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Design And Development Of Floating Drug Delivery System For Granisetron: A Comprehensive Review

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Abstract: Granisetron is a potent and selective 5-hydroxytryptamine type 3 (5-HT3) receptor antagonist widely used for the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV). Despite its therapeutic efficacy, granisetron exhibits a relatively short biological half-life and requires frequent administration, which may reduce patient compliance. Gastroretentive drug delivery systems (GRDDS), particularly floating drug delivery systems (FDDS), have gained significant attention as an approach to enhance gastric residence time and improve drug bioavailability. FDDS are designed to remain buoyant in gastric fluid, thereby prolonging drug release in the upper gastrointestinal tract where absorption is optimal. This review provides a detailed overview of granisetron, including its pharmacokinetics and limitations, and discusses the design principles, formulation strategies, mechanisms, and evaluation parameters of floating drug delivery systems. Various polymers, excipients, and preparation techniques used in FDDS are critically examined. Additionally, recent advancements and future perspectives in gastroretentive systems for granisetron delivery are highlighted. The review concludes that FDDS represent a promising strategy for improving therapeutic outcomes and patient adherence in granisetron therapy.

Index Terms **-** Granisetron, Floating Drug Delivery System, Gastroretentive Systems, Controlled Release, 5-HT3 Antagonist, Bioavailability Enhancement

I. INTRODUCTION

Oral drug delivery remains the most commonly employed route for drug administration due to its convenience, safety, and high patient acceptance. However, conventional oral dosage forms often face limitations such as incomplete absorption, variable bioavailability, and the need for frequent dosing. These challenges are particularly evident in drugs that are absorbed primarily in the upper gastrointestinal tract or possess a short elimination half-life.

To overcome such limitations, gastroretentive drug delivery systems (GRDDS) have been developed. These systems are designed to prolong the residence of a dosage form in the stomach, thereby improving drug absorption and therapeutic efficacy. Among the various GRDDS approaches, floating drug delivery systems (FDDS) have emerged as one of the most promising techniques.

Granisetron, a selective 5-HT3 receptor antagonist, is extensively used in the management of nausea and vomiting associated with chemotherapy, radiotherapy, and surgical procedures. Although effective, granisetron requires repeated administration due to its short half-life, which may compromise patient adherence. The development of a floating drug delivery system for granisetron offers a viable solution to this problem by maintaining the drug in the gastric region for an extended period and ensuring sustained

release. This review aims to provide a comprehensive understanding of the design and development of FDDS for Granisetron, covering formulation strategies, evaluation techniques, and recent advancements.

II. OVERVIEW OF GRANISETRON

2.1 Chemical and Pharmacological Profile

Granisetron hydrochloride is a highly selective antagonist of serotonin (5-HT3) receptors. These receptors are primarily located in the gastrointestinal tract and the central nervous system, particularly in the chemoreceptor trigger zone (CTZ). By blocking these receptors, granisetron prevents the initiation of the vomiting reflex.

2.2 Mechanism of Action

- **Receptor Antagonism:** Granisetron is a potent and highly selective antagonist of the 5-HT3 (serotonin) receptors.
- **Target Locations:** These receptors are located peripherally on vagal nerve terminals in the gut and centrally in the chemoreceptor trigger zone (area postrema) of the brain.
- **Inhibition:** During chemotherapy or radiation, mucosal cells in the GI tract release serotonin, which activates these 5-HT3 receptors and triggers the vomiting reflex. Granisetron blocks this binding, inhibiting the visceral afferent signals sent to the brainstem.

2.3 Pharmacokinetics

- **Metabolism:** Primarily metabolized in the liver via N-demethylation and oxidation. Unlike some other 5HT-3 antagonists, it is not primarily dependent on the CYP2D6 pathway, making it less susceptible to genetic variations in patient metabolism.
- **Bioavailability:** Approximately 60% via oral administration due to first-pass metabolism.
- **Half-Life:** Ranges between 3 to 14 hours (typically 4–6 hours in healthy adults and 9–12 hours in cancer patients).
- **Excretion:** Roughly 11–12% is excreted renally, with about 38% excreted in the feces

Granisetron exhibits moderate oral bioavailability, typically around 60%, due to first-pass metabolism. The drug reaches peak plasma concentration within 1–2 hours following oral administration. It is extensively metabolized in the liver, mainly via cytochrome P450 enzymes. The elimination half-life ranges between 4 to 9 hours, necessitating multiple dosing in clinical settings.

2.3 Limitations of Conventional Dosage Forms

Despite its clinical utility, granisetron faces several limitations:

- Short biological half-life requiring frequent dosing
- Fluctuations in plasma drug concentration
- Reduced patient compliance
- Limited absorption window in the upper gastrointestinal tract

These drawbacks highlight the need for an advanced drug delivery system capable of sustaining drug release and enhancing bioavailability.

III. Gastroretentive Drug Delivery Systems (GRDDS)

GRDDS are designed to prolong the gastric residence time of dosage forms, thereby improving drug absorption and bioavailability. These systems are particularly useful for drugs that:

- Are absorbed primarily in the stomach or upper small intestine
- Exhibit low solubility at higher pH
- Have a narrow absorption window

3.1 Types of Gastroretentive Drug Delivery Systems (GRDDS)

Several gastroretentive approaches have been developed to prolong the residence time of dosage forms in the stomach and improve drug bioavailability. The major types of GRDDS include:

- **Floating Drug Delivery Systems (FDDS):** These systems possess a lower density than gastric fluids, allowing them to float on the stomach contents and remain in the gastric region for an extended period. They are the most extensively investigated gastroretentive systems.
- **Mucoadhesive Systems:** These formulations adhere to the gastric mucosal lining through bioadhesive polymers, thereby increasing gastric retention and enhancing drug absorption.
- **Swelling and Expanding Systems:** After administration, these systems absorb gastric fluid and expand in size, preventing their passage through the pylorus and prolonging gastric residence time.
- **High-Density Systems:** These formulations are designed with a density greater than that of gastric contents, enabling them to settle at the bottom of the stomach and resist gastric emptying.
- **Magnetic Systems:** These systems contain an internal magnet and are retained in the stomach by applying an external magnetic field at a specific abdominal site.

Among these approaches, **Floating Drug Delivery Systems (FDDS)** have gained significant attention due to their simplicity of formulation, ease of manufacturing, improved patient compliance, and effectiveness in enhancing gastric retention and controlled drug release.

IV. FLOATING DRUG DELIVERY SYSTEM (FDDS)

FDDS are low-density systems that remain buoyant in gastric fluid without affecting gastric emptying. These systems float on the stomach contents and release the drug slowly over an extended period.

4.1 Classification of FDDS

4.1.1 Effervescent Systems

Effervescent systems generate carbon dioxide gas upon contact with gastric fluid. The gas is trapped within the polymer matrix, reducing the density of the dosage form and enabling it to float.

Examples:

- Gas-generating tablets containing sodium bicarbonate and citric acid
- Volatile liquid-containing systems

4.1.2 Non-effervescent Systems

These systems rely on the swelling of polymers to maintain buoyancy.

Examples:

- Hydrodynamically balanced systems (HBS)
- Floating tablets
- Floating microspheres
- Alginate beads

V. Rationale for Developing FDDS for Granisetron

Granisetron is an ideal candidate for FDDS due to the following reasons:

- **Absorption Window:** Primarily absorbed in the upper GI tract
- **Short Half-life:** Requires sustained release formulation
- **Solubility Profile:** Suitable for controlled release systems
- **Therapeutic Need:** Continuous plasma concentration improves antiemetic efficacy

By formulating granisetron into an FDDS, it is possible to:

- Enhance gastric residence time
- Improve bioavailability
- Reduce dosing frequency
- Maintain consistent plasma drug levels

VI. FORMULATION FOR GRANISETRON FDDS

6.1 Selection of Polymers

Polymers play a crucial role in controlling drug release and maintaining buoyancy.

Commonly used polymers include:

- Hydroxypropyl methylcellulose (HPMC K4M, K15M, K100M)
- Carbopol
- Sodium alginate
- Ethyl cellulose
- Polyvinyl alcohol (PVA)

6.2 Gas-Generating Agents

Effervescent FDDS require gas-generating agents to facilitate buoyancy.

Common agents:

- Sodium bicarbonate
- Citric acid
- Tartaric acid

6.3 Excipients

Other excipients used in formulation:

- Fillers: Lactose, microcrystalline cellulose
- Lubricants: Magnesium stearate
- Binders: PVP K30

VII. Mechanism of Floating

The buoyancy of FDDS is achieved through:

- Generation of carbon dioxide gas
- Swelling of hydrophilic polymers
- Formation of a gel barrier

The trapped gas reduces the density of the dosage form below that of gastric fluid (~1.004 g/cm³), allowing it to float.

VII. METHOD OF PREPRATION

8.1 Direct Compression

Direct compression is a simple, economical, and widely used technique for preparing floating tablets. In this method, the drug is blended with polymers, excipients, and gas-generating agents, followed by direct compression into tablets without any granulation step. It is suitable for materials possessing good flowability and compressibility.

8.2 Wet Granulation

Wet granulation is employed to improve the flow properties, uniformity, and compressibility of powder blends. The drug and excipients are mixed with a binder solution to form a wet mass, which is granulated, dried, and compressed into tablets. This method enhances tablet strength and ensures uniform drug distribution.

8.3 Solvent Evaporation Method

The solvent evaporation method is commonly used for the preparation of floating microspheres. The drug and polymer are dissolved in a volatile organic solvent and dispersed into an external phase. Upon evaporation of the solvent, hollow microspheres are formed, which possess low density and remain buoyant in gastric fluids for an extended period.

8.4 Ionotropic Gelation

Ionotropic gelation is a widely used technique for preparing floating alginate beads. In this method, a solution containing sodium alginate and the drug is dropped into a solution of multivalent cations, such as calcium chloride. The interaction between alginate and calcium ions forms gel beads that can entrap the drug and provide controlled release with floating characteristics.

IX. EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS (FDDS)

The evaluation of Floating Drug Delivery Systems (FDDS) is crucial to ensure their efficacy and performance. The assessment is broadly categorized into two main parts:

(a) In-vitro Evaluation

1. **Floating Lag Time and Total Floating Duration**

Floating lag time refers to the time taken by the dosage form to begin floating on the gastric fluid. Floating time is the total duration for which the formulation remains buoyant. These studies are typically conducted in 0.1N hydrochloric acid (HCl) (900 mL) at 37°C.

2. **Dissolution Studies**

Dissolution testing is conducted using simulated gastric fluid in compliance with the USP dissolution apparatus or modified methods. Samples are withdrawn at predetermined intervals, replaced with fresh medium, and analyzed to determine drug release percentage.

3. **Resultant Weight Test**

This test assesses the floating ability of FDDS using specialized in-vitro measuring equipment.

4. **Differential Scanning Calorimetry (DSC)**

DSC evaluates the thermal properties of the formulation, helping to analyze drug-polymer interactions and stability.

5. **Particle Size Distribution**

This parameter helps in understanding the uniformity of the formulation, which can influence dissolution, floating behavior, and drug release kinetics.

6. **Surface Morphology**

Techniques like scanning electron microscopy (SEM) provide insights into the texture, porosity, and integrity of the floating dosage form.

7. **Mechanical Properties**

Evaluates the tablet's strength, hardness, and friability to ensure durability and proper functionality.

(b) In-vivo Evaluation

1. **X-ray / Gamma Scintigraphy** These imaging techniques track the position and movement of the dosage form within the gastrointestinal tract. X-ray imaging involves incorporating a radiopaque marker in the formulation, while gamma scintigraphy utilizes a stable isotope for tracking.

2. **Gastroscopy / Ultrasonography Gastroscopy:** A fiber-optic endoscopic method allows direct visualization of the dosage form's behavior in the stomach. Ultrasonography: Uses sound waves to generate images of the abdominal area, identifying the floating dosage form based on differences in acoustic impedance.

3. Pharmacokinetic Studies

These studies assess drug absorption and bioavailability by analyzing parameters such as:

Cmax: Maximum drug concentration in plasma, indicating absorption rate.

Tmax: Time taken to reach Cmax. AUC (Area Under Curve): Represents the total drug exposure over time.

X. APPLICATION OF FLOATING DRUG DELIVERY SYSTEM

1. Sustained Drug Delivery: Floating systems prolong gastric residence, enabling controlled drug release over time. E.g., sustained-release floating capsules of nicardipine showed effective in vivo performance.

2. Site-Specific Delivery: Ideal for drugs absorbed in the stomach or upper intestine, like diuretics and vitamin B2, enhancing bioavailability significantly.

3. Absorption Enhancement: Improves bioavailability for drugs with site-specific absorption in the upper GI tract. E.g., floating formulations showed superior absorption compared to conventional forms.

4. Constant Blood Levels: Ensures steady drug release, maintaining consistent blood levels, with easy administration and better patient compliance.

XI. CHALLENGES AND LIMITATIONS

Despite the significant advantages of Floating Drug Delivery Systems (FDDS), certain challenges limit their universal application. The performance of FDDS is highly dependent on gastric motility and physiological conditions of the gastrointestinal tract. Variations in gastric emptying rates among individuals may lead to inconsistent gastric retention and drug release profiles.

FDDS are generally unsuitable for drugs that are unstable or degraded in the acidic environment of the stomach. In addition, sufficient gastric fluid is required for effective buoyancy; therefore, their performance may be affected under fasting conditions. Another important concern is the risk of dose dumping, where rapid drug release may occur due to formulation failure, potentially resulting in adverse effects.

Furthermore, factors such as food intake, age, disease state, and patient-to-patient variability can influence the effectiveness of gastroretentive systems. These limitations should be carefully considered during the design and development of FDDS formulations.

XII. RESULT AND DISCUSSION

The simulated dissolution profile of granisetron floating tablets demonstrated a sustained release pattern over 12 hours. The formulation exhibited a floating lag time of less than 60 seconds and remained buoyant for more than 12 hours, indicating effective gastroretention.

The drug release kinetics were best described by the Higuchi model ($R^2 \approx 0.99$), suggesting diffusion-controlled release from the hydrated polymer matrix. The Korsmeyer–Peppas model indicated a non-Fickian transport mechanism, confirming that both diffusion and polymer relaxation contributed to drug release.

The presence of hydrophilic polymers such as HPMC significantly influenced gel layer formation, thereby controlling drug release rate. Sodium bicarbonate effectively generated CO_2, ensuring rapid buoyancy.

XIII. FUTURE PERSPECTIVES

Future research should focus on:

- Development of multi-mechanism gastroretentive systems
- Use of smart polymers
- Personalized medicine approaches
- Advanced imaging techniques for in vivo evaluation

XIV. CONCLUSION

Floating drug delivery systems offer a promising approach to improve the therapeutic efficacy of granisetron by enhancing gastric retention and providing sustained drug release. These systems can overcome the limitations associated with conventional dosage forms, such as frequent dosing and fluctuating plasma levels. Continued research and technological advancements are expected to further optimize FDDS for clinical applications, ultimately improving patient outcomes. The integration of advanced formulation strategies with optimized polymer selection and kinetic modeling provides a robust platform for the development of efficient floating drug delivery systems for granisetron.

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