INTRODUCTION

The GRDDS is a controlled drug delivery system that aims to improve clinical effectiveness and minimize toxicity by providing a coordinated and predetermined release rate of drugs. It represents a departure from conventional drug delivery systems and offers distinct advantages, particularly in addressing the limitations of oral drug delivery.

One of the major challenges in oral drug delivery is the low bioavailability and poor permeability of certain drugs, often due to their limited solubility. However, GRDDS has been shown to overcome these drawbacks and enhance the therapeutic efficacy of orally administered drugs. By prolonging the retention time of the dosage form in the gastrointestinal tract, it ensures more efficient drug absorption and distribution. The gastro-retentive approach is primarily employed for orally administered drugs and leverages the increased gastro-retentivity of the dosage form. This means that the drug delivery system is designed to remain in the stomach for an extended period, allowing for controlled drug release and absorption. It achieves this through various mechanisms, such as buoyancy, bio-adhesion, swelling, or expansion. By maintaining the drug within the stomach, the GRDDS offers several advantages.

Firstly, it enhances the bioavailability of drugs with poor solubility or low permeability by facilitating their prolonged exposure to the absorbing surfaces in the gastrointestinal tract. Secondly, it enables localized drug delivery to specific regions within the gastrointestinal tract, which can be beneficial for drugs targeting specific sites or diseases. Additionally, it reduces the frequency of drug administration, improves patient compliance, and minimizes potential side effects. The development and optimization of GRDDS involve a thorough understanding of the physicochemical and biological parameters related to the drug, as well as the design and formulation of the drug delivery system. Pharmaceutical scientists worldwide have been actively involved in researching and developing innovative...
approaches to create effective and safe gastro-retentive drug delivery systems. Overall, the GRDDS represents a promising advancement in drug delivery technology, offering the potential for improved clinical outcomes and reduced toxicity. Its ability to overcome the limitations of conventional oral drug delivery systems makes it an important area of research and development in the field of pharmaceutical sciences.

**Benefits**
- Enhance the therapeutic efficacy and bioavailability.
- Change in portion size.
- Improved drug solubility for drugs like domperidone, which are not particularly soluble in a pH environment.
- Decrease drug waste.
- Designated drug conveyance to the small digestive system and stomach.

**Stomach Physiology**
Understanding the anatomy and physiology of the stomach is indeed crucial in the development and functioning of the GRDDS. The stomach can be divided into two distinct anatomical sections: the proximal (upper) and distal (lower) stomach. The proximal stomach consists of the body and fundus, which serve as reservoirs for undigested food. The distal stomach comprises the antrum and pylorus. The antrum plays a vital role in propelling the gastric contents and acts as a pump to facilitate gastric emptying. The pylorus is the muscular valve located at the distal end of the stomach, which controls the flow of partially digested food (chyme) into the small intestine. Gastric emptying can occur regardless of whether the individual is in a fasted or fed state, although there are significant differences in the pattern of emptying between these conditions. In the fed state, the ingestion of food triggers motor activity in the stomach. This activity usually begins around 5 to 10 minutes after food intake and continues until the food has emptied from the stomach. The antrum’s pumping action and coordinated muscular contractions facilitate the movement of chyme towards the pylorus, promoting gastric emptying. During the fasting state, there are multiple sequential electrical events that occur in both the stomach and small intestine at intervals of approximately 90 to 120 minutes. These electrical events are known as the migrating motor complex (MMC) and serve to sweep residual undigested material through the gastrointestinal tract. The MMC activity may delay the emptying of the stomach and result in the retention of chyme in the stomach for a longer duration. In the context of GRDDS, understanding the dynamics of gastric emptying and the patterns of gastrointestinal motility during fasting and fed states is essential. This knowledge helps in designing drug delivery systems that can achieve the desired gastro-retentive properties. By formulating dosage forms with specific characteristics such as buoyancy, bio-adhesion, or controlled release, the GRDDS can prolong the residence time of drugs in the stomach, improve drug absorption, and enhance therapeutic outcomes.

**Strategies of GRDDS**
**Strategies utilized for prolongation of GRT are mentioned below**
- Pharmacological approach
- Physiological approach
- Pharmaceutical approach

The various pharmaceutical approaches utilized in gastro-retentive drug delivery system

**Aspects of GRDDS that are affected by various factors**
The success and performance of GRDDS can be influenced by several factors, including pharmaceutical, physiological, and patient-related factors. These factors have been extensively studied in surveys and research to understand their impact on gastro-retentive dosage forms.

**Pharmaceutical Factors**

**Drug Solubility**
The solubility of the drug can affect the formulation of gastro-retentive dosage forms. Poorly soluble drugs may require specific formulation techniques to enhance their dissolution and absorption.

**Drug stability**
The stability of the drug within the dosage form and during gastric retention is crucial. The formulation should protect the drug from degradation or chemical reactions in the stomach.

**Drug release rate**
Controlling the release rate of the drug from the dosage form is essential to achieve the desired therapeutic effect. Various formulation techniques, such as controlled release matrices or coatings, are employed to regulate drug release.

**Formulation design**
The choice of excipients, polymers, and additives in the formulation can significantly impact the gastro-retentive properties of the dosage form. These components determine factors such as buoyancy, bio adhesion, or swelling behavior.

**Physiological Factors**

**Gastric emptying**
The rate of gastric emptying can affect the residence time of the dosage form in the stomach. Factors such as food intake, gastrointestinal motility, and gastric pH can influence gastric emptying and consequently affect the performance of the GRDDS.
Gastrointestinal transit
The transit time of the dosage form through the gastrointestinal tract can impact drug absorption. Factors like motility, pH, and interactions with other components of the gastrointestinal system can influence drug release and absorption.17

Patient-related Factors
Age and gender
Age and gender can affect gastrointestinal physiology and transit time, which may impact the performance of gastro-retentive dosage forms.

Disease conditions
Certain disease conditions, such as gastroparesis or gastrointestinal disorders, can alter gastric motility and emptying, potentially affecting the performance of GRDDS.

Patient compliance
Patient-related factors, such as the ability to follow dosing instructions, adherence to medication, and acceptance of the dosage form, can impact the effectiveness of the GRDDS. In-depth surveys and studies have examined these factors to understand their influence on gastro-retentive dosage forms. By considering and optimizing these factors during the formulation and design of GRDDS, pharmaceutical scientists aim to enhance the clinical efficacy, safety, and patient acceptance of these novel drug delivery systems.18

Current trends in the delivery of pharmaceutical drugs to GRDDS
The increased gastric residence time (GRT) is a key objective in the development of GRDDS. Various approaches have been devised to enhance the gastro-retentivity of dosage forms, either indirectly or directly.19 Let’s discuss each of these approaches:

Buoyancy-based systems
Floating Systems: These systems are designed to float on the gastric fluid, thereby prolonging the GRT. They contain low-density materials or incorporate gas-generating agents that create buoyancy, keeping the dosage form afloat in the stomach.20

Examples: Floating tablets, capsules, or multiparticulate systems, such as floating microspheres or floating pellets.

Floating system classification
GRDDS can be classified into two types based on the mechanism of achieving gastro retentivity: effervescent systems and non-effervescent systems.21 Let’s discuss each type:

Effervescent systems
Effervescent systems rely on the generation of carbon dioxide gas within the stomach to achieve gastroretentivity. These systems contain effervescent agents that react with gastric fluid to produce bubbles of gas, leading to buoyancy and prolonged gastric residence time.22 The gas bubbles help to keep the dosage form afloat in the stomach, allowing for controlled drug release. As the effervescent reaction occurs, the dosage form gradually disintegrates, releasing the drug.20

Non-effervescent Systems
Non-effervescent systems achieve gastro retentivity through mechanisms other than gas generation. These systems employ various approaches like buoyancy, bio-adhesion, swelling, or geometrical factors to prolong the gastric residence time.23

Both effervescent and non-effervescent systems aim to enhance the gastro-retentive properties of the dosage form and overcome the limitations of conventional oral drug delivery systems.24 By prolonging the gastric residence time, these systems improve drug absorption, increase bioavailability, and optimize therapeutic outcomes. The choice between effervescent and non-effervescent systems depends on factors such as drug characteristics, desired release profile, and the specific mechanism required to achieve gastro-retentivity.25

High-density systems
The high-density system is a type of GRDDS where the pharmacological formulation has a density higher than that of the gastric fluid. The objective of this approach is to extend the transit time of the dosage form in the stomach, thereby delaying its passage to the small intestine, where most drug absorption takes place. By increasing the density of the dosage form, it becomes less buoyant and tends to sink in the gastric fluid instead of being rapidly emptied from the stomach. This prolonged gastric retention allows for a slower release and absorption of the drug, resulting in a delayed response and potentially extending the duration of therapeutic effect.26

The high-density system can be achieved by incorporating high-density materials or using specific formulation techniques that increase the overall density of the dosage form. This can be advantageous for drugs that require a sustained release or a delayed onset of action.
Expandable systems

Indeed, expandable systems, also known as plug-type systems, are another type of GRDDS. In these systems, the drug formulation is designed to exhibit delayed gastrointestinal transit by expanding in volume and shape. Initially, these systems were widely used in veterinary applications before their clinical significance in humans was established.  

The expandable systems utilize various mechanisms to achieve expansion, such as swelling, unfolding, or unfolding triggered by factors like pH, temperature, or enzymes present in the gastrointestinal tract. These mechanisms allow the dosage form to change its shape or increase in size, prolonging its gastric residence time.  

Overall, expandable systems represent a unique approach in GRDDS, allowing for delayed gastrointestinal transit and controlled drug release. By meeting the specific pharmaceutical requirements mentioned, these systems hold potential for improving drug delivery and therapeutic outcomes.

Superporous hydrogel system

The superporous hydrogel system is indeed one of the promising types of GRDDS. Hydrogels are crosslinked polymeric structures composed of acidic, basic, or neutral monomers.  

Superporous hydrogels are utilized in GRDDS because of their ability to absorb and retain a large amount of water. When they come into contact with gastric fluid, they rapidly absorb water and swell to a significant extent. This swelling behavior allows them to remain in the stomach for an extended period, leading to prolonged drug release.

Superporous hydrogels can exhibit significant swelling ratios, often swelling over 250 times their initial volume. Continued research and development in super porous hydrogel systems offer promising opportunities for the design of advanced gastro-retentive drug delivery systems, enhancing drug bioavailability, patient compliance, and overall treatment outcomes.

Magnetic system

Magnetic systems are employed in GRDDS to increase the residence time in the gastrointestinal tract. These systems utilize magnets to control and enhance the retention of the developed pharmaceutical formulation within the stomach.

The magnetic system consists of two main components: an internal magnet incorporated into the drug dosage form and an extracorporeal magnet placed externally over the stomach region. The magnetic attraction between the internal and external magnets allows for precise positioning and retention of the dosage form within the stomach.

However, it is important to note that the use of magnetic systems in GRDDS is still an area of active research, and further studies are required to optimize their design, evaluate their safety, and assess their clinical effectiveness. Nonetheless, magnetic systems hold promise as a targeted approach for gastro-retentive drug delivery, offering opportunities for improved drug delivery strategies and therapeutic outcomes.

System of ion-exchange resin

The experimental work conducted by Saunders and Srivastava in 1950 was significant in demonstrating the potential of ion-exchange resins for developing formulations with sustained drug release. They proposed the use of ion-exchange resins as effective chemical carriers in drug delivery systems, based on their experiments involving the uptake and release of alkaloids by the resin.

Ion-exchange resins possess the property of hosting a drug and releasing it in the gastrointestinal tract (GIT) in the presence of other ions or pH changes in the surrounding environment. This property makes them suitable candidates for GRDDS. When formulated with a drug, the resin particles are ingested along with the drug particles by the gastric mucosa. They can then be either eliminated through biological breakdown or excreted with the faces.

Further research and development in this field continue to explore the potential of ion-exchange resins and coatings to improve drug delivery systems and enhance therapeutic outcomes.

Raft-forming System

The raft-forming system in GRDDS utilizes effervescent agents and polymers that form gels. When these components interact, they generate carbon dioxide, resulting in the formation of a raft-like structure in the stomach. This raft is resistant to peristaltic movement, making it difficult for it to enter the small intestine.

The mechanism of action of the raft-forming system is similar to that of the floating system. It remains in the stomach, gradually releasing the drug. However, the raft-forming system offers limited mechanical strength and can be easily disrupted by vigorous gastric motility.

It is important to note that the success of the raft-forming system relies on the appropriate selection of effervescent agents and polymers to achieve the desired raft formation and drug release profile. The choice of components and formulation parameters should be carefully optimized to ensure optimal performance and therapeutic efficacy.

Mucoadhesive system

In GRDDS, both synthetic and natural polymers are used as mucoadhesive agents. These polymers possess the ability to adhere to the mucosal surface of the stomach, thereby enhancing the GRT of the medication. By binding to the epithelial layer of the stomach, these polymers prolong the contact between the drug and the absorption site.

Various theories have been proposed to explain the mechanism of mucoadhesion, including wettability, diffusion, adsorption, electronic, and fracture theories (Table 1). These theories aim to elucidate the specific molecular interactions that occur between the mucoadhesive polymer and the mucosal surface, leading to the adhesive properties.

Micro balloons/Hollow microspheres

Microballoons, in combination with other polymers, are utilized to increase the gastric residence time (GRT) of the
dosage form. Various polymers such as cellulose acetate, calcium alginate, polycarbonate, low methoxylated pectin, and Eudragit S, among others, are used to construct the micro balloons. The micro balloons filled with surfactants demonstrate continuous floating behavior for more than 12 hours on the surface of the acidic dissolution medium. By employing these micro balloons or floating beads, a gastric residence time of more than 5.5 hours can be achieved. This extended retention time in the stomach can improve the controlled release of drugs and enhance their therapeutic efficacy.

**Evaluation Parameters of GRDDS**

**In vivo evaluation parameters of GRDDS**

Animal models and human research are essential to validate the efficacy of GRDDS *in vivo*. In these studies, the bioavailability of the developed pharmaceutical formulation and the GRT are evaluated.

Various imaging techniques are employed to assess the in vivo performance of GRDDS. These include gastroscopy, radiology, scintigraphy (including gamma scintigraphy), and magnetic resonance imaging (MRI). Each method provides valuable insights into the behavior and location of the dosage forms within the GIT.

Gamma scintigraphy has been particularly useful in studying GRDDS. It allows for the assessment of parameters such as location, size, and movement of the dosage forms throughout the GIT. This method utilizes small doses of radiation, which have a favorable safety profile, to track and visualize the behavior of the dosage forms.

Gastroscopy, a procedure in which a flexible tube with a camera is inserted into the stomach, is also employed to locate and examine GRDDS *in vivo*. It allows for direct visualization and assessment of the dosage forms in the stomach.

MRI is another effective method for evaluating GRDDS in live animals and human subjects. By utilizing a strong magnetic field, MRI provides detailed imaging of anatomical structures and enables visualization of the location and residence time of ingested medication forms.

Through the combination of these imaging techniques and in vivo studies, researchers can gather valuable data on the performance and behavior of GRDDS, confirming their efficacy and optimizing their formulation parameters.

It is worth noting that ethical considerations and regulatory guidelines must be followed when conducting animal and human studies to ensure the safety and well-being of the subjects involved.

**In-vitro evaluation parameters of GRDDS**

In vitro evaluations of GRDDS can provide valuable insights and help predict their in vivo behavior. Several parameters can be assessed to evaluate the floating behavior of low-density systems, including total floating length and floating lag time. These measurements help determine the ability of the dosage form to float and remain buoyant in the gastric fluid. The floating force of a floating tablet can also be measured to assess its floating capacity. This parameter quantifies the force required to displace the dosage form from the surface of the dissolution medium, indicating its ability to resist sinking and maintain buoyancy.

Additionally, dissolution studies can be conducted over an extended period, typically around 8 hours, to evaluate other important parameters of the polymeric dosage form. These include the swelling rate, gel strength, and water uptake capacity. These parameters provide insights into the drug release behavior, floating mechanism, and gel strength of the dosage form.

**Future prospective**

In-vitro evaluations of GRDDS can provide valuable insights and help predict their in-vivo behavior. Several parameters can be assessed to evaluate the floating behavior of low-density systems, including total floating length and floating lag time. These measurements help determine the ability of the dosage form to float and remain buoyant in the gastric fluid.

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**CONCLUSION**

The development of a comprehensive understanding of the stomach's anatomy and physiology is essential for GRDDS. Factors such as gastric emptying, motility patterns and pH variations in different regions of the stomach play a significant role in determining the performance of GRDDS.

In the literature, various types of GRDDS have been explored to improve drug delivery and overcome the limitations of conventional dosage forms. Bio/mucoadhesive systems, both low density and high density, are designed to adhere to the gastric mucosa, prolonging the residence time and enhancing drug absorption. These systems utilize polymers
with mucoadhesive properties to achieve effective adhesion to the mucosal surface.

Magnetic systems involve the use of extracorporeal magnets to position and control drug delivery in the stomach. The internal magnet within the formulation interacts with the external magnet, allowing for precise localization and retention in the desired region of the stomach.

Other GRDDS approaches, such as floating systems, expandable systems, and super porous hydrogels, have also been investigated. Floating systems aim to float on the gastric contents, thereby prolonging the gastric residence time. Expandable systems expand in volume or shape to prevent passage through the pyloric sphincter and prolong gastric retention. Super porous hydrogels possess a high capacity for water absorption, leading to significant swelling and retention in the stomach.

These various GRDDS approaches offer different advantages and mechanisms to achieve extended gastric retention and enhanced drug delivery. By considering the specific needs of the drug and the target therapeutic outcome, researchers can select and design the most suitable GRDDS to optimize drug delivery and improve therapeutic efficacy.

REFERENCES

A review on Gastro Retentive Drug Delivery System


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