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FORMULATION, OPTIMIZATION, AND IN-VITRO EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF LAFUTIDINE USING NATURAL POLYMERS

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ABSTRACT :

This study aims to design, develop, and evaluate gastroretentive floating tablets of lafutidine a potent anti-ulcer drug to prolong gastric residence time and enhance therapeutic efficacy. Preformulation characterization confirmed the identity, purity, and appropriate lipophilicity (log P = 3.8) of lafutidine. Tablets containing 10 mg of lafutidine were prepared via wet granulation using varying concentrations of synthetic (HPMC K100) and natural (chitosan) hydrophilic swellable polymers. Pre-compression evaluations demonstrated excellent flow properties for all powder blends. Post-compression parameters confirmed compliance with official pharmacopeial specifications regarding weight variation, hardness (4.8-6.5kp), friability (< 0.6%), floating lag time (32–82 sec), total floating time (> 12 hours for optimized batches), and drug content uniformity (97.9–100.2%). In-vitro dissolution studies over 12 hours in 0.1 N HCl (pH 1.2) identified batch F4 (50 mg HPMC K100) and batch F7 (30 mg Chitosan) as optimal configurations, achieving cumulative drug releases of 84.56% and 98.25%, respectively. Kinetic modeling of the optimized batch F7 revealed that drug release followed the Higuchi model ($R^2 = 0.942$), indicating diffusion-controlled matrix release. Accelerated stability testing for 90 days) established the robustness and stability of the formulation, with similarity factors (F2) remaining above 50.

Keywords: Lafutidine, Floating Drug Delivery System (FDDS), HPMC K100, Chitosan, Release Kinetics, Gastroretentive.

1. Introduction:

Lafutidine is a second-generation histamine H2-receptor antagonist possessing gastroprotective properties, making it widely useful in the management of gastric ulcers and gastritis. However, conventional oral formulations often experience limited gastric residence times and absorption windows in the upper gastrointestinal tract, which can compromise bioavailability.Gastroretentive Floating Drug Delivery Systems (FDDS) provide an effective strategy to retain dosage forms in the stomach, thereby sustaining drug release, improving local therapeutic action, and maximizing absorption. This study investigates the development of single-unit floating matrix tablets of lafutidine utilizing two distinct swellable polymers: hydroxypropyl methylcellulose (HPMC K100) and chitosan, alongside a gas-generating agent ($NaHCO_3$) to achieve buoyancy and extended release.

2. Materials and Methods

2.1. Preformulation Studies and Physicochemical Characterization

- **Organoleptic Properties:** The color, odor, and physical nature (crystalline/amorphous) of pure lafutidine were visually and organoleptically examined.
- **Melting Point and Partition Coefficient:** Determined using standard capillary melting point apparatus and the shake-flask method in an n-octanol/water system, respectively.
- **Solubility Profile:** Evaluated across multiple media including water, 0.1 N HCl (pH 1.2), pH 4.5 acetate buffer, pH 6.8 phosphate buffer, methanol, and methylene chloride.
- **FTIR Spectroscopy:** Fourier-transform infrared spectra of pure drug, excipients, and their physical mixtures were recorded to identify principal functional groups (N-H, C=O, S=O, C-O-C) and evaluate drug-excipient compatibility.
- **Standard Calibration Curve:** Prepared in 0.1 N HCl (pH 1.2) by measuring absorbance at 290 nm using a UV-visible spectrophotometer

across concentrations ranging from 5 to 40 µg/mL.

- **Drug-Excipient Compatibility:** Evaluated by storing binary and tertiary mixtures (drug + polymers + gas generators + diluents) at 25C/60% RH and 40C/75\%RH for one month, followed by visual and physical examination.

2.2. Preparation of Floating Tablets

Tablets were prepared via wet granulation. Ten distinct formulations (**F1 to F10**) containing 10 mg of lafutidine were formulated using varying concentrations of HPMC K100 (F1–F5) or Chitosan (F6–F10), combined with sodium bicarbonate $NaHCO_3$, 60 mg) as a gas-generating agent, citric acid (10 mg), microcrystalline cellulose (MCC 3%, 30 mg), and lactose as a diluent to a total tablet weight of 200 mg.

2.3. Evaluation of Pre-Compression Powder Blends

The prepared granules/powder blends were evaluated for bulk density, tapped density, Carr's compressibility index, Hausner's ratio, and angle of repose (θ) using standard pharmacopeial methods.

2.4. Post-Compression Evaluation of Floating Tablets

The compressed tablets were assessed for:

- **Weight Variation:** Determined on 20 tablets.
- **Hardness & Thickness:** Measured using a Monsanto hardness tester and digital caliper (n=6).
- **Friability:** Determined using a Roche friabilator on 20 tablets.
- **Floating Lag Time (FLT) & Total Floating Time (TFT):** Measured in 0.1 N HCl (pH 1.2) at 37C
- **Drug Content Uniformity:** Assayed spectrophotometrically on 10 pulverized tablets.

2.5. In-Vitro Dissolution and Release Kinetics

In-vitro drug release studies were performed over 12 hours using USP dissolution apparatus in 900 mL of 0.1 N HCl (pH 1.2) at 37C and 50 rpm. Aliquots were withdrawn at predetermined time intervals, filtered, and analyzed spectrophotometrically. The release data for the optimized formulation were fitted into various mathematical kinetic models (Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models) to determine the mechanism of drug release.

2.6. Accelerated Stability Studies

The optimized formulation (**F7**) was subjected to stability studies under accelerated conditions of 37C and 75%RH for 90 days. Samples were evaluated periodically for appearance, hardness, drug content, in-vitro release profile, and analyzed via difference (f_1) and similarity (f_2) factors.

3. Results and Discussion

3.1. Preformulation and Physicochemical Findings

Organoleptic analysis confirmed lafutidine to be a white, odorless, crystalline powder. The melting point was recorded at **93.6 °C**, and the partition coefficient ($\log P$) was found to be **3.8 ± 0.2**, demonstrating high lipophilicity suitable for membrane permeability.
Solubility studies indicated that lafutidine is practically insoluble in water and pH 4.5 buffer, very slightly soluble in pH 6.8 phosphate buffer, but freely soluble in 0.1 N HCl at pH 1.2 (**195 mg/mL**), , confirming its suitability for gastric release. FTIR spectra confirmed absolute drug purity, exhibiting characteristic peaks at **3292.2 cm^{-1} (N-H stretch) 1655.6 cm^{-1} (C=O stretch), 1040.9 cm^{-1} (S=O stretch), and 1265 cm^{-1} (C-O-C stretch)**. Drug-excipient compatibility studies verified that lafutidine remained chemically and physically stable with all selected matrix ingredients.

3.2. Pre-Compression Parameters

The powder blends for batches **F1 to F10** exhibited good flow characteristics:

- **Angle of Repose:** Ranged between 24.45^∘ and 29.22^∘.
- **Carr's Index:** All values remained below **18.3%**.
- **Hausner's Ratio:** Maintained below **1.19**.

3.3. Post-Compression Tablet Properties

All formulations complied with official weight variation limits (average weight $\sim 200\text{ mg}$). Hardness ranged from **4.8 to 6.5 kp**, and

friability remained under **0.6% w/w**, indicating robust mechanical resistance.

Increasing polymer concentration (HPMC K100 or Chitosan) enhanced matrix cohesion and carbon dioxide gas entrapment, effectively reducing the **Floating Lag Time (FLT)** down to 32 seconds (F5) and extending the **Total Floating Time (TFT)** beyond 12 hours for optimized batches.

3.4. In-Vitro Drug Release Performance

- **HPMC Series (F1–F5):** Cumulative release at 12 hours varied from 63.57% (F1, 20 mg polymer) to 84.56% (F4, 50 mg polymer). Batch **F4** was identified as the optimal HPMC formulation, showing controlled structural integrity and diffusion behavior.
- **Chitosan Series (F6–F10):** Chitosan-based matrices exhibited faster initial release profiles driven by protonation of primary amino groups ($-NH_2 \rightarrow -NH_3^+$) in acidic media, facilitating rapid gel swelling and relaxation. Cumulative 12-hour releases ranged from 89.65% to 98.25%. Batch **F7** (30 mg Chitosan) demonstrated the most optimal controlled-release trajectory, reaching **98.25%** cumulative release at 12 hours.

3.5. Release Kinetics

The in-vitro release data of the optimized batch **F7** were fitted into mathematical kinetic models. The regression coefficient (R2) values were:

- **Zero-order Model:** R2=0.628
- **First-order Model:** R2=0.786
- **Higuchi Model:** R2=0.942
- **Korsmeyer-Peppas Model:** R2=0.6951

The highest linearity was observed with the **Higuchi model** (R2=0.942), indicating that drug release from the chitosan floating matrix occurred primarily via a square root of time-dependent diffusion process.

3.6. Stability Studies

Accelerated stability testing of batch **F7** at 40∘C/75% RH for 90 days revealed no significant alterations in appearance, hardness, or drug content (retaining **97.67%** assay value at 90 days). The similarity factor (f2) remained well above the acceptable threshold of 50 (**72.37** at 90 days), confirming excellent shelf-life stability.

4. Conclusion

Gastroretentive floating tablets of lafutidine were successfully formulated using HPMC K100 and chitosan. Batch **F4** (containing 50 mg HPMC K100) and batch **F7** (containing 30 mg Chitosan) exhibited ideal buoyancy, excellent mechanical properties, and extended release profiles over 12 hours. With superior release kinetics obeying the Higuchi diffusion model and proven accelerated stability, the optimized chitosan-based floating matrix tablet demonstrates strong potential for improved clinical efficacy in anti-ulcer therapy.