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Research Article

GASTRORETENTIVE DRUG DELIVERY SYSTEMS- A NOVEL APPROACH TO ENHANCE THE BIOAVAILABILITY OF POORLY SOLUBLE DRUGS

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A B S T R A C T

A gastro-retentive drug delivery system (GRDDS) can be defined as a system that remains in the stomach for a sufficient time interval against all the physiological barriers, releasing the active moiety in a controlled manner. GRDDSs can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site. Oral route is most preferable route of administration but it has certain limitations for those drugs which absorb from specific region of gastrointestinal tract. It has to improve the solubility and prolongation of the retention time of those drugs having low solubility at high intestinal pH in stomach. The bioavailability of drugs can be improved by increasing their retention time in the stomach. This novel approach has proved to be efficient in systemic actions as well as in local actions to treat gastric or duodenal ulcers. Local activity in the upper part of the small intestine can be obtained by improving the residence time of delivery system in the stomach. This system is useful for drugs which are unstable or low solubility in the small intestine. A variety of GRDDS approaches comprise high density (sinking) systems, low-density (floating systems), mucoadhesive, expandable, unfoldable, superporous hydrogel systems, and magnetic systems.

INTRODUCTION

The development of effective drug delivery systems is crucial for enhancing the therapeutic efficacy of poorly soluble drugs. Gastroretentive drug delivery systems have gained prominence in recent years as an innovative approach to tackle this issue. They aim to prolong the residence time of drugs in the stomach[(1)], which can lead to improved drug absorption and bioavailability.

Gastroretentive Approaches

GRDDS employ various approaches to achieve gastric retention, including: Gastric retention approaches are diverse and aim to prolong the residence time of drugs or dosage forms in the stomach for various therapeutic purposes. Here are some different approaches to achieving gastric retention[(2,3)]

a. Floating Systems

Floating Tablets or Capsules: These dosage forms contain low-density materials or gas-generating agents that enable them to float on the gastric fluid. The buoyancy keeps the drug in the stomach for an extended period, allowing for slow and controlled drug release[(4).]

Hollow Floating Systems: Hollow structures like balloons or reservoirs can be filled with drug formulations. They remain buoyant and release the drug over time as they float on the gastric contents[(5)].

b. Mucoadhesive Systems

Mucoadhesive Tablets or Patches: These systems use polymers (e.g., chitosan, sodium alginate) that adhere to the gastric mucosa, prolonging contact with the absorption sites and ensuring retention in the stomach.

Bioadhesive Hydrogels: Hydrogel-based formulations can adhere to the gastric mucosa upon hydration,[(6)] leading to sustained drug release and gastric retention.

Swelling and Expandable Systems: Swelling Tablets or Hydrocolloid-Based Systems: These formulations swell upon contact with gastric fluid, increasing in size and reducing gastric emptying rates. Superporous hydrogels are also employed for this purpose.

Shape Memory Polymers: Materials with shape-memory properties can change shape in response to environmental stimuli such as temperature or pH, allowing them to adapt and fit into the stomach's shape.

c. High-Density Systems

High-Density Tablets or Beads: These dosage forms have densities greater than gastric fluids, preventing their passage

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into the intestines. They rely on the principle of sedimentation to maintain gastric retention[7].

d. Magnetic Systems

Magnetic Tablets or Particles: Magnetic materials are incorporated into the dosage form, and an external magnetic field is applied externally to retain the drug in the stomach. This approach is less commonly used but offers precise control over retention.

e. Expandable Systems

Expandable Pill Systems: These are ingestible devices that expand within the stomach after ingestion,[8] effectively preventing their passage through the pyloric sphincter.

f. Hydrodynamically Balanced Systems (HBS)

HBS Tablets or Pellets: These systems are designed to maintain a balance between their buoyancy and gravitational forces,[9] allowing them to remain in the stomach while avoiding floating to the surface or sinking.

g. pH-Responsive Systems

pH-Triggered Systems: Certain polymers or materials respond to the changing pH levels along the gastrointestinal tract [10]. They may change shape or release the drug in response to the pH environment of the stomach.

h. Controlled Drug Release Systems

Osmotic Pumps: Osmotic pump systems release drugs through a semipermeable membrane, driven by osmotic pressure. They can be designed for gastric retention.

Microspheres and Nanoparticles: Drug-loaded microspheres or nanoparticles can be incorporated into formulations that promote gastric retention. These small particles are less likely to be rapidly emptied from the stomach.

Each of these approaches offers unique advantages and challenges, and the choice of the most suitable gastric retention approach depends on the specific drug, therapeutic goals, and patient requirements. Additionally, combining multiple strategies or utilizing advanced materials and technologies can further enhance the effectiveness of gastric retention systems[11,12].

Mechanism of floating drug delivery systems

Floating drug delivery systems (FDDS) are a type of gastroretentive drug delivery system designed to prolong the residence time of oral dosage forms (such as tablets or capsules) in the stomach. This extended retention allows for controlled and sustained drug release, making FDDS particularly useful for drugs that have a narrow absorption window in the upper gastrointestinal tract or require targeted delivery to the stomach[4,10].

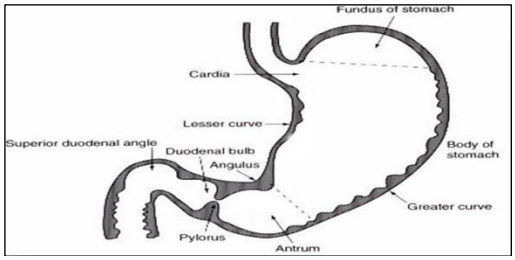

Figure 1 Schematic view on the anatomy of Stomach [13]

The mechanism behind floating drug delivery systems involves the following key elements:

1. **Low-Density Formulations:** FDDS contain one or more low-density components that enable them to float on the gastric fluid. These low-density materials are typically included in the formulation to ensure buoyancy. Common materials used for this purpose include:

Gas-Generating Agents: Some FDDS formulations contain effervescent agents like sodium bicarbonate or citric acid. When these agents come into contact with gastric acid, they produce carbon dioxide gas, creating a buoyant force that keeps the dosage form afloat.

Hollow Structures: In some cases, the dosage form may be designed with hollow portions or chambers that trap air, providing buoyancy.

2. **Gas Entrapment:** FDDS often incorporate gas-filled compartments or voids within the tablet or capsule. These compartments are sealed to prevent the gas from escaping until the dosage form is exposed to gastric fluid. When the FDDS reaches the stomach, the gas inside the compartments is released, creating an internal pressure that drives the dosage form to float on the gastric contents.
3. **Density Lower Than Gastric Fluid:** The density of the FDDS is carefully engineered to be lower than that of the gastric fluid. This difference in density ensures that the dosage form remains buoyant and does not sink in the stomach.
4. **Gastric Residence Time:** As the FDDS floats on the gastric fluid, it resists rapid emptying through the pyloric sphincter into the small intestine. This prolonged residence time allows for controlled drug release over an extended period.
5. **Controlled Drug Release:** FDDS may have a drug layer that is designed to release the drug in a controlled and sustained manner. The rate of drug release can be influenced by factors such as the formulation, drug solubility, and the physical characteristics of the dosage form.
6. **Drug Absorption:** While the FDDS is retained in the stomach, the drug is available for absorption through the stomach's mucosa. This can be advantageous for drugs that are absorbed more effectively in the stomach or for those that require localized therapy in the gastric region.
7. **Eventually Emptying:** After a certain period, the FDDS loses its buoyancy due to the dissolution of the low-density components or the release of the gas. At this point, it becomes denser and is eventually emptied from the stomach into the small intestine[14,15].

Advantages of GRDDS

a. Enhanced Bioavailability: By prolonging drug residence in the stomach, GRDDS improve drug absorption, especially for poorly soluble compounds.
b. Reduced Variability: GRDDS minimize the impact of inter- and intra-patient variability in gastric emptying

rates, leading to more consistent drug levels in the bloodstream.

c. Improved Patient Compliance: The reduced dosing frequency associated with GRDDS can enhance patient compliance, especially for drugs with frequent dosing requirements.
d. Targeted Delivery: GRDDS can be designed to release drugs at specific locations within the gastrointestinal tract, allowing for targeted drug delivery.

Disadvantages of GRDDS

- The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- Not suitable for drugs that have solubility or stability problem in GIT.
- Drugs which are irritant to gastric mucosa are also not suitable.
- These systems do not offer significant[16].

Applications of GRDDS

- Sustained Drug Delivery: GRDDS float on the gastric contents over a prolonged period of time, as these systems have bulk density.
- Site-Specific Drug delivery: This delivery system is very useful for drugs that are absorbed from the stomach or the proximal part of the small intestine, especially with respect to their application for the treatment of H. Pylori infections.
- The fluctuation of Drug Concentrations can be minimized: This feature is important for drugs with a narrow therapeutic index. Fluctuations in drug effects are minimized and concentration-dependent adverse effects that are associated with peak concentration can be prevented.
- Absorption Enhancement: This is important in the case of drugs that are absorbed from the upper part if the GIT and by formulating this type of drugs as GRDDS can improve the poor bioavailability, thereby maximising their absorption[17].

Classification of floating system

Floating drug delivery systems (FDDS) can be classified based on various factors, including their mechanism of buoyancy, formulation, and release kinetics. Here, providing a classification of floating drug delivery systems based on these factors:

1. Mechanism of Buoyancy

Gas-Generating Systems: These FDDS formulations contain gas-generating agents (e.g., sodium bicarbonate, citric acid) that produce carbon dioxide gas upon contact with gastric fluid, leading to buoyancy.

Non-Effervescent Systems: These systems achieve buoyancy without relying on gas generation. They often use low-density materials, hollow structures, or microspheres that remain buoyant in the stomach.

2. Formulation Types

Single-Unit Systems: These FDDS consist of a single dosage form, such as a tablet or capsule, designed to float in the stomach.

Multiple-Unit Systems: In these systems, multiple smaller units (e.g., pellets, microspheres, beads) are administered together as a dosage form. They provide flexibility in dosing and can improve drug release profiles.

Bilayer or Multilayer Systems: Some FDDS incorporate multiple layers within a single dosage form. This can include layers for immediate drug release and delayed drug release, allowing for controlled release profiles.

Floating Pulsatile Systems: These systems combine floating mechanisms with a pulsatile drug release profile. They release the drug in bursts at predetermined intervals.

3. Formulation Components

Hydrogel-Based Systems: These FDDS contain hydrogel materials that swell upon contact with gastric fluid, increasing the dosage form's size and buoyancy.

Matrix Systems: In matrix-based FDDS, the drug is uniformly dispersed in a matrix, and the matrix material plays a crucial role in achieving buoyancy.

Coating-Based Systems: FDDS may be coated with polymers that provide buoyancy and control drug release. The coating may be impermeable or selectively permeable.

Osmotic Systems: Some FDDS use osmotic principles to release the drug. They contain an osmotic core that swells, pushing the drug out through an orifice or through the membrane.

4. Release Kinetics

Immediate-Release Floating Systems: These FDDS provide rapid drug release upon contact with gastric fluid, followed by prolonged gastric retention.

Sustained-Release Floating Systems: FDDS designed for sustained release provide a gradual and continuous release of the drug over an extended period.

Controlled-Release Floating Systems: These systems offer controlled and predictable drug release rates, often achieved through specialized formulation and coating techniques.

Zero-Order Release Systems: FDDS in this category release a consistent amount of drug per unit of time, ensuring a linear release profile.

5. Other Factors

Magnetic Systems: In this classification, FDDS contain magnetic materials that can be controlled using an external magnetic field.

pH-Responsive Systems: FDDS that respond to the pH changes in the stomach, altering their buoyancy or drug release behavior based on acidity.

It's important to note that these classifications are not mutually exclusive, and some FDDS may belong to multiple categories simultaneously. The choice of FDDS classification depends on the specific therapeutic requirements of the drug, desired release profile, and patient compliance considerations (17,18).

Evaluation of floating drug delivery systems: The evaluation of a floating drug delivery system (FDDS) is a crucial step in the development of such a system to ensure its effectiveness, safety, and reliability for drug delivery. Here are key aspects to consider when evaluating an FDDS:

1. Buoyancy and Gastric Retention

Buoyancy Testing: Assess the buoyancy of the FDDS by placing it in a simulated gastric fluid and monitoring its ability to float. The dosage form should remain afloat for an extended period[18].

In vitro Gastric Retention: Conduct in vitro studies to determine the gastric retention time of the FDDS in a simulated gastric environment. This can involve measuring the time it takes for the dosage form to exit the stomach model.

2. Drug Release and Dissolution

Dissolution Testing: Evaluate the drug release characteristics of the FDDS using dissolution testing in simulated gastric conditions. Measure the release kinetics, including the rate and extent of drug release.

In vitro Release Profile: Generate in vitro release profiles under conditions that mimic the gastric environment, including pH and temperature.

3. Drug Content and Uniformity

Content Uniformity: Ensure that the drug is uniformly distributed within the dosage form to prevent dose variability.

Drug Assay: Quantify the amount of drug in each FDDS unit to confirm that it meets the labeled dose[19,20].

4. Physical Characteristics

Physical Stability: Assess the physical stability of the FDDS over time, including changes in appearance, hardness, and integrity.

Size and Shape: Measure the size and shape of the FDDS to ensure consistency and to verify that it can be easily administered[21].

5. *In vitro* pH-Dependent Swelling

If the FDDS relies on swelling to achieve buoyancy, evaluate its swelling behavior under varying pH conditions to mimic the changing pH levels along the gastrointestinal tract.

6. Drug Compatibility

Confirm that the drug remains stable within the FDDS formulation and does not degrade or interact with excipients or components of the dosage form.

7. *In vivo* Studies

Conduct pharmacokinetic studies in animals or human subjects to assess the bioavailability and pharmacokinetics of the drug when delivered through the FDDS compared to conventional dosage forms[22]. Measure gastric retention time, drug absorption, and plasma drug concentration profiles.

8. Drug Release Mechanism

Investigate the drug release mechanism by fitting the release data to mathematical models (e.g., zero-order, first-order) to understand the kinetics and mechanisms involved.

9. Stability Testing

Conduct stability testing under various storage conditions (e.g., temperature, humidity) to determine the shelf-life and storage requirements of the FDDS.

Recent Advancements

Recent developments in GRDDS include the use of 3D printing technology to create customized dosage forms, smart polymers that respond to changes in pH or temperature, and the incorporation of nanotechnology to improve drug solubility and release kinetics. These advancements hold promise for addressing the challenges associated with poorly soluble drugs[23,24].

Challenges

Despite their potential, GRDDS face challenges such as variability in gastric emptying, potential for dose dumping, and regulatory hurdles. Additionally, the choice of excipients and the manufacturing process can significantly affect the performance of these systems[25].

CONCLUSION

Gastroretentive drug delivery systems have emerged as a novel approach to enhance the bioavailability of poorly soluble drugs. Their various approaches offer versatility in design, and recent advancements hold the potential to revolutionize drug delivery for challenging compounds. However, addressing regulatory concerns and optimizing formulation and manufacturing processes are essential for the successful translation of GRDDS from the lab to the market. Nevertheless, GRDDS remain a promising avenue in pharmaceutical research and development for improving drug delivery and patient outcomes.

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