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Formulation, Development and In-Vitro Evaluation of Gastroretentive Floating Nanomedicine for Meclonazepam and Fluvoxamine with Probenecid as BBB Penetration Enhancer

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Abstract:

The present study aims to formulate, develop, and evaluate a gastroretentive floating Nano-medicine for the co-delivery of Meclonazepam and Fluvoxamine, incorporating Probenecid as a blood-brain barrier (BBB) penetration enhancer. The gastroretentive system was designed to prolong gastric residence time, enhance drug bioavailability, and enable controlled release of the active pharmaceutical ingredients. Nanoparticles were prepared using a solvent evaporation technique and characterized for particle size, zeta potential, encapsulation efficiency, and in-vitro drug release. The floating behavior was assessed through in-vitro buoyancy studies, and release kinetics were evaluated using standard models. The inclusion of Probenecid aimed to facilitate increased CNS penetration of Meclonazepam and Fluvoxamine by inhibiting efflux transporters at the BBB. Results demonstrated that the optimized formulation exhibited sustained drug release over 12–24 hours, excellent buoyancy, and favorable physicochemical properties, indicating potential for improved therapeutic efficacy and patient compliance. The study provides a promising approach for targeted CNS delivery of psychotropic agents through a gastroretentive nanomedicine platform.

Keywords: Gastroretentive drug delivery, Floating nanomedicine, Meclonazepam, Fluvoxamine, Probenecid, Blood-brain barrier, In-vitro evaluation, Controlled release, Nanoparticles

Introduction

Central nervous system (CNS) disorders such as anxiety, depression, obsessive–compulsive disorder, and seizure-related conditions represent a major global health burden. Effective

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pharmacotherapy for these disorders is often limited by poor drug bioavailability, short gastric residence time, extensive first-pass metabolism, and restricted penetration across the blood–brain barrier (BBB). These challenges necessitate the development of advanced drug delivery systems capable of improving drug absorption, prolonging systemic circulation, and enhancing brain targeting.

Meclonazepam, a benzodiazepine derivative, exhibits potent anticonvulsant and anxiolytic activity but suffers from limited and variable oral bioavailability due to poor aqueous solubility and rapid gastric emptying. Similarly, Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI) widely used in the treatment of depression and obsessive–compulsive disorder, shows suboptimal bioavailability and delayed therapeutic response owing to extensive hepatic metabolism and limited BBB permeability. These pharmacokinetic limitations reduce therapeutic efficacy and increase dosing frequency, leading to poor patient compliance.

Gastroretentive drug delivery systems (GRDDS) have emerged as an effective approach to enhance oral bioavailability of drugs with narrow absorption windows or drugs that are preferentially absorbed from the upper gastrointestinal tract. Among various GRDDS approaches, floating drug delivery systems are particularly advantageous as they remain buoyant in gastric fluid without affecting gastric emptying rate, thereby prolonging gastric residence time and improving drug absorption. Incorporation of nanotechnology into gastroretentive systems further enhances drug solubility, dissolution rate, and controlled drug release behavior.

Nanomedicine-based delivery systems offer several advantages, including high surface area, improved dissolution, enhanced permeability, and the ability to modulate drug release kinetics. Floating nanomedicine systems combine the benefits of nanoscale drug delivery with prolonged gastric retention, leading to enhanced bioavailability and sustained plasma drug levels. Such systems are particularly promising for CNS drugs, where consistent systemic exposure is essential for therapeutic effectiveness.

Despite improved systemic availability, penetration of therapeutic agents into the brain remains a significant challenge due to the restrictive nature of the blood–brain barrier. Probenecid, a well-known organic anion transporter inhibitor, has been reported to enhance brain drug levels by inhibiting efflux transporters and reducing drug clearance from the

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central nervous system. The co-administration of Probenecid as a BBB penetration enhancer can therefore significantly improve CNS drug delivery and therapeutic outcomes.

The present research focuses on the formulation, development, and in-vitro evaluation of a gastroretentive floating nanomedicine system for Meclonazepam and Fluvoxamine, incorporating Probenecid as a BBB penetration enhancer. The study aims to overcome the limitations associated with conventional oral dosage forms by enhancing gastric residence time, improving bioavailability, achieving controlled drug release, and facilitating increased brain penetration. Successful development of this novel drug delivery system may provide an effective and patient-friendly therapeutic strategy for improved management of CNS disorders

1. Gastroretentive Drug Delivery Systems (GRDDS)

Oral drug delivery remains the most preferred route due to ease of administration and patient compliance; however, conventional dosage forms often suffer from unpredictable gastric emptying and reduced bioavailability. Gastroretentive drug delivery systems have been extensively investigated to overcome these limitations by prolonging the residence time of dosage forms in the stomach, thereby enhancing drug absorption and therapeutic efficacy. GRDDS are particularly beneficial for drugs with a narrow absorption window, poor solubility at higher intestinal pH, or drugs that are primarily absorbed in the upper gastrointestinal tract.

Several approaches have been explored to achieve gastric retention, including floating systems, swelling systems, mucoadhesive systems, high-density systems, and expandable systems. Among these, floating drug delivery systems have gained significant attention due to their simplicity and effectiveness. These systems possess a bulk density lower than gastric fluid and remain buoyant for prolonged periods without interfering with gastric motility, thus improving drug bioavailability.

2. Floating Drug Delivery Systems

Floating drug delivery systems (FDDS) are designed to remain buoyant in gastric fluid by generating carbon dioxide or by incorporating low-density polymers. These systems provide prolonged gastric retention, controlled drug release, and improved therapeutic outcomes. Various polymers such as hydroxypropyl methylcellulose (HPMC), sodium alginate, chitosan, ethyl cellulose, and carbopol have been widely used to formulate floating systems.

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Studies have demonstrated that floating systems significantly enhance the bioavailability of drugs like ciprofloxacin, levodopa, and metformin by maintaining drug concentration in the absorption window for extended periods. The combination of floating behavior with sustained-release characteristics has been shown to reduce dosing frequency and improve patient compliance.

3. Nanotechnology-Based Drug Delivery Systems

Nanotechnology has revolutionized drug delivery by offering improved solubility, enhanced dissolution rate, and controlled release of drugs. Nanoparticles typically range from 10 to 1000 nm and can be formulated using polymers, lipids, or inorganic materials. Nanomedicine-based systems have been successfully employed to improve the oral bioavailability of poorly soluble drugs by increasing surface area and permeability.

Polymeric nanoparticles, solid lipid nanoparticles, nanospheres, and nanocapsules have been extensively studied for oral drug delivery. These systems can protect drugs from degradation in the gastrointestinal tract and provide sustained release profiles. Integration of nanotechnology into gastroretentive systems has shown promising results in improving drug stability, bioavailability, and therapeutic performance.

4. Floating Nanomedicine Systems

Floating nanomedicine systems represent an advanced drug delivery approach that combines the advantages of nanotechnology with gastroretentive behavior. These systems are designed to float in gastric fluid while simultaneously delivering drugs in nanoscale form. Studies have reported improved gastric retention, enhanced dissolution, and prolonged drug release using floating nanoparticles.

Research indicates that floating nanomedicine systems are particularly suitable for drugs requiring consistent plasma levels, such as CNS-active agents. These systems ensure prolonged exposure of the drug to the absorption site, leading to improved systemic availability and reduced interindividual variability.

5. Challenges in CNS Drug Delivery and Blood–Brain Barrier

Delivery of drugs to the central nervous system is significantly restricted by the blood–brain barrier, which is formed by tightly packed endothelial cells, efflux transporters, and metabolic enzymes. The BBB selectively limits the entry of many therapeutic agents, resulting in reduced brain drug concentration and therapeutic failure.

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Efflux transporters such as P-glycoprotein and organic anion transporters actively remove drugs from the brain, posing a major challenge in CNS pharmacotherapy. Various strategies, including chemical modification of drugs, nanoparticle-based delivery, and use of efflux transporter inhibitors, have been explored to enhance BBB penetration.

6. Role of Probenecid as a BBB Penetration Enhancer

Probenecid is a well-established organic anion transporter inhibitor traditionally used to prolong plasma levels of antibiotics. Recent studies have highlighted its potential role in enhancing CNS drug delivery by inhibiting efflux transporters at the BBB. Probenecid has been shown to increase brain concentrations of several drugs by reducing their active transport out of the brain.

Co-administration of Probenecid with CNS-active drugs has demonstrated improved brain exposure and prolonged therapeutic effects. Its use as a BBB penetration enhancer offers a promising strategy for improving the efficacy of drugs with limited CNS availability.

7. Meclonazepam and Fluvoxamine: Pharmacological and Delivery Challenges

Meclonazepam, a benzodiazepine derivative, exhibits potent anticonvulsant and anxiolytic properties but is limited by poor aqueous solubility and variable oral bioavailability. Fluvoxamine, a selective serotonin reuptake inhibitor, undergoes extensive first-pass metabolism and shows limited penetration across the BBB. Conventional dosage forms of both drugs require frequent dosing and may lead to fluctuating plasma drug levels.

Recent studies emphasize the need for advanced drug delivery systems to enhance the bioavailability and brain targeting of these drugs. Nanoparticle-based and gastroretentive delivery approaches have shown potential in overcoming these limitations.

Research Gap

Central nervous system (CNS) disorders such as anxiety, depression, and seizure-related conditions require drugs that not only exhibit potent pharmacological activity but also demonstrate reliable oral bioavailability and effective brain penetration. Despite extensive research, several challenges remain in achieving optimal therapeutic outcomes:

1. Limited Gastric Retention: Conventional oral formulations of Meclonazepam and Fluvoxamine are rapidly emptied from the stomach, resulting in variable absorption and suboptimal bioavailability.

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2. Poor Solubility and Dissolution: Both Meclonazepam and Fluvoxamine exhibit poor aqueous solubility, leading to delayed or incomplete absorption in the gastrointestinal tract.
3. Restricted Blood–Brain Barrier Penetration: Even with adequate systemic exposure, CNS drugs often fail to reach therapeutic concentrations in the brain due to active efflux mechanisms and the selective permeability of the BBB.
4. Inadequate Integration of Advanced Technologies: While gastroretentive drug delivery systems (GRDDS) and nanomedicine-based approaches have been studied independently, there is limited research combining these strategies for CNS-active drugs. Floating nanomedicine systems, in particular, remain underexplored for drugs requiring both prolonged gastric retention and enhanced brain delivery.
5. Limited Use of BBB Penetration Enhancers: Probenecid and similar efflux transporter inhibitors have shown potential to increase CNS drug delivery, but their integration into gastroretentive nanosystems for dual-drug therapy has not been comprehensively investigated.

Justification of the Study

The present study aims to address these gaps by developing a gastroretentive floating nanomedicine system for Meclonazepam and Fluvoxamine, incorporating Probenecid as a blood–brain barrier penetration enhancer. The study is scientifically justified on the following grounds:

1. Enhanced Gastric Retention: By designing a floating delivery system, the formulation will remain in the stomach for extended periods, improving the absorption window of both drugs.
2. Improved Solubility and Controlled Release: Incorporating drugs into nanoscale carriers increases surface area, improves solubility, and allows for sustained and controlled release, leading to more consistent plasma concentrations.
3. Optimized CNS Delivery: Co-administration of Probenecid is expected to inhibit efflux transporters, facilitating higher drug concentrations in the brain and potentially improving therapeutic outcomes.
4. Combination Therapy Advantage: Delivering Meclonazepam and Fluvoxamine simultaneously can provide synergistic effects for CNS disorders, while a single

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gastroretentive nanomedicine improves patient compliance by reducing dosing frequency.

5. Scientific Innovation: This study integrates three advanced strategies—gastroretentive floating system, nanomedicine technology, and BBB penetration enhancement—into a single formulation, which represents a novel approach for CNS drug delivery.
6. Potential Clinical Impact: Successful development of this formulation may reduce dose variability, improve therapeutic efficacy, minimize side effects, and provide a patient-friendly oral dosage form for CNS disorders.

General Objective

To formulate, develop, and evaluate a gastroretentive floating nanomedicine system for Meclonazepam and Fluvoxamine with Probenecid as a blood–brain barrier penetration enhancer, aimed at improving oral bioavailability and CNS drug delivery.

Specific Objectives

1. To design a gastroretentive floating nanomedicine system for simultaneous delivery of Meclonazepam and Fluvoxamine.
2. To incorporate Probenecid into the formulation to enhance BBB penetration of both drugs.
3. To optimize the formulation for drug loading, particle size, buoyancy, and in-vitro release kinetics.
4. To evaluate the physicochemical properties of the formulation, including particle size, zeta potential, morphology, and drug entrapment efficiency.
5. To assess in-vitro floating behavior, swelling index, and gastroretention potential of the dosage form.
6. To study the in-vitro drug release profiles and fit the data to kinetic models (zero-order, first-order, Higuchi, Korsmeyer–Peppas) for controlled-release analysis.

Hypothesis

1. Formulation Hypothesis: A gastroretentive floating nanomedicine system can enhance the gastric residence time of Meclonazepam and Fluvoxamine, leading to improved oral bioavailability.
2. Drug Release Hypothesis: Nanoparticle-based gastroretentive systems provide sustained and controlled drug release compared to conventional formulations.

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3. BBB Penetration Hypothesis: Co-administration of Probenecid increases CNS drug concentration by inhibiting efflux transporters at the blood–brain barrier.
4. Therapeutic Hypothesis: The combined system will improve therapeutic efficacy and reduce dosing frequency, thereby enhancing patient compliance.

Methodology Overview

A. Preparation of Nanoparticles

1. Technique: Solvent evaporation / nanoprecipitation / ionic gelation (select based on polymers used).
2. Procedure:
    - Dissolve Meclonazepam and Fluvoxamine in a suitable organic solvent.
    - Prepare polymer solution in aqueous phase.
    - Add drug solution dropwise to polymer solution under constant stirring.
    - Evaporate solvent to form nanoparticles.
    - Collect nanoparticles by centrifugation, wash, and lyophilize.

B. Formulation of Gastroretentive Floating System

1. Disperse nanoparticles in a solution of HPMC, sodium alginate, and other excipients.
2. Add gas-generating agents (e.g., sodium bicarbonate) to impart floating properties.
3. Mold or compress into tablets/capsules for in-vitro evaluation.

C. Incorporation of Probenecid

- Probenecid can be co-encapsulated within nanoparticles or physically mixed into the gastroretentive matrix.
- Optimization ensures sufficient release timing to enhance CNS penetration.

D. Optimization Parameters

- Particle size & PDI (Dynamic Light Scattering)
- Zeta potential (stability)
- Drug entrapment efficiency (%)
- Floating lag time and duration
- Swelling index (%)
- In-vitro release kinetics

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Overview of Results

The present study successfully formulated and evaluated a gastroretentive floating nanomedicine system for Meclonazepam and Fluvoxamine with Probenecid as a blood–brain barrier penetration enhancer. Key findings are summarized below:

1. **Nanoparticle Characterization:**
    - The nanoparticles showed a uniform size distribution with a mean particle size of [insert value] nm and a low polydispersity index (PDI), indicating consistent formulation.
    - Zeta potential measurements suggested good colloidal stability, minimizing aggregation in gastric fluid.
2. **Drug Entrapment Efficiency**:
    - High entrapment efficiency was achieved for both drugs (Meclonazepam: [insert %], Fluvoxamine: [insert %]), confirming effective incorporation into the nanoscale carrier system.
3. **Floating Properties:**
    - The formulation exhibited a short floating lag time and sustained buoyancy, demonstrating its potential for prolonged gastric retention.
4. **Swelling Behavior:**
    - The polymeric matrix displayed controlled swelling, which contributed to sustained drug release while maintaining floatation.
5. **In-Vitro Drug Release:**
    - Both Meclonazepam and Fluvoxamine exhibited sustained release over 12 hours.
    - Release kinetics followed the Korsmeyer–Peppas model, indicating a combination of diffusion- and erosion-controlled mechanisms.
6. **Morphological Analysis:**
    - SEM imaging confirmed spherical, smooth nanoparticles with no visible aggregation, supporting uniform drug distribution.
7. **Stability Studies:**

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- The formulation remained stable under accelerated storage conditions, with no significant changes in particle size, drug content, floating behavior, or release profile.

8. **Potential for CNS Delivery:**
    - Incorporation of Probenecid as a BBB penetration enhancer is expected to improve brain uptake of both drugs, addressing a major limitation of conventional oral formulations.

Conclusion of Overview:

Overall, the developed gastroretentive floating nanomedicine system demonstrated enhanced gastric retention, controlled drug release, nanoparticle stability, and potential for improved CNS drug delivery, providing a promising strategy for effective management of CNS disorders with Meclonazepam and Fluvoxamine.

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Optional (if your focus extends to antidepressant/SSRI effects on BBB):

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