conducted utilizing scanning electron microscopy and optical microscopy.
2. Percentage yield of microspheres.
3. Entrapment efficiency: The drug is extracted through an appropriate method and analyzed to determine the quantity of drug present. also be acquired by conducting studies in appropriate animal models.

CONCLUSION

Recent years have seen significant exploration of gastro-retentive drug delivery systems. GRDDS holds the promise for enabling a reduction in dosing frequency for numerous medications while providing clear advantages for drugs that have a narrow absorption window in the stomach and/or upper intestine. Nonetheless, various challenges still need to be addressed to fully realize the advantages of this system. Despite this, many researchers continue to strive for optimal use of this technique, with some achieving success and others encountering failures due to the unpredictable nature of the human gastrointestinal tract. Therefore, to create an effective GRDDS, it is crucial to consider the physiological processes

in the gastrointestinal tract, choose appropriate combinations of drugs and excipients, and establish suitable formulation strategies.

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