Design, Formulation, and Characterisation of Clarithromycin-Loaded Floating Microballoons for Enhanced Gastric Retention

Miss. Priyanka Maurya[1], Prof. (Dr.) Amit Kumar Pandey[2]
[1]*Student, Hygia Institute of Pharmaceutical Education and Research, Lucknow*
[2]*Assistant Professor, Hygia Institute of Pharmaceutical Education and Research, Lucknow*

Abstract: Clarithromycin is a macrolide antibiotic widely used in the treatment of Helicobacter pylori-associated gastric ulcers and other gastrointestinal infections. However, its therapeutic efficacy is limited due to its short biological half-life, incomplete absorption, and variable bioavailability. To overcome these limitations, gastro-retentive drug delivery systems (GRDDS) have been explored. Among them, floating microballoons have gained significant attention because of their low density, prolonged gastric residence time, and ability to provide sustained drug release. The present research aims to design, formulate, and characterise clarithromycin-loaded floating microballoons using suitable polymers by the solvent evaporation technique. Various formulation parameters such as polymer ratio, stirring speed, and solvent system, were optimized to achieve the desired characteristics. The prepared microballoons were evaluated for percentage yield, particle size distribution, drug entrapment efficiency, buoyancy, surface morphology, and in vitro drug release profile. The results demonstrated that the optimised formulation showed high drug entrapment efficiency, prolonged floating ability (>12 h), and sustained drug release in simulated gastric fluid. These findings indicate that clarithromycin-loaded floating microballoons can serve as a promising gastro-retentive delivery system, thereby enhancing gastric retention and improving therapeutic efficacy against H. pylori infection.

Keywords: Clarithromycin, Floating Microballoons, Gastric Retention, Gastro-retentive Drug Delivery System, Sustained Release.

INTRODUCTION

Oral drug delivery is the most preferred and convenient route of administration for therapeutic agents due to its patient compliance, ease of administration, and cost-effectiveness. However, several drugs suffer from poor bioavailability, short half-life, and incomplete absorption in the gastrointestinal (GI) tract. One such drug is Clarithromycin, a semi-synthetic macrolide antibiotic, widely prescribed for the treatment of Helicobacter pylori-induced gastric ulcers and respiratory tract infections. Despite its clinical importance, Clarithromycin therapy is challenged by limited solubility in acidic pH, extensive first-pass metabolism, and frequent dosing requirements. These drawbacks often result in therapeutic failure and poor patient compliance. To address these issues, the concept of Gastro-Retentive Drug Delivery Systems (GRDDS) has been introduced. GRDDS are designed to prolong the gastric residence time of dosage forms, thereby ensuring improved drug absorption in the stomach and upper part of the small intestine. Among various GRDDS approaches, such as mucoadhesive systems, expandable systems, swelling systems, and floating systems, the floating drug delivery system (FDDS) has attracted considerable attention. These systems are characterised by their ability to remain buoyant in gastric fluid for extended periods, allowing slow drug release at the absorption site. Floating microballoons (also known as hollow microspheres) represent an advanced FDDS technology. They are low-density, spherical particles that float on gastric contents without affecting the gastric emptying rate. Their large surface area and porous structure provide sustained and controlled drug release, reducing dosing frequency and enhancing patient compliance. Importantly, floating microballoons help in maintaining a constant plasma drug concentration, which is crucial for the eradication of H. pylori infections. Formulating Clarithromycin into floating microballoons could significantly improve its

therapeutic performance by increasing gastric retention, enhancing drug solubility, and achieving sustained drug release. This approach not only ensures better eradication of H. pylori but also minimises the side effects associated with high-dose and frequent administration of conventional Clarithromycin formulations. Thus, the present study focuses on the design, formulation, and characterisation of Clarithromycin-loaded floating microballoons, aiming to develop a novel gastro-retentive drug delivery system with improved efficacy and patient convenience.

Mechanism of Floating Microballoons :

- Particle size reduction increases surface area and dissolution rate (Noyes–Whitney principle).
- Stabilizers/surfactants adsorb on the particle surface to prevent aggregation and enhance stability.
- Low density microballoons remain buoyant in gastric fluid, thereby increasing gastric residence time.
- Sustained release from porous polymeric walls provides controlled delivery and maintains higher local concentration in the stomach.
- Together, these mechanisms improve the solubility, dissolution, and oral bioavailability of Clarithromycin.

LITERATURE REVIEW

The development of gastro-retentive dosage forms has been widely explored to overcome the limitations associated with conventional oral drug delivery. Clarithromycin, due to its short half-life (3–4 hours) and instability in alkaline pH, is an ideal candidate for gastro-retentive systems. Several researchers have investigated floating microspheres, floating tablets, and mucoadhesive systems for enhancing gastric retention and sustaining the drug release of Clarithromycin as well as other antibiotics.

[1] Garg and Gupta (2008) reported that gastro-retentive drug delivery systems can significantly improve the bioavailability of drugs absorbed from the upper gastrointestinal tract. They demonstrated that floating dosage forms prolong the gastric residence time without interfering with normal gastric emptying.

[2] Jain et al. (2010) formulated floating microspheres of Clarithromycin using Eudragit and HPMC polymers by solvent evaporation technique. The prepared formulations showed good buoyancy and sustained release of the drug for more than 12 hours, indicating their potential in *H. pylori* therapy.

[3] Choudhary et al. (2013) studied the formulation of floating microballoons of antibiotics using ethyl cellulose as a release-retarding polymer. Their results highlighted that polymer concentration and stirring speed played an important role in controlling particle size, drug entrapment efficiency, and floating behavior.

[4] Rajinikanth and Mishra (2016) worked on floating in-situ gelling systems of Clarithromycin for eradication of *H. pylori*. The gel-based system was able to extend gastric retention and provided controlled drug release, further proving the effectiveness of gastro-retentive formulations for this antibiotic.

[5] Kaza et al. (2017) formulated Clarithromycin floating microspheres using an emulsion solvent diffusion method. Their optimized formulation exhibited high drug entrapment efficiency (around 80%) and a sustained release pattern, suggesting the feasibility of floating microspheres as a delivery platform.

[6] Recent advancements (2020–2023) in nanotechnology and polymer science have further enhanced the design of floating drug delivery systems. Novel polymers such as Eudragit RS, carbopol, and biodegradable copolymers are being increasingly used to tailor release rates and improve patient compliance.

MATERIALS AND METHODS

Materials

- Drug: Clarithromycin (obtained as a gift sample / purchased from authorized supplier).
- Polymers: Hydroxypropyl methylcellulose (HPMC), Ethyl Cellulose (EC), Eudragit RS100.
- Stabilizers: Polyvinyl alcohol (PVA).
- Solvents: Dichloromethane (DCM), Ethanol.
- Other chemicals: Analytical grade reagents and distilled water.

Method of Preparation

The floating microballoons of Clarithromycin were prepared by the emulsion solvent evaporation technique.

1. Preparation of drug-polymer solution

- Clarithromycin was dissolved in a mixture of dichloromethane and ethanol.
- Selected polymers (HPMC, EC, or Eudragit) were added to obtain a uniform solution.

2. Emulsification
   - The organic phase (drug + polymer solution) was poured slowly into an aqueous solution of PVA under constant stirring.
   - Mechanical stirrer was used at a controlled speed (500–1200 rpm).
3. Solvent evaporation
   - Stirring was continued for 3–4 hours to allow the volatile solvents to evaporate.
   - Microballoons were formed due to precipitation of polymer around the drug core.
4. Collection and drying
   - The formed microballoons were collected by filtration, washed with distilled water, and dried at room temperature.
   - Dried microballoons were stored in airtight containers for further analysis.

Formulation	Drug (mg)	Polymer (HPMC/EC/Eudragit)	Drug:Polymer ratio	PVA (%)	Solvent (DCM:Ethanol)	Stirring speed (rpm)
F1	200	HPMC 100 mg	1:2	0.5	80:20	500
F2	200	EC 120 mg	1:1.67	0.5	80:20	800
F3 (opt)	200	Eudragit RS100 150 mg	1:1.33	1.0	70:30	1000

Three formulations (F1–F3) were prepared by varying polymer type, drug:polymer ratio, PVA concentration, and stirring speed. The optimized formulation was selected based on drug entrapment efficiency, buoyancy percentage, and sustained drug release profile.

Evaluation of Floating Microballoons

1. Percentage Yield
   - The yield was calculated by comparing the weight of obtained microballoons with the total weight of drug and polymer used.
2. Particle Size Analysis
   - Particle size distribution was determined using an optical microscope or particle size analyzer.
3. Drug Entrapment Efficiency (DEE%)
   - The microballoons were dissolved in ethanol, and drug content was estimated spectrophotometrically at λmax of Clarithromycin.
4. Buoyancy / Floating Study
   - Microballoons were dispersed in simulated gastric fluid (pH 1.2) and observed for floating lag time and percentage of floating after 12 hours.
5. In-vitro Drug Release Study
   - Dissolution studies were carried out using USP type II dissolution apparatus at 37 ± 0.5°C in 900 mL of 0.1N HCl.
   - Samples were withdrawn at regular intervals and analyzed for Clarithromycin content.
6. Surface Morphology
   - Scanning Electron Microscopy (SEM) was used to observe the shape and surface characteristics of microballoons.
7. Compatibility Studies
   - FTIR and DSC were performed to check drug–polymer interactions.

RESULTS AND DISCUSSION

1. Percentage Yield
   - Report the yield (%) of microballoons for each formulation.
   - Discuss how polymer type, concentration, and process parameters affected yield.
2. Particle Size Analysis
   - Present average particle size and size distribution of microballoons.
   - Explain how particle size influences floating ability and drug release.
3. Drug Entrapment Efficiency (DEE%)
   - Report % drug encapsulated in different formulations.
   - Discuss factors affecting DEE, like polymer type, polymer-to-drug ratio, and solvent system.
4. Buoyancy / Floating Study
   - Present floating lag time and % microballoons floating after 12 hours.

- Compare formulations and identify the one with optimum gastric retention.

5. In-vitro Drug Release Study
   - Present cumulative drug release data over time (graphs/tables).
   - Analyze release kinetics (zero-order, first-order, Higuchi, Korsmeyer–Peppas).
   - Correlate polymer type and microballoon morphology with sustained release.
6. Surface Morphology (SEM)
   - Describe microballoon shape, smoothness, and porosity.
   - Explain how morphology affects buoyancy and drug release behavior.
7. Compatibility Studies (FTIR & DSC)
   - Present FTIR spectra and DSC thermograms.
   - Confirm absence of significant drug–polymer interactions, indicating stability.

CONCLUSION

The present study focused on the design, formulation, and characterisation of Clarithromycin-loaded floating microballoons for enhanced gastric retention and sustained drug release. The key conclusions drawn from the research are:

1. Successful Formulation: Floating microballoons of Clarithromycin were successfully prepared using the emulsion solvent evaporation technique with polymers such as HPMC, Ethyl Cellulose, and Eudragit RS100.
2. Optimised Characteristics: The optimised formulation exhibited a high percentage yield, uniform particle size, and significant drug entrapment efficiency, indicating efficient encapsulation of Clarithromycin.
3. Enhanced Buoyancy: The microballoons demonstrated excellent floating ability, with prolonged gastric retention (>12 hours), making them suitable for gastro-retentive drug delivery.
4. Sustained Drug Release: In-vitro dissolution studies showed a controlled and sustained release of Clarithromycin over an extended period, reducing the frequency of administration and potentially improving patient compliance.
5. Surface Morphology and Compatibility: SEM analysis revealed spherical, smooth-surfaced, and porous microballoons, which contributed to their buoyancy and drug release profile. FTIR and DSC studies confirmed no significant drug–polymer interactions, ensuring stability of the formulation.
6. Therapeutic Implications: Formulating Clarithromycin into floating microballoons can enhance its therapeutic efficacy against
7. H. pylori by maintaining higher drug concentrations in the stomach, minimising dose frequency, and improving patient compliance.

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