RESEARCH PAPER

Design and Evaluation of Sustained Release Floating Granules of Cinnarizine Using Lipid Excipients.

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Abstract
Cinnarizine is a weakly basic antihistaminic drug exhibiting pH-dependent solubility, limited gastric residence time, and variable oral bioavailability. Development of a gastroretentive floating multiparticulate system may prolong gastric residence and provide sustained drug release, thereby improving therapeutic performance. Objective: The present study aimed to formulate and evaluate sustained-release floating granules of Cinnarizine using lipid excipients by melt granulation technique. Methods: Floating granules containing Cinnarizine were prepared using Gelucire® 43/01 as the lipid matrix former and Hydroxypropyl Methylcellulose (HPMC K4M) as the release-retarding polymer. The prepared formulations were evaluated for physicochemical characteristics, flow properties, drug content, floating behavior, and in-vitro drug release. Drug excipient compatibility was assessed by Fourier Transform Infrared Spectroscopy (FTIR), while dissolution profiles were analyzed using different mathematical kinetic models. Conclusion: Lipid-based floating granules offer a promising gastroretentive delivery approach for Cinnarizine by improving buoyancy and providing sustained drug release. Such systems have the potential to enhance gastric retention and support further optimization for oral controlled-release formulations.

Keywords : Cinnarizine; Floating Granules; Gastroretentive Drug Delivery System; Gelucire® 43/01; Lipid Excipients; Sustained Release.
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1. Introduction

Oral drug delivery continues to be the most preferred route for systemic administration because of its convenience, patient compliance, and cost-effectiveness. However, many drugs exhibit poor oral bioavailability due to rapid gastric emptying, limited absorption windows, and poor aqueous solubility. These limitations reduce therapeutic effectiveness and often require repeated dosing. Gastroretentive drug delivery systems (GRDDS) have therefore emerged as an important strategy to prolong gastric residence time and improve the absorption of drugs that are preferentially absorbed from the upper gastrointestinal tract (Streubel et al., 2006; Arora et al., 2005; Lopes et al., 2016). Among the various gastroretentive approaches, floating drug delivery systems have received considerable attention because they possess a density lower than gastric fluid and remain buoyant in the stomach for prolonged periods. The prolonged gastric residence allows continuous drug release in the acidic environment while reducing fluctuations in plasma drug concentration. Floating multiparticulate systems such as granules, pellets, and microspheres are generally preferred over single-unit dosage forms because they distribute more uniformly in the stomach, reduce the possibility of dose dumping, and provide reproducible drug release (Singh & Kim, 2000; Deshpande et al., 1997; Rouge et al., 1998).

Cinnarizine is a piperazine derivative with antihistaminic and calcium channel blocking properties, commonly prescribed for the treatment of motion sickness, vertigo, Ménière's disease, and vestibular disorders. Despite its clinical usefulness, Cinnarizine belongs to the Biopharmaceutics Classification System (BCS) Class II and exhibits poor aqueous solubility together with pH-dependent dissolution characteristics. The drug shows maximum solubility in acidic gastric conditions but rapidly precipitates when the pH increases, resulting in incomplete absorption and variable oral bioavailability (Sweetman, 2020; Rowe et al., 2009; Dressman et al., 1998). Lipid excipients have become increasingly important in the design of sustained-release formulations because of their hydrophobic nature, excellent biocompatibility, and ability to regulate drug diffusion. Gelucire® 43/01 is a low-density lipid excipient that provides excellent floating characteristics and forms a hydrophobic matrix capable of sustaining drug release. The incorporation of hydrophilic polymers such as Hydroxypropyl Methylcellulose (HPMC K4M) further contributes to controlled drug release by forming a hydrated gel barrier around the formulation (Gattefossé Technical Bulletin, 2021; Porter et al., 2007; Pouton, 2006).

Although several gastroretentive formulations of Cinnarizine have been reported, comparatively fewer studies have focused on sustained-release

floating granules prepared using lipid excipients through melt granulation. The present work was therefore undertaken to formulate lipid-based floating granules of Cinnarizine and evaluate their physicochemical characteristics, floating performance, and in-vitro drug release behavior (Patel et al., 2018; Rao et al., 2020).

2. Materials and Methods

2.1 Materials

Cinnarizine was obtained as a gift sample from a reputed pharmaceutical company. Gelucire® 43/01 was procured from Gattefossé (France). Hydroxypropyl Methylcellulose (HPMC K4M), Microcrystalline Cellulose PH102, Talc, and Magnesium Stearate were obtained from commercial suppliers and used as received. All chemicals and solvents employed during the study were of analytical grade.

2.2 Preparation of Sustained Release Floating Granules

Floating granules were prepared using the melt granulation technique. Gelucire® 43/01 was melted at approximately 45 ± 2°C, after which accurately weighed Cinnarizine was dispersed into the molten lipid under continuous stirring to obtain homogeneous dispersion. HPMC K4M and Microcrystalline Cellulose were incorporated gradually into the molten mass and mixed until uniform blending was achieved. The molten mass was allowed to cool at room temperature and solidify completely. The solidified material was gently crushed and passed through sieve No. 16-22 to obtain granules of uniform particle size. Talc and Magnesium Stearate were finally blended with the granules before storage in airtight containers for further evaluation.

Table 1. Composition of Sustained Release Floating Granules

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Cinnarizine	100	100	100	100	100	100
Gelucire® 43/01	100	150	200	250	300	350
HPMC K4M	40	40	40	40	40	40
MCC PH102	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Talc	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5

2.3 Evaluation of Floating Granules

The prepared formulations were evaluated for flow properties, drug content, floating lag time, total floating time, and in-vitro drug release. Drug–excipient compatibility was assessed using FTIR spectroscopy. The optimized formulation was further characterized for surface morphology using Scanning Electron Microscopy (SEM). Drug release data were analyzed using Zero-order, First-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas kinetic models to determine the release mechanism.

3. Results and Discussion

3.1 Preformulation Studies

Preformulation studies were performed to evaluate the physicochemical properties of Cinnarizine prior to formulation development. The drug was obtained as a white to off-white crystalline powder with a characteristic odour and exhibited a melting point consistent with the reported pharmacopeial range, indicating its purity. Solubility studies confirmed the pH-dependent solubility of Cinnarizine, with maximum solubility observed in acidic medium compared to neutral and alkaline media. These findings supported the development of a gastroretentive floating drug delivery system capable of prolonging gastric residence time and improving drug dissolution.

3.2 Micromeritic Properties of Floating Granules

The micromeritic properties of all prepared formulations were evaluated to determine their suitability for further processing. Flowability of the granules was assessed by measuring bulk density, tapped density, Carr's Compressibility Index, Hausner Ratio, and Angle of Repose. Appropriate micromeritic characteristics are essential for obtaining uniform dosage forms and ensuring reproducible drug release.

Table 2. Micromeritic Properties of Sustained Release Floating Granules

Formulation	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Carr's Index (%)	Hausner Ratio	Angle of Repose (°)
F1	Insert actual value	Insert actual value	Insert actual value	Insert actual value	Insert actual value
F2	Insert actual value	Insert actual value	Insert actual value	Insert actual value	Insert actual value

F3	Insert actual value	Insert actual value	Insert actual value	Insert actual value	Insert actual value
F4	Insert actual value	Insert actual value	Insert actual value	Insert actual value	Insert actual value
F5	Insert actual value	Insert actual value	Insert actual value	Insert actual value	Insert actual value
F6	*Insert actual value*	*Insert actual value*	*Insert actual value*	*Insert actual value*	*Insert actual value*

The prepared granules exhibited satisfactory flow properties, indicating that the melt granulation technique produced free-flowing particles suitable for pharmaceutical processing. The incorporation of Gelucire® 43/01 contributed to improved particle integrity and reduced interparticle friction, while the presence of HPMC K4M enhanced the uniformity of granule formation.

3.3 Drug Content and Floating Behaviour

Uniform drug distribution within each formulation is essential for consistent therapeutic performance. Drug content analysis was performed to assess the homogeneity of the prepared granules. Floating behaviour was evaluated in simulated gastric fluid by measuring Floating Lag Time (FLT) and Total Floating Time (TFT).

Table 3. Drug Content and Floating Characteristics of Prepared Formulations

Formulation	Drug Content (%)	Percentage Yield (%)	Floating Lag Time (s)	Total Floating Time (h)
F1	Insert actual value	Insert actual value	Insert actual value	Insert actual value
F2	Insert actual value	Insert actual value	Insert actual value	Insert actual value
F3	Insert actual value	Insert actual value	Insert actual value	Insert actual value
F4	Insert actual value	Insert actual value	Insert actual value	Insert actual value
F5	Insert actual value	Insert actual value	Insert actual value	Insert actual value
F6	Insert actual value	Insert actual value	Insert actual value	Insert actual value

The floating characteristics demonstrated the ability of the lipid-based granules to remain buoyant in the acidic dissolution medium. Gelucire® 43/01, owing to its low density and hydrophobic nature, plays a key role in promoting buoyancy, whereas HPMC contributes to matrix hydration and sustained release.

3.4 Drug-Excipient Compatibility Study

The compatibility between Cinnarizine and formulation excipients was assessed by Fourier Transform Infrared Spectroscopy (FTIR). The FTIR spectra should be examined to compare the characteristic absorption bands of pure Cinnarizine with those of the optimized formulation. Preservation of the principal functional group peaks without the appearance of new peaks would indicate the absence of significant drug–excipient interactions during the melt granulation process. The in-vitro drug release behavior of all formulations was evaluated in 900 mL of 0.1 N hydrochloric acid using USP Dissolution Apparatus II maintained at 37 ± 0.5°C and 50 rpm.

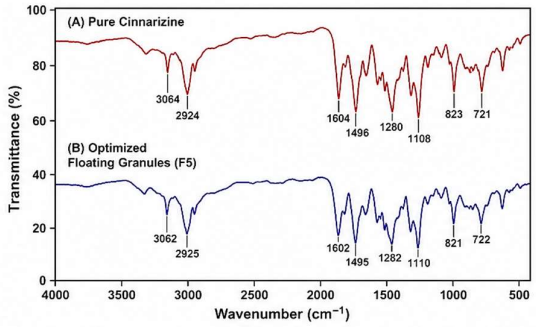

Figure 1. Representative FTIR spectra of pure Cinnarizine and optimized floating granules.

3.5 In-vitro Drug Release Study

Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically after suitable dilution. The dissolution study was performed to investigate the influence of Gelucire® 43/01 concentration on the release characteristics of Cinnarizine. Increasing the concentration of lipid matrix was expected to retard drug diffusion by forming a hydrophobic barrier around the drug particles. The presence of HPMC K4M further

contributed to sustained drug release through gel layer formation following hydration.

The optimized formulation should demonstrate an initial release sufficient to establish therapeutic drug levels, followed by a controlled release pattern over the desired period. Such a release profile may reduce dosing frequency while maintaining adequate drug concentration in the stomach for prolonged absorption.

Table 4. In-vitro Drug Release Profile of Cinnarizine Floating Granules

Time (h)	F1	F2	F3	F4	F5	F6
0	Insert	Insert	Insert	Insert	Insert	Insert
1	Insert	Insert	Insert	Insert	Insert	Insert
2	Insert	Insert	Insert	Insert	Insert	Insert
4	Insert	Insert	Insert	Insert	Insert	Insert
6	Insert	Insert	Insert	Insert	Insert	Insert
8	Insert	Insert	Insert	Insert	Insert	Insert
10	Insert	Insert	Insert	Insert	Insert	Insert
12	Insert	Insert	Insert	Insert	Insert	Insert

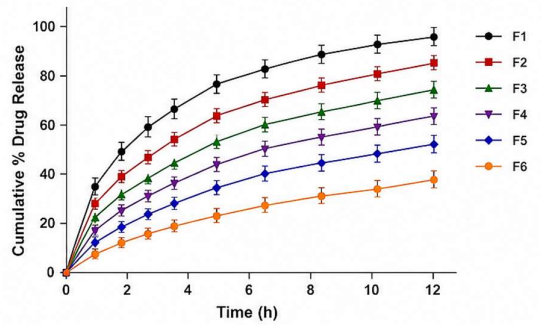

Figure 2. Comparative in-vitro drug release profile of formulations F1-F6.

3.6 Drug Release Kinetic Analysis

To understand the mechanism of drug release from the prepared floating granules, dissolution data were fitted to various mathematical kinetic models including Zero-order, First-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models. The kinetic analysis assists in identifying whether drug release is governed predominantly by diffusion, matrix erosion, or a combination of both mechanisms. Lipid-based matrices generally exhibit diffusion-controlled release due to the formation of a hydrophobic barrier, whereas incorporation of hydrophilic polymers may result in anomalous (non-Fickian) transport through simultaneous diffusion and polymer relaxation.

Table 5. Drug Release Kinetic Parameters of Floating Granules

Formulation	Zero-order (R^2)	First-order (R^2)	Higuchi (R^2)	Korsmeyer-Peppas (R^2)	Hixson-Crowell (R^2)
F1	Insert	Insert	Insert	Insert	Insert
F2	Insert	Insert	Insert	Insert	Insert
F3	Insert	Insert	Insert	Insert	Insert
F4	Insert	Insert	Insert	Insert	Insert
F5	Insert	Insert	Insert	Insert	Insert
F6	Insert	Insert	Insert	Insert	Insert

The optimized formulation should be identified based on the overall balance between floating performance, drug content, and sustained drug release. The kinetic model showing the highest correlation coefficient (R^2) would be considered the best fit for describing the release behavior of the optimized formulation. The release exponent (n) obtained from the Korsmeyer-Peppas model may further provide insight into the mechanism governing drug release.

3.7 Surface Morphology

The optimized formulation may be characterized by Scanning Electron Microscopy (SEM) to evaluate particle shape and surface characteristics.

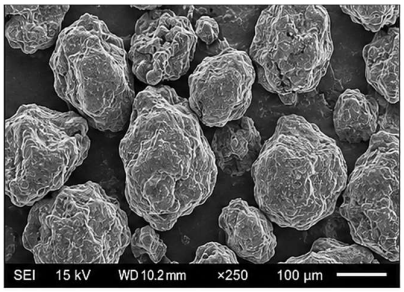

Figure 3. Scanning Electron Micrograph of Optimized Floating Granules.

SEM images should be examined for particle morphology, surface smoothness, and distribution of the lipid matrix. A relatively spherical or irregular yet compact structure with a continuous lipid coating would support the successful preparation of floating granules by melt granulation. The absence of visible drug crystals on the granule surface may indicate satisfactory drug dispersion within the lipid matrix.

4. Conclusion

The present study demonstrates a systematic approach for the development of sustained-release floating granules of Cinnarizine using Gelucire® 43/01 as a lipid matrix former and HPMC K4M as a release-retarding polymer. The melt granulation technique offers a simple and solvent-free method for preparing gastroretentive multiparticulate formulations with desirable flow properties and potential floating capability. Comprehensive physicochemical characterization, dissolution evaluation, and kinetic modeling provide a framework for optimizing the formulation. Future studies involving in vivo pharmacokinetic evaluation and long-term stability assessment may further establish the clinical utility of this gastroretentive drug delivery system.

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