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FORMULATION AND EVALUATION OF CIMETIDINE SUSTAINED RELEASE TABLETS USING NATURAL POLYMERS

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ABSTRACT

The present study aimed to formulate and evaluate gastroretentive sustained-release tablets of Cimetidine using natural polymers. Preformulation studies confirmed the purity and suitable physicochemical properties of the drug. Sustained-release tablets were prepared by the direct compression method using polymers such as Xanthan Gum, Gellan Gum, Chitosan, and Carbopol 940. The formulations were evaluated for pre-compression and post-compression parameters such as hardness, friability, weight variation, drug content, and floating behavior. All formulations met pharmacopeial limits and showed floating duration of more than 12 hours. In-vitro dissolution studies indicated controlled drug release up to 12 hours, with formulations F7 and F8 showing the best sustained-release profile. The results suggest that natural polymer-based floating tablets of Cimetidine HCl can provide prolonged gastric retention and controlled drug release.

KEYWORDS: Cimetidine HCl; Sustained release tablets; Gastroretentive system; Floating tablets; Natural polymers.

INTRODUCTION

Oral drug delivery systems are the most widely accepted and commonly used method for the administration of therapeutic agents due to their convenience, safety, ease of manufacturing, and improved patient compliance. Conventional oral dosage forms such as tablets and capsules usually release the drug immediately after administration, resulting in rapid absorption and fluctuations in plasma drug concentration. These fluctuations may lead to periods of sub-therapeutic levels followed by potential toxicity when the drug concentration becomes too high. For drugs that possess a short biological half-life, frequent dosing is required to maintain effective plasma concentrations, which may reduce patient adherence to therapy. To overcome these limitations, sustained release drug delivery systems have been developed to provide controlled and prolonged drug release over an extended period of time.

Sustained release formulations are designed to release the drug at a predetermined rate in order to maintain constant drug levels in the systemic circulation for a prolonged duration. Such systems offer several advantages, including reduced dosing frequency, improved patient compliance, minimized side effects, and enhanced therapeutic efficacy. Sustained release systems also help in maintaining a uniform drug concentration within the therapeutic window for a longer time, thereby reducing the chances of peak and trough effects commonly observed with conventional dosage forms. Among the various techniques used to develop sustained release dosage forms, matrix tablet systems are considered one of the simplest and most effective approaches due to their ease of preparation and ability to control drug release.

In matrix tablets, the drug is uniformly dispersed within a polymeric matrix that acts as a release-controlling barrier. The release of the drug from the matrix occurs through mechanisms such as diffusion, swelling, erosion, or a combination of these processes. The choice of polymer and its concentration significantly influence the rate and pattern of drug release. Polymers used in sustained release formulations can be synthetic, semi-synthetic, or natural in origin. In recent years, natural polymers have gained increasing attention in

pharmaceutical research because of their biodegradability, biocompatibility, low toxicity, availability, and cost-effectiveness.

Natural polymers derived from plant or microbial sources are widely used as release-retarding agents in sustained release formulations. These polymers have the ability to swell in the presence of gastrointestinal fluids and form a gel layer around the tablet, which controls the diffusion of the drug into the surrounding medium. Examples of commonly used natural polymers include Guar Gum, Xanthan Gum, and Sodium Alginate. These polymers are not only safe and environmentally friendly but also provide effective control over drug release kinetics. The use of natural polymers in sustained release tablets has therefore become an important area of pharmaceutical formulation research.

Cimetidine is a widely used drug belonging to the class of histamine H_2-receptor antagonists. It is primarily used in the treatment and management of acid-related disorders such as peptic ulcer disease, gastric ulcers, duodenal ulcers, and Gastroesophageal Reflux Disease. Cimetidine works by blocking histamine H_2 receptors present in the gastric parietal cells, thereby inhibiting gastric acid secretion. By reducing gastric acid production, it helps in the healing of ulcers and provides relief from symptoms associated with acid reflux and hyperacidity.

Despite its therapeutic importance, cimetidine has certain pharmacokinetic limitations that affect its clinical effectiveness. The drug has a relatively short biological half-life of approximately 2–3 hours, which necessitates frequent administration to maintain effective plasma drug levels. Frequent dosing may lead to poor patient compliance and inconsistent therapeutic outcomes. Therefore, the development of sustained release formulations of cimetidine is highly desirable as it can provide prolonged drug release, maintain steady plasma concentrations, and reduce the need for multiple daily doses.

The formulation of sustained release tablets using natural polymers offers a promising strategy to overcome these limitations. Natural polymers can effectively control the drug release rate by forming a gel barrier that regulates the diffusion of drug molecules from the tablet matrix. Additionally, these polymers are economical and widely available, making them suitable for large-scale pharmaceutical applications.

Therefore, the present study is envisaged to develop sustained-release tablets of Cimetidine using plant mucilage as a natural pharmaceutical excipient. The research focuses on utilizing plant-derived mucilage as a binder and release-retarding agent to control the drug release from the tablet matrix and provide prolonged therapeutic action.

Initially, plant mucilage will be extracted, purified, and evaluated for its physicochemical properties to determine its suitability for pharmaceutical use. Subsequently, sustained-release tablets of cimetidine will be prepared using varying concentrations of the extracted mucilage along with suitable excipients.

The formulated tablets will be evaluated for important physical parameters such as hardness, friability, thickness, weight variation, and drug content uniformity. In addition, in-vitro dissolution studies will be carried out to study the drug release pattern and to ensure controlled and prolonged release of the drug over an extended period. The study aims to improve therapeutic efficacy, reduce dosing frequency, and minimize side effects through the use of natural polymers in sustained-release formulations.

Cimetidine is a histamine H_2-receptor antagonist widely used for the treatment of acid-related gastrointestinal disorders. It works by inhibiting histamine-mediated gastric acid secretion from the parietal cells of the stomach, thereby reducing gastric acidity and promoting ulcer healing.

Chemical Name: N-cyano-N-methyl-N"-[2-[(5-methyl-1H-imidazol-4-yl) methyl]thio]ethyl]guanidine hydrochloride
Category: Anti-ulcer agent / H_2 receptor antagonist
Molecular Formula: $C_{10}H_{16}N_6S{\cdot}HCl$

Mechanism of Action
Cimetidine blocks H_2 receptors in the gastric parietal cells, which reduces the secretion of gastric acid and pepsin, leading to decreased acidity in the stomach.

Indications
- Peptic ulcer disease
- Gastric ulcer
- Duodenal ulcer
- Gastroesophageal Reflux Disease
- Zollinger–Ellison syndrome

Half-Life: Approximately 2–3 hours.

Route of Administration: Oral and intravenous.

Side Effects: Headache, dizziness, diarrhea, and occasionally hormonal effects with prolonged use.

Due to its short half-life and frequent dosing requirement, cimetidine is considered a suitable candidate for the development of sustained-release formulations.

Preformulation Studies of Cimetidine HCl

Preformulation studies were carried out to evaluate the physicochemical properties of Cimetidine before formulation development. These studies help in selecting suitable excipients and designing a stable and effective dosage form.

1. Organoleptic Properties

The drug sample was observed for its colour, odour, and physical appearance to characterize its basic properties.

2. Solubility Analysis

About 5 mg of Cimetidine HCl was added separately to 10 ml of different solvents such as methanol, ethanol, chloroform, and distilled water. The solutions were shaken for a few minutes at room temperature to determine the solubility of the drug.

3. Loss on Drying (LOD)

Approximately 5 g of the drug sample was placed in an IR moisture balance and heated at 100–105°C for about 15 minutes. The percentage loss in weight was recorded to determine moisture content.

4. Melting Point Determination

The melting point was determined using the open capillary method. A small amount of drug powder was filled in a capillary tube and heated in a melting point apparatus. The temperature at which the drug melted completely was recorded.

5. UV–Visible Spectrophotometric Analysis

A stock solution of Cimetidine HCl (1000 µg/ml) was prepared using methanol and 0.1 N HCl. Further dilutions were made and analyzed using a UV–Visible spectrophotometer to determine the maximum absorption wavelength (λmax) at 282 nm. A calibration curve of concentration versus absorbance was plotted.

FTIR Spectroscopy of Cimetidine HCl

The purity and identification of Cimetidine were confirmed using FTIR spectroscopy. About 10 mg of the drug was triturated with 100 mg of dry potassium bromide (KBr) in a mortar. A pellet was prepared using the KBr press pellet method and scanned in an FTIR spectrophotometer in the range of 400–2000 cm^{-1}. The spectrum obtained was analyzed to identify the characteristic peaks of the drug.

Formulation of Sustained Release Tablets

Sustained-release tablets of Cimetidine HCl were prepared by the **direct compression method**. Nine different formulations (F1–F9) were prepared using plant mucilage and other excipients. All the ingredients were passed through sieve no. 40 before mixing. The required quantities of drug, polymers, and excipients were weighed accurately, mixed uniformly, and compressed into tablets for further evaluation.

Optimization of Sustained Release Tablets

The formulation was optimized using the OVAT (One Variable At a Time) method by varying the concentration of different polymers. Polymers such as Xanthan Gum, Gellan Gum, Chitosan, and Carbopol 940 were selected for the formulation study along with Sodium Bicarbonate, Citric Acid, and Magnesium Stearate. Sodium bicarbonate and citric acid were used as gas-generating agents.

The drug Cimetidine and other excipients were passed through a 40-mesh sieve. The required quantities of drug and polymers were accurately weighed and transferred into a polyethylene bag and mixed for 15 minutes to obtain a uniform blend. After that, magnesium stearate and talc were added as lubricant and glidant, and the mixture was further blended for another 5 minutes before compression into tablets.

Formulation of Cimetidine HCl of sustain release tablets containing plant mucilage

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cimetidine HCl	200	200	200	200	200	200	200	200	200
Xanthan gum	80	100	120	-	-	-	40	50	60
Gellan gum	-	-	-	80	100	120	40	50	60
Carbopol 940 P	-	-	-	-	-	-	20	20	20
Chitosan	30	30	30	30	30	30	30	30	30
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)_2$	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Lactose	100	80	60	100	80	60	80	60	40
Total Weight	450	450	450	450	450	450	450	450	450

Evaluation of Pre-compression Parameters

1. Bulk Density (LBD) and Tapped Density (TBD)

An accurately weighed quantity of powder blend was transferred into a 50 ml measuring cylinder. The initial volume was noted to determine the **loose bulk density (LBD)**. The cylinder was then tapped 100 times on a hard surface to obtain the **tapped volume**, and **tapped bulk density (TBD)** was calculated using the ratio of mass of powder to the tapped volume.

2. Carr's Compressibility Index

Carr's index was calculated using bulk and tapped density values to determine the compressibility and flow properties of the powder blend. Lower values indicate better flow properties of the powder.

3. Hausner's Ratio

Hausner's ratio was calculated as the ratio of tapped density to bulk density. A value less than 1.25 indicates good flowability of the powder mixture.

Evaluation of Sustained-Release Tablets

1. General Appearance

Tablets from different batches were visually inspected for organoleptic properties such as color, shape, surface texture, and uniformity of appearance.

2. Thickness and Diameter

Thickness and diameter of the tablets were measured using a Vernier caliper. Five tablets from each batch were evaluated and the average value was recorded.

3. Drug Content Uniformity

Twenty tablets were weighed and powdered. A quantity of powder equivalent to 10 mg of Cimetidine was transferred into a volumetric flask and dissolved in 0.1 N HCl. The solution was filtered and appropriately diluted. The absorbance was measured using a UV-Visible spectrophotometer at 218 nm to determine drug content.

4. Hardness Test

The hardness of tablets was determined using a Monsanto hardness tester. Five tablets from each formulation were tested and the average hardness value was recorded.

5. Friability Test

Friability was determined using a friabilator. Ten tablets were weighed and rotated at 25 rpm for 4 minutes. After dedusting, tablets were reweighed and percentage weight loss was calculated to determine friability.

6. Uniformity of Weight

Twenty tablets from each batch were randomly selected and individually weighed. The average weight and standard deviation were calculated to ensure uniformity.

7. In-vitro Buoyancy Study

The floating behavior of tablets was evaluated in simulated gastric fluid (pH 1.2). Each tablet was placed in the medium and the time taken to float on the surface (floating lag time) was recorded.

8. In-vitro Dissolution Study

Drug release studies were performed using a **USP Type II dissolution apparatus (paddle type)**. The dissolution medium consisted of 900 ml of 0.1 N HCl maintained at **37 ± 0.5°C** and rotated at **75 rpm**. One tablet was placed in each vessel and samples of 5 ml were withdrawn at regular intervals for up to 10 hours. The withdrawn volume was replaced with fresh dissolution medium. Samples were analyzed using a UV-Visible spectrophotometer at 218 nm.

Drug Release Kinetics

To understand the mechanism of drug release, dissolution data were fitted to different kinetic models.

1. Zero-Order Kinetics

This model describes systems where the drug release rate is constant over time and independent of drug concentration.

2. First-Order Kinetics

In this model, the drug release rate depends on the concentration of drug remaining in the dosage form.

3. Higuchi Model

The Higuchi model explains drug release from matrix systems as a diffusion-controlled process based on Fick's law.

4. Korsmeyer–Peppas Model

This model is used to analyze the mechanism of drug release from polymeric systems. The release exponent (n) indicates whether the mechanism follows.

\Fickian diffusion, non-Fickian transport, or anomalous diffusion.

RESULTS AND DISCUSSION

Results of Preformulation Studies

Organoleptic Properties

The organoleptic characteristics of Cimetidine were evaluated to identify its physical appearance and sensory properties. The drug was found to be a **white to off-white crystalline powder** with a **characteristic odor** and **bitter taste**, which agrees with reported literature values. These properties confirm the identity and purity of the drug sample.

Solubility Analysis

The solubility study indicated that Cimetidine HCl was **freely soluble in distilled water and 0.1 N hydrochloric acid**, **soluble in ethanol, methanol, and phosphate buffer (pH 7.2)**, and **slightly soluble in chloroform and 0.1 N NaOH**. The good solubility in aqueous acidic media suggests that the drug can dissolve effectively in gastric fluid, making it suitable for oral sustained-release formulations.

Loss on Drying

The loss on drying value of Cimetidine HCl was found to be **0.532 ± 0.001%**, indicating a very low moisture

content. This confirms the stability of the drug and suggests that it is suitable for tablet formulation without significant risk of moisture-related degradation.

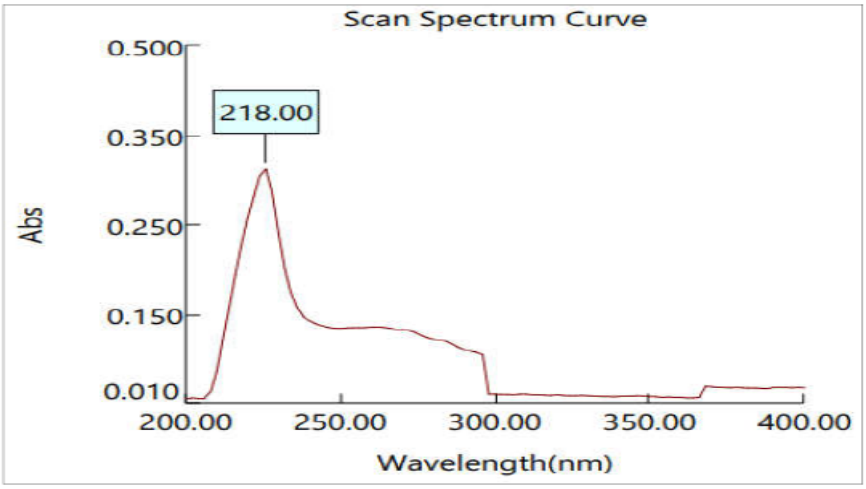
Melting Point

The melting point of Cimetidine HCl was observed in the range of **185–187°C**, which is consistent with reported literature values. This result confirms the purity and identity of the drug sample used in the study.

UV Spectrophotometric Analysis

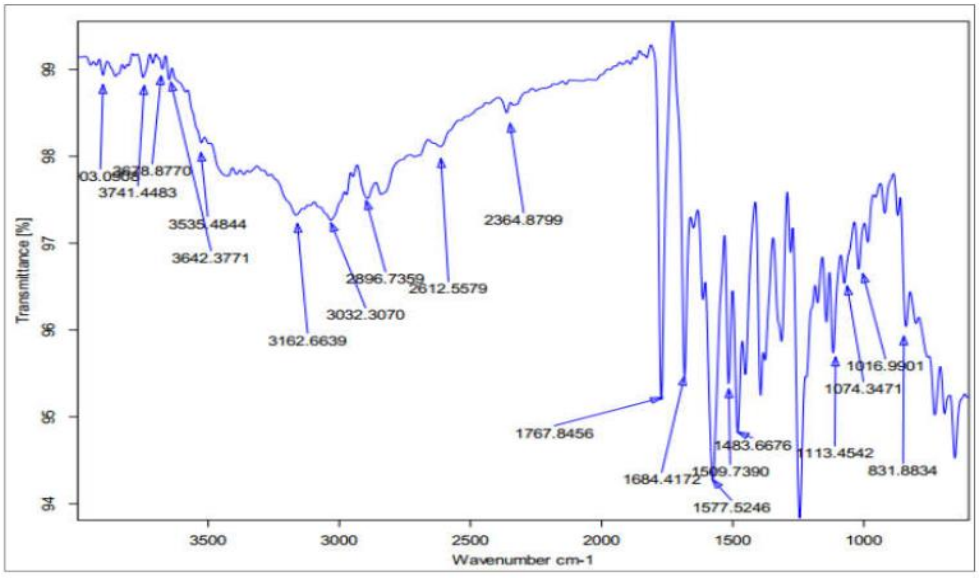
The maximum absorption wavelength (λmax) of Cimetidine HCl was determined using UV-Visible spectrophotometry and was found at **282 nm**. A calibration curve was prepared in the concentration range of **5–25 µg/ml**, showing a linear relationship between concentration and absorbance. This linearity confirms the suitability of the method for quantitative analysis of the drug during dissolution studies.

Results of UV Spectrophotometric analysis



FTIR Spectroscopy

The FTIR spectrum of Cimetidine HCl showed characteristic peaks corresponding to its functional groups. A broad peak at **3535 cm⁻¹** indicated **N–H stretching** of secondary amine groups. Peaks around **3162 cm⁻¹** represented **aromatic C–H stretching** of the imidazole ring, while **2896 cm⁻¹** corresponded to **aliphatic C–H stretching**. A sharp peak at **1684 cm⁻¹** confirmed **C=N stretching**, and peaks near **1509 cm⁻¹** indicated **aromatic C=C stretching**. Additional bands at **1113 cm⁻¹** and **1074 cm⁻¹** were attributed to **C–N** and **C–S stretching**, respectively. These characteristic peaks confirmed the identity and structural integrity of the drug.



Results of Pre-compression Properties

The powder blends of different formulations (F1–F9) were evaluated for pre-compression parameters including bulk density, tapped density, compressibility index, and Hausner's ratio. The **bulk density** ranged from **0.345 to 0.365 g/ml**, while the **tapped density** ranged from **0.452 to 0.478 g/ml**. The **compressibility index** values were

found between **22.19% and 24.63%**, and **Hausner's ratio** ranged from **1.287 to 1.322**.

These results indicate that the powder blends possessed **acceptable flow properties and compressibility**, which are suitable for tablet compression. The small difference between bulk and tapped density values suggests uniform packing ability of the powder mixture, ensuring smooth processing during tablet manufacturing.

Evaluation of Tablets

The prepared sustained-release tablets of Cimetidine HCl were evaluated for various **post-compression parameters**, including.

- Thickness
- Hardness
- Weight variation
- Friability
- Drug content
- Floating lag time
- Total floating duration
- In-vitro drug dissolution

These parameters were assessed to ensure the **quality, mechanical strength, uniformity, and sustained drug release performance** of the formulated tablets. The results confirmed that the tablets met acceptable pharmacopeial standards and were suitable for further dissolution and release kinetic studies.

Results of Post-Compression Properties of Sustained-Release Tablets

The prepared formulations (F1–F9) of Cimetidine sustained-release tablets were evaluated for physicomechanical parameters such as **thickness, hardness, weight variation, friability, drug content, and total floating duration** to determine their suitability as gastroretentive floating tablets.

The **tablet thickness** ranged from **3.1 ± 0.1 to 3.3 ± 0.2 mm**, indicating uniform die filling and consistent compression during tablet manufacturing. The minimal variation in thickness among different batches suggests good powder flow properties and uniform tablet dimensions.

The **hardness** of the tablets was found between **7.0 ± 0.1 and 7.4 ± 0.2 kg/cm²**, indicating sufficient mechanical strength to withstand handling and transportation. This hardness range is suitable for floating tablets as it maintains tablet integrity while allowing proper swelling and buoyancy.

The **weight variation** of all formulations ranged from **447 ± 3 to 456 ± 9 mg**, which falls within acceptable pharmacopeial limits. This result confirms uniform distribution of drug and excipients and consistency in the compression process.

The **friability** values of most formulations were below **1%**, indicating good mechanical resistance. Formulation **F6** showed slightly higher friability (**0.985 ± 0.006%**), but it still remained within acceptable limits, suggesting only minor differences in interparticle bonding.

The **drug content** ranged from **97.95 ± 0.15% to 99.85 ± 0.016%**, indicating excellent uniformity of drug distribution within the tablets. Among all formulations, **F8** showed the highest drug content, reflecting efficient mixing and minimal drug loss during processing.

All the formulations exhibited **total floating duration greater than 12 hours**, demonstrating good buoyancy and suitability for gastroretentive drug delivery. This prolonged floating ability can enhance gastric residence time and improve therapeutic effectiveness of the sustained-release formulation.

Table: Results of post compression properties of Cimetidine HCl tablets

Formulation code	Thickness (mm)	Hardness (kg/cm2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3	Total floating duration (h)
F1	3.1±0.1	7.2±0.1	455±9	0.708±0.007	99.05±0.15	>12
F2	3.2±0.2	7.1±0.2	450±3	0.658±0.005	98.85±0.25	>12
F3	3.2±0.2	7.0±0.1	448±6	0.745±0.003	98.78±0.31	>12
F4	3.1±0.1	7.3±0.2	447±5	0.712±0.005	97.95±0.15	>12
F5	3.2±0.1	7.2±0.2	452±8	0.698±0.004	98.12±0.21	>12
F6	3.3±0.2	7.2±0.1	456±6	0.985±0.006	99.03±0.17	>12
F7	3.2±0.1	7.4±0.2	451±3	0.674±0.004	98.65±0.15	>12
F8	3.2±0.2	7.3±0.1	449±7	0.854±0.003	99.85±0.016	>12
F9	3.1±0.2	7.2±0.1	447±4	0.712±0.002	98.14±0.25	>12

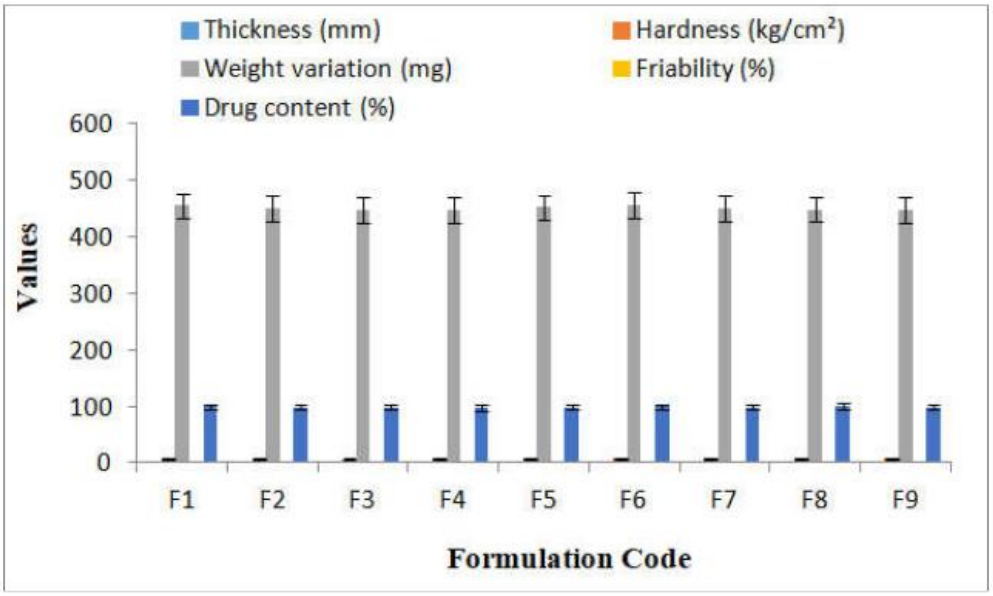


Table: *In-vitro* drug release study of sustain release tablets.

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	38.85	35.65	32.56	36.65	33.65	30.25	28.85	25.65	23.32
1	65.56	45.65	42.25	48.85	45.52	43.32	35.85	30.25	36.65
1.5	75.65	65.52	56.65	59.98	55.36	51.14	46.65	43.32	43.32
2	86.65	78.85	65.85	73.32	70.23	65.85	63.32	55.65	46.65
3	99.12	86.65	75.65	88.85	83.32	75.45	72.25	63.32	53.32
4	-	98.89	85.65	98.78	97.78	89.98	89.98	78.85	65.56
6	-	-	98.85	-	99.12	92.23	93.32	86.65	78.85
8	-	-	-	-	-	99.05	99.15	96.65	86.65
12	-	-	-	-	-	-	99.25	99.45	91.15

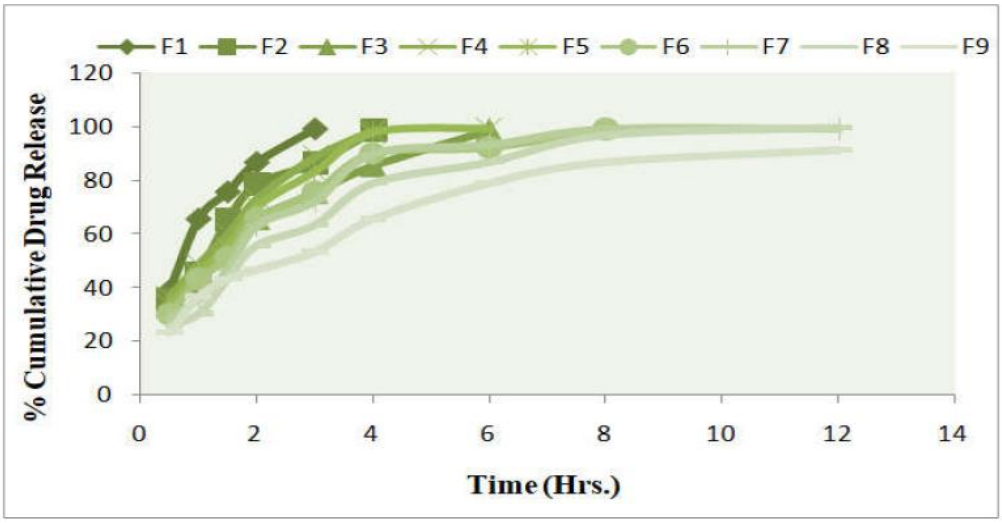


Figure: *In-vitro* drug release study of GRF tablets.

SUMMARY AND CONCLUSION

The present study was undertaken to formulate and evaluate gastroretentive sustained-release tablets of Cimetidine using plant-derived mucilages as natural release-retarding polymers. Preformulation investigations confirmed that Cimetidine HCl possesses suitable physicochemical characteristics such as good aqueous solubility, appropriate melting point, low moisture content, and characteristic FTIR peaks, indicating the purity and stability of the drug.

Sustained-release tablets were prepared using different concentrations of polymers such as Xanthan Gum, Gellan Gum, Chitosan, and Carbopol 940. Evaluation of pre-compression parameters showed acceptable flow properties of the powder blends. Post-compression evaluation demonstrated that all formulations complied with pharmacopeial standards for hardness, friability, weight variation, thickness, and drug content. Buoyancy studies showed short floating lag times and prolonged floating duration exceeding 12 hours, confirming their suitability for gastroretentive drug delivery.

The in-vitro drug release studies revealed that the concentration and type of polymer significantly influenced the drug release behavior. Among the prepared formulations, **F7 and F8** showed more controlled and sustained drug release for up to 12 hours with minimal initial burst effect. Kinetic analysis of the dissolution data indicated that the drug release mainly followed **first-order and Higuchi models**, while the **Korsmeyer–Peppas model** suggested a **non-Fickian (anomalous) diffusion mechanism**, involving both diffusion and matrix erosion.

In conclusion, the study demonstrates that sustained-release floating tablets of Cimetidine HCl can be successfully developed using plant-based polymers. Such gastroretentive formulations are capable of prolonging gastric residence time, providing controlled drug release, reducing dosing frequency, and improving patient compliance, making them a promising strategy for the effective management of acid-related gastrointestinal disorders.

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