Journal of Pharmacy

ORIGINAL ARTICLE

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Pulsatile Tablet of Famotidine Using Core in Cup Method

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ABSTRACT

Introduction: The present work aims to formulate a pulsatile delivery system using a "core-in-cup" system for famotidine, a H2-Receptor antagonist prescribed for benign gastric ulcers, duodenal ulcers, gastroesophageal reflux disease and nocturnal acid breakthrough. In such a situation, pulsatile drug release is preferable, with a lag time between 3 and 4 hours.

Method: Core tablets were prepared by employing the direct compression method using HPMC K4M, sodium bicarbonate and MCC. Ethyl cellulose, HPMC K4M and Xanthan gum were used for the preparation of Core-in-cup tablets.

Results: Results: Pre-compression parameters were within the admissible limits. The *in-vitro* study indicated core tablet with 40% HPMC K4M showed 85.4± 0.15% drug release at the end of 3hrs and *in-vitro* buoyancy indicated formulation remained floating for >3hrs. Thus, 40% HPMC K4M was selected. Drug excipient compatibility studies indicated drug and excipients to be compatible. The prepared core-in-cup tablets were evaluated for hardness (6.0±0.12 to 7.0±0.12kg/cm2), thickness (3.0±0.15 to 3.5±0.13mm), weight variation (285±0.20 to 314±1.06mg), friability (0.53±0.14 to 0.65±0.12%), floating lag-time (99±0.42 to 120±0.84sec), and swelling index (120±0.56 to 030±0.60%). *In-vitro* studies indicated formulations with xanthan gum (F1 & F2) showed a lag time of 2±0.12 to 2.4±0.15hrs and percentage drug release at the 7th hour was 97±0.90% and 90±0.12% respectively. Formulations with HPMC K4M (F3 & F4) showed a lag time of 3.5±0.10 to 4.2±0.18hrs and percentage drug release at the 7th hour was 86±0.34% and 83±0.20% respectively. Model dependent kinetics depicted, F4 follows zero-order release kinetics, 'n' value of korsmeyer-peppas model indicated anomalous transport mechanism, release process being swelling controlled. Optimized formulation was found to be stable for a period of one month.

Conclusion: Pulsatile release dosage forms are more preferred than conventional dosage forms for nocturnal acid breakthrough. "Core-in-Cup" pulsatile tablets of famotidine were successfully designed to ensure drug release occurs in the morning when administered at bedtime.

ARTICLE HISTORY:

Received: 27 August 2022
Accepted: 5 December 2022
Published: 31 January 2023

KEYWORDS:

Pulsatile delivery system, Famotidine, Core-in-cup tablet, Nocturnal acid breakthrough, H2-receptor antagonist

HOW TO CITE THIS ARTICLE:

Rajguru, S. A., Fatima, M., Kumar, B. H., Ahmed, S. F., Vipanchi, V., & Prasanthi, D. (2023) Pulsatile Tablet of Famotidine Using Core in Cup Method. *Journal of Pharmacy,* 3(1), 27-37.

doi: 10.31436/jop.v3i1.190

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Introduction

"Pulsatile drug delivery system (PDDS) is described as the release of a specific amount of drug molecules instantaneously in short duration immediately following a predetermined lag time i.e., no drug release period". These are time-controlled DDS developed so as to attain time-specific and site-specific delivery of drugs (Abdul & Poddar, 2004). Delivery of the drug from the body is as per the circadian rhythm of the body.

Conventional systems for the continuous release of a drug are not ideal as it results in the prompt elimination of a drug from the body, Dose administered is not maintainable within the therapeutic window whereby significant therapeutic effect cannot be achieved, usage of multiple doses may cause plasma drug level fluctuations and poor patient compliance (Adepu et al., 2021) therefore, a controlled drug delivery system is more preferable. PDDS are useful for drugs used in Chrono-pharmacological behaviour diseases (Jagdale et al., 2009; Jagdale et al., 2014). In recent times, PDDS piqued interest as it delivers drugs to suitable place, at correct time and in the appropriate amount, hence providing spatial, temporal and smart delivery, resulting in enhanced patient compliance (Arora et al., 2006; Kumar & Murthy, 2019).

Many conditions require pulsatile release such as, body functions following a circadian rhythm. (e.g.: Secretion of hormones, gastric emptying, acid secretion in stomach, etc.) (Goo et al., 1987), chronopharmacotherapy of disease exhibiting circadian rhythm in its pathophysiology (like myocardial infarction, bronchial asthma, rheumatic disease, angina pectoris, hypertension and ulcer), (Lemmer, 1999; Mali & Bathe, 2015) drugs displaying degradation in gastric fluids (e.g.: peptide drugs), drugs that cause irritation of gastric mucosa or induces nauseousness and vomitings, distal organs targeting drugs in GIT like colon (Gazzaniga et al., 1994).

Drug release from PDDS occurs either by erosion, diffusion, osmosis (Adhikari et al., 2018; Singh et al., 2012). PDDS can be broadly classified into 3 classes (Thakur et al., 2021; Jadhav et al., 2016):

1. Time controlled PDDS
2. Stimuli induced PDDS
3. Externally regulated PDDS

The class of layered tablet (Time-controlled PDDS) in which the upper part of the core is exposed instead of being completely surrounded by coating on both sides is the "inlay Tablet". Core-in-cup tablet is a type of inlay tablet developed by Danckwerts that shows zero-order drug release of aqueous-soluble and aqueous-insoluble drugs. This system comprises a matrix core which is disc-shaped subjected to compression-coated at the circumference and on one surface to create a cup on all sides of the core. Drug release occurs in sustained form from a stable surface with a constant surface area. In the case of core-in-cup tablets, the surface area of contact is less and the release of drug can be sustained completely.

Famotidine is a H2 receptor antagonist belonging to BCS class IV that binds competitively to the H2 receptors, the blocking histamine effect. The competitive inhibition marks declined basal and nocturnal gastric acid secretion and deduction in acidity, gastric volume and amount of gastric acid that is released in response to stimuli including food, caffeine, etc. (Conte et al., 1993) The gastric acid secretion normally shows circadian rhythm, but a sudden upsurge of gastric acidity is seen when the pH level is <4 for a minimum of 1 hour at midnight (2.00am to 4.00am). This physiological condition is called nocturnal acid breakthrough. In such conditions, instead of maintaining a constant plasma drug level, the release of the drug at a particular time is advantageous. (Munde et al., 2022) When the drug is administered at bedtime, it shows release after a few hours of administration (during morning hours), which is ideal in this case. (Kharwade et al., 2022; Jain et al., 2011) Earlier researchers have tried to sustain the drug release of famotidine by formulating it using various carrier systems. Mahajan and coworkers have formulated graphene oxide assisted famotidine formulations but an initial release of almost 56% in the first hour (Mahajan et al., 2019) results in immediate therapeutic effect which is not ideal in case of nocturnal acid breakthrough. Jaimini and coworkers have formulated famotidine based floating tablets which ensured site-specific release of the drug (Jaimini et al., 2007); but in case of nocturnal acid breakthrough site-specific as well as time-specific release is required which improves patient compliance and therapeutic efficacy. Based on the evaluation results of the present optimized famotidine core-in-cup tablets drug release occurs in the desired location (i.e., stomach) after predetermined lag time which is desirable in case of nocturnal acid breakthrough.

Here, in the formulation of famotidine pulsatile tablet, buoyant layer contains HPMC K4M which on contact with gastric fluid forms a gelatinous mass, cohesively binding drug release layer and effervescent component $NaHCO_3$ which upon exposure to gastric contents in the stomach liberates carbon dioxide that gets trapped in the jellified hydrocolloid resulting in the upward movement of the formulation thus imparting buoyancy. The famotidine PDDS possessing floating property is favourable as it ensures enhanced gastric residence with drug release at the expected site after the lag time which corresponds with the circadian rhythm thereby imparting enhanced patient compliance by assuring the presence of the famotidine in required quantity at the right place and the right time.

Methodology

Materials

Digital analytical balance (Contech Instruments Ltd. Mumbai, India), UV-Visible Double beam Spectrophotometer (Chemito instruments Pvt. Ltd. Mumbai, India), Dissolution test apparatus (Electrolab Pvt.Ltd. Mumbai, India), FTIR Spectrophotometer Shimadzu 8400 (Tokyo, Japan) Hot air oven Oswald world laboratory oven (India), pH meter (Elico LI 127), Tablet compression machine (Rimek Rotary Ahmedabad, India), Hardness tester (Cintex Ind. Corporation Mumbai, India).

Famotidine (Dr.Reddy's laboratories Hyderabad, India), Hydroxy Propyl Methyl Cellulose K4M (Yarrow chemical products Mumbai, India), Hydroxy Propyl Methyl Cellulose K100M (Yarrow chemical products Mumbai, India), Hydroxy Propyl Methyl Cellulose E15 (Yarrow chemical products Mumbai, India), Xanthan gum (Yarrow chemical products Mumbai, India), Ethyl cellulose (Balaji drugs, India), Sodium bicarbonate (S.D. Fine Chemicals Ltd., India), Methanol (S.D. Fine Chemicals Ltd., India), Potassium Dihydrogen Phosphate (S.D. Fine Chemicals Ltd., India), Hydrochloric acid (S.D. Fine Chemicals Ltd., India)

All the chemicals used were of analytical grade.

Drug-Excipient Compatibility Study by FTIR

Spectrum analysis of pure drug and the physical mixture was carried by FTIR using KBr pellet technique. The disc obtained was placed in an appropriate holder within an IR spectrophotometer and IR spectrum was recorded from 4000cm-1 to 500 cm-1. The spectrum obtained was observed for the presence of characteristic peaks of the respective functional group and compared for any spectral changes.

Preparation of Core Tablets

Direct compression method was employed for preparing famotidine core tablets using 6mm punch, utilizing different polymers (HPMC K4M, HPMC K100M, HPMC E15) and effervescent material (sodium bicarbonate).

Preliminary Trial formulation of core tablet:

Placebo formulations were prepared as follows, using 6mm punch powder blend is subjected to compression and checked for floating:

1. Using HPMC E15 polymer, sodium bicarbonate ($NaHCO_3$) and citric acid in different ratios as gas-generating agent.
2. Using different polymers i.e., HPMC K4M, HPMC K15M and HPMC K100M along with $NaHCO_3$ as gas-generating agent.

Table 1: Famotidine core tablet Formulation

Ingredients	C1	C2	C3	C4
Famotidine	20	20	20	20
HPMC K4M (%)	10	20	30	40
Sodium bicarbonate	5	10	15	20
Microcrystalline cellulose	82	67	52	37
Magnesium stearate	3	3	3	3

Based on the above placebo trials, the formulation containing polymer HPMC K4M and gas-generating agent sodium bicarbonate showed good floating properties. Thus, using HPMC K4M with different concentrations of sodium bicarbonate core tablets were formulated (Table 1). For formulating the core tablet, (Figure 1) the drug is thoroughly mixed with the excipients and compressed using a 6mm punch.

Evaluation of Core Tablet

A. Pre-compression evaluation

Flow properties: The prepared powder blend was evaluated for bulk density, tapped density, Hausner's ratio, compressibility index and Angle of repose (Subramanyam, 2000).

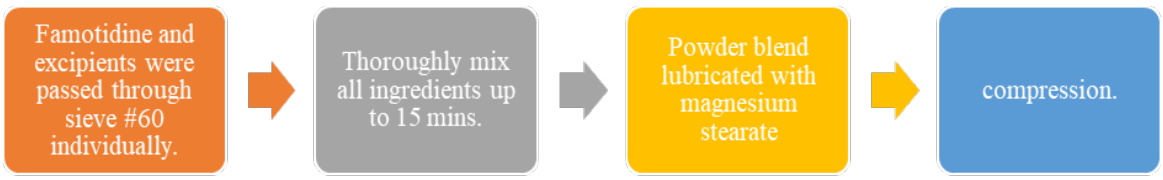

Figure 1: Preparation of core tablet.

B. Post-compression evaluation

Hardness and thickness: The hardness and thickness of core tablets were measured using Monsanto hardness tester and screw gauge respectively. (Chavda et al., 2016)

Friability: 20 tablets were correctly weighed and placed in friability testing apparatus which was operated for 100 revolutions. Then these tablets were taken out and dusted followed by reweighing tablets. The %friability calculated by

$$\% \text{ Friability} = \frac{initial\ weight - final\ weight}{initial\ weight} \times 100$$

Weight variation: 20 tablets were weighed individually and the average weight was calculated. The individual weight was compared with the average weight.

In-vitro buoyancy studies: Tablets were taken in 200ml 0.1N HCl containing measuring cylinder and Floating lag time i.e., the time needed for a tablet to reach the surface and float and Floating time i.e., period of time during which the tablet remained floating is noted.

Determination of %drug content: Tablets were powdered in a mortar. 20mg of drug equivalent powder was weighed and dissolved in distilled water. Using a membrane filter (0.45 mm) stock solutions were filtered, diluted with 0.1N HCl and drug content analysed at 267 nm by UV spectrophotometer. (Malladi & Jukanti, 2016)

Swelling index determination: Tablets were initially weighed ($W1$) then placed in 200 ml of 0.1N HCl containing beaker and incubated at 37±1°C. For 24 h, periodically tablets were taken and carefully using paper excess surface liquid was removed. Swollen tablets were again weighed ($W2$) for calculating the swelling index (SI), (Deepika et al., 2011; Malladi & Jukanti, 2016)

$$SI = \frac{W2 - W1}{W1} \times 100$$

In-vitro dissolution studies: *In-vitro* dissolution studies were carried out using USP Type II apparatus (paddle) with 0.1N HCl as dissolution medium at 50rpm, 37±0.5°C for 3 hours. 5ml samples were taken at different time intervals and absorbance was analysed using UV visible spectrophotometer at 267nm. (Conte et al., 1993)

Preparation of famotidine core-in-cup tablets

For preparing Core-in-cup tablet ethyl cellulose was selected as an impermeable cup; (Singh et al., 2012) Xanthan gum and HPMC K4M as hydrophilic top layer. Optimized core tablets were subjected to press coating for preparing core-in-cup tablets. 11mm punch was used. (Table 2, Figure 2). Prepared Core in Cup Tablets are illustrated in Figure 3.

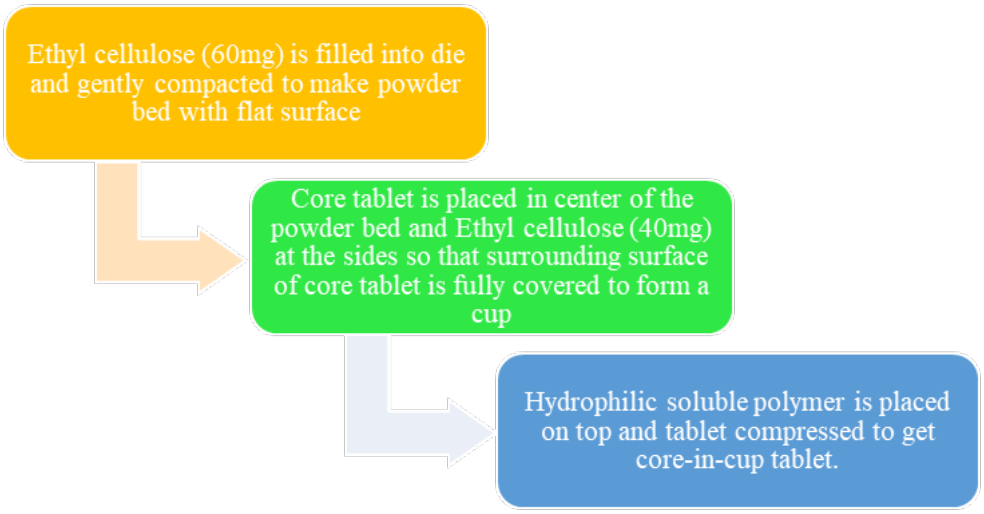

Figure 2: Famotidine Core-in-cup tablet preparation.

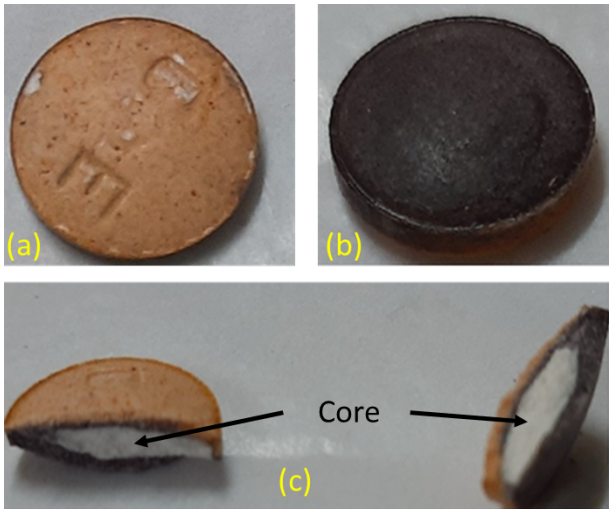

Figure 3: (a) Hydrophilic top layer (b) Cup and (c) Core part of the prepared famotidine core-in-cup tablet

Table 2: Famotidine Core-in-cup tablet Formulation

Ingredients	C1	C2	C3	C4
Core tablet	120	120	120	120
Ethyl cellulose	100	100	100	100
Sodium bicarbonate	20	20	20	20
Xanthan gum	50	75	-	-
HPMC K4M	-	-	50	75

Evaluation of Prepared Core-in-Cup Tablet

Hardness, thickness, friability, weight variation, *in-vitro* dissolution test and *in-vitro* buoyancy test was carried out as mentioned in the evaluation of core tablets.

Water uptake and erosion studies for core-in-cup tablets: Different time points were marked on beakers used for dissolution, i.e., 0.5, 1, up to 6.5 hrs. In each beaker, 0.1N HCl was taken and maintained at 37±0.5°C. To the beaker, one tablet was added and subjected to stirring at 50 rpm. These tablets were collected after completion of the respective time and excess water from the surface was removed using filter paper. Tablets were reweighed and a gain in weight indicates water uptake. It is estimated by equation:

$$Q = 100\frac{Wf - Wi}{Wf}$$

Where Q is %liquid uptake; Wf and Wi are the weight of the hydrated sample and initial dry weight respectively. (Borgaonkar et al., 2012)

Lag time: The duration before the bursting of tablets and release of the core tablet out of press coating is lag time. This is regarded as a pre-determined off-release period.

Calculation of model-dependent kinetics: Drug release kinetics can be explained by testing various models. The mechanism of drug release rate kinetics of dosage form was analyzed by fitting the acquired release data into different release models.

Stability Studies: F4 was tested for its stability according to the International Conference of Harmonization (ICH) guidelines. At designated time intervals, tablets were assessed for their floating property, lag time, drug content and *in vitro* drug release. (Sokar et al., 2013)

Results

Drug Excipient Compatibility Studies by FTIR

FTIR spectra of both pure drug and various excipients individually and in combination are illustrated in Figure 4. The FTIR studies of the physical mixture of drug with various polymers revealed no sign of interaction. Thus, it is regarded that a combination of famotidine and polymer is appropriate for formulating a famotidine cup-in-core pulsatile delivery system. Other excipients used in the formulation are common excipients which do not offer any compatibility issues hence were not analysed by FTIR.

Preparation of Core Tablets

Trial placebos were tested for floating properties and it was observed that placebos containing HPMC K4M polymer and $NaHCO_3$ as gas-generating agent showed good floating property. Based on this, further famotidine core tablets were formulated using $NaHCO_3$ as a gas-generating agent and HPMC K4M in different percentages.

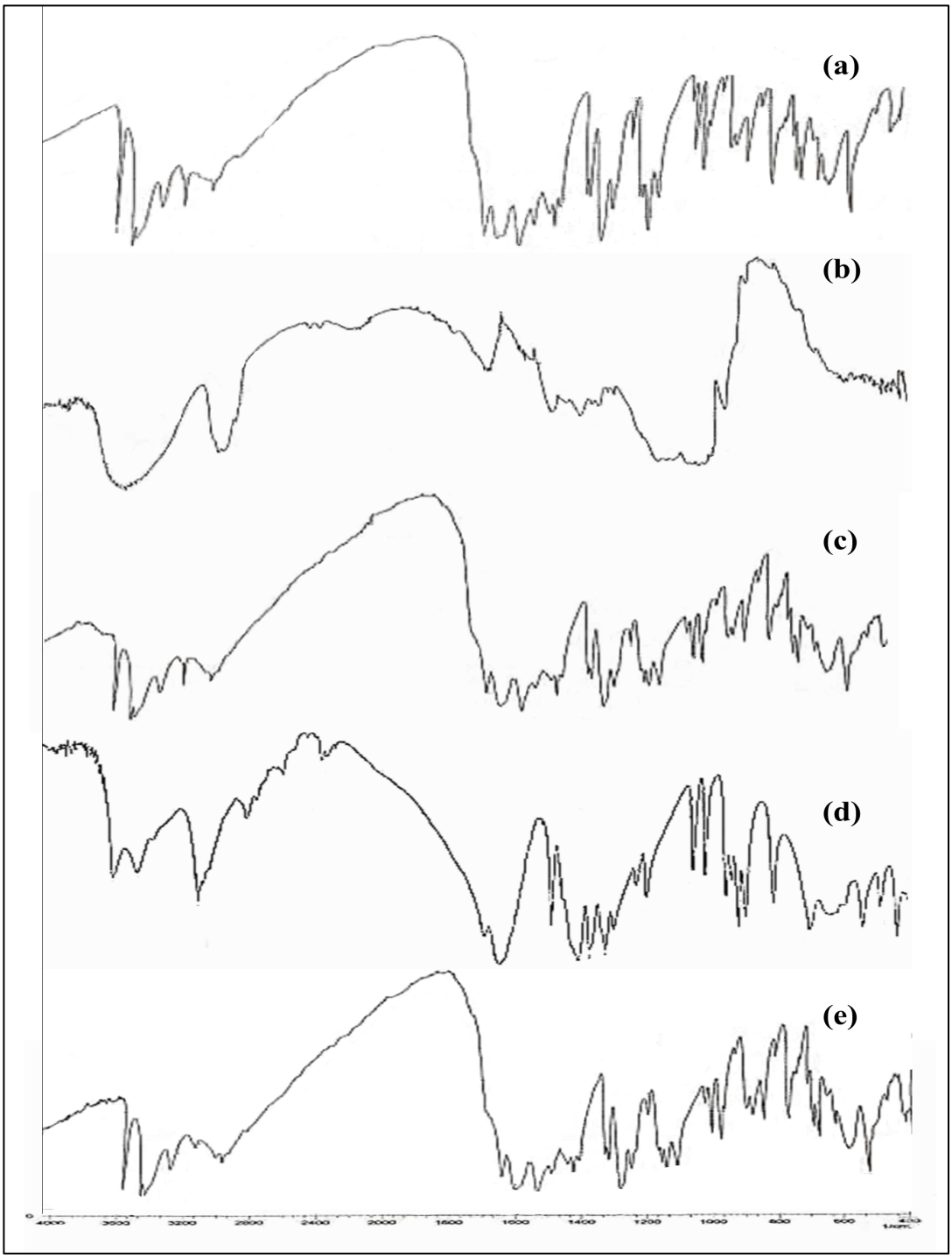

Figure 4: FTIR drug-excipient interaction studies of famotidine (a) Famotidine (b) HPMC K4M (c) Famotidine + HPMC K4M (d) Ethyl cellulose (e) Famotidine + ethyl cellulose.

Evaluation of Core Tablets

Pre-compression evaluation of the powder blend and post-compression evaluation of famotidine core tablets was carried out; the results of which are displayed in Table 3, Figure 5.

From *In-vitro* buoyancy studies, it was found that only formulation with 40% HPMC K4M remained floating for more than 3 hours. Therefore, 40% HPMC K4M was chosen for further preparation of Core-in-cup tablets.

Table 3: Evaluation of Core tablets.

Formulation	C1	C2	C3	C4
Pre-Compression				
b	0.464 ± 0.12	0.360 ± 0.14	0.482 ± 0.11	0.565 ± 0.15
Tapped density (g/ml)	0.564 ± 0.16	0.409 ± 0.11	0.554 ± 0.12	0.612 ± 0.13
Carr's Index (%)	15.0 ± 0.20	13.1 ± 0.14	12.9 ± 0.18	14.4 ± 0.16
Hausner's ratio	1.17 ± 0.13	1.13 ± 0.18	1.14 ± 0.15	1.12 ± 0.22
Angle of repose (º)	25.2 ± 0.25	21.6 ± 0.16	29.5 ± 0.35	27.9 ± 0.29
Post-Compression				
Hardness ± SD (kg/cm^2)	3.5 ± 0.12	3.8 ± 0.15	4.0 ± 0.12	3.5 ± 0.16
Thickness ± SD (mm)	2.6 ± 0.13	2.5 ± 0.15	2.0 ± 0.12	1.7 ± 0.13
Friability ± SD (%)	0.55 ± 0.19	0.59 ± 0.22	0.50 ± 0.18	0.53 ± 0.14
Drug content (%)	98.51 ± 0.52	99.36 ± 0.68	99.12 ± 0.74	98.89 ± 0.57
Weight variation (mg)	116 ± 1.20	118 ± 0.18	119 ± 1.15	118 ± 1.06
Floating lag time (sec)	125 ± 0.14	100 ± 0.19	85 ± 0.12	85 ± 0.18
Total floating time (min)	30 ± 0.16	50 ± 0.17	Up to 90± 0.13	>180±0.15

*All values represent n= 3± S.D.

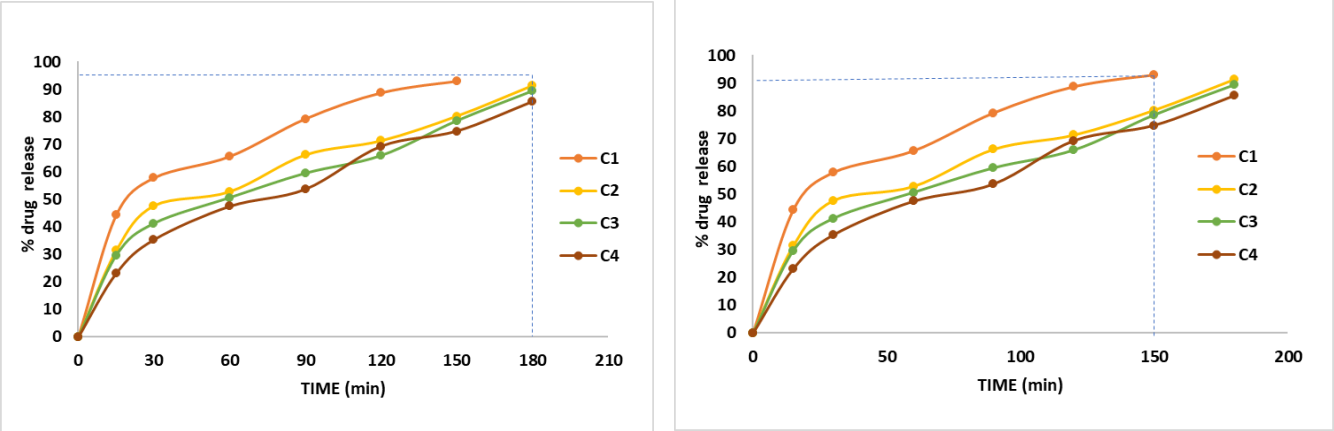

Figure 5: *In- vitro* drug dissolution of core tablets.

Evaluation of Core-in-Cup Tablets

Prepared famotidine core-in-cup tablets were assessed for various parameters Table 4, Figure 6.

With increasing concentration of xanthan gum lag time increased and it showed rapid release of the drug while with an increase in the concentration of HPMC K4M lag time extended and then followed delayed release profile.

F4 was selected as the optimized formulation from the dissolution studies as it successfully showed a lag time of about 4.2 ± 0.18 hours.

Model-dependent kinetics was performed for all four formulations to determine the release mechanism, release kinetics and transport mechanism for the drug (Table 5).

Table 4: Evaluation of Core-in-cup tablets.

Formulation	F1	F2	F3	F4
Hardness ± SD (kg/cm^2)	6.0 ± 0.12	6.5 ± 0.15	7.0 ± 0.12	6.0 ± 0.16
Thickness ± SD (mm)	3.5 ± 0.13	3.0 ± 0.15	3.2 ± 0.12	3.5 ± 0.13
Friability ± SD (%)	0.65 ± 0.12	0.59 ± 0.24	0.63 ± 0.13	0.53 ± 0.14
Drug content (%)	99.12 ± 0.31	98.71 ± 0.82	98.56 ± 1.00	99.57 ± 0.65
Weight variation (mg)	285 ± 0.20	312 ± 0.18	287 ± 1.15	314 ± 1.06
Swelling index (%)	120.8 ± 0.56	124.2 ± 0.23	130.6 ± 0.60	129.5 ± 0.37
Floating lag time (Sec.)	109 ± 0.62	120 ± 0.84	99 ± 0.42	102 ± 0.71
Lag Time (Hr.)	2.0 ± 0.12	2.4 ± 0.15	3.5 ± 0.10	4.2 ± 0.18

*All values represent n= 3± S.D.

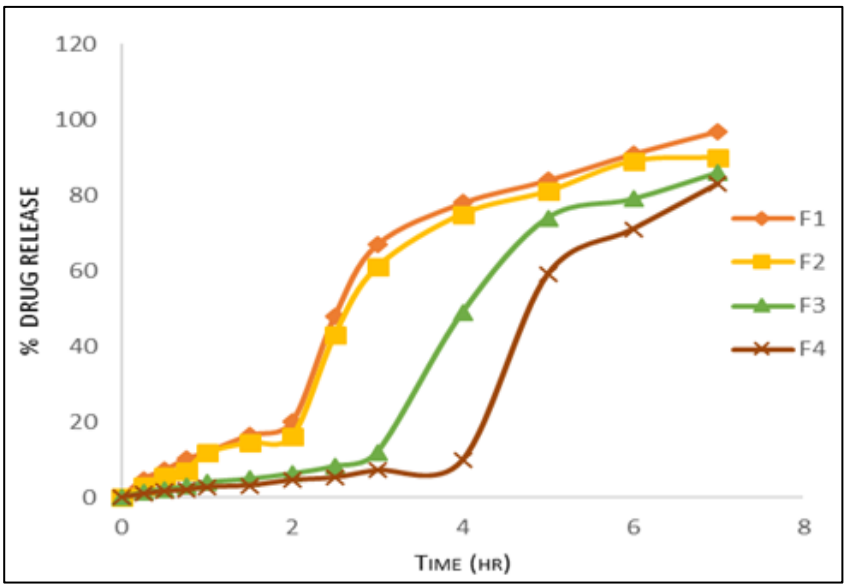

Figure 6: *In- vitro* drug dissolution of core-in-cup tablets.

Figure 5: Model-dependent kinetics.

Formulation	R^2				N	Drug transport mechanism
	Zero	First	Higuchi	Korsemeyer-peppas		
F1	0.937	0.945	0.923	0.949	1.172	Super case-II
F2	0.931	0.964	0.914	0.956	1.075	Super case-II
F3	0.915	0.909	0.778	0.900	0.661	Anomalous transport
F4	0.943	0.890	0.673	0.939	0.542	Anomalous transport

Table 6: Stability Studies for optimized tablets (F4).

Parameter	0 week	1st week	2nd week	3rd week	4th week
Floating lag Time	102 ± 0.71	100 ± 0.85	103 ± 0.52	102 ± 0.70	103 ± 0.11
Lag Time (Hr.)	4.2 ± 0.18	4.2 ± 0.28	4.2 ± 0.57	4.2 ± 0.22	4.2 ± 0.19
Drug content (%)	99.57±0.65	99.52±0.55	99.47±0.64	99.48±0.68	99.37±0.45
% Drug release	83±0.20	83±0.15	83±0.20	83±0.17	83±0.09

*All values represent n= 3± S.D.

Drug release kinetics illustrates that optimized formulation F4 follows zero-order release kinetics and the korsemeyer-peppas release mechanism. The value of release component 'n' indicates that F4 exhibit Anomalous transport and the release process is swelling controlled.

Stability Studies

According to ICH guidelines, stability study for F4 was conducted. At each sampling time (i.e., every week), F4 was assessed for its floating property, lag time, drug content and *in-vitro* drug release (Table 6).

F4 showed no substantial (P >0.05) difference in %drug release of famotidine, after 7 hrs., throughout the storage period of 1 month, when corresponded with release from the same formulation prior to storage. Additionally, no difference in drug content, floating property and lag time was observed during the span of storage.

In case of nocturnal acid breakthrough, more than maintenance of constant plasma drug level diurnal progress of disease is desired (Ravichandiran et al., 2009). Nocturnal acid breakthrough occurs in patients taking Proton Pump Inhibitors, it is basically presence of <4 intragastric pH during night time for almost 60 minutes (Tutuian et al., 2004). Nocturnal acid breakthrough follows circadian rhythm with intensity of peak more between morning hours (2:00 AM- 4:00 AM), by adding H2 receptor antagonist along with Proton Pump Inhibitors. Chrontherapeutic approach can be achieved wherein, drug release occurs after predetermined lag time creating synchrony between drug concentration in plasma and peak symptoms of Nocturnal acid breakthrough. Based on the evaluation results, the optimized famotidine core-in-cup tablets ensures drug release occurs in the desired location (i.e., stomach) after predetermined lag time which is desirable in case of nocturnal acid breakthrough.

Conclusion

Nocturnal acid breakthrough is a phenomenon that occurs at midnight. Conventional delivery systems are inconvenient for delivering famotidine, a H2 receptor antagonist due to the fact that, patients are asleep at this time, and the tablet cannot be administered when the symptoms start showing. So, oral pulsatile release dosage forms with gastric retention abilities were designed to be administered at bedtime offering drug release in the morning. Therefore, famotidine was formulated as PDDS employing a "Core-in-Cup" system.

Ethyl cellulose was selected as a cup, HPMC K4M as a hydrophilic-plug layer and sodium bicarbonate as a gas-generating agent for the preparation of core-in-cup tablets based on preliminary trials. The optimized formulation F4 was evaluated for various parameters including hardness (6.0 ± 0.16kg/cm^2), thickness (3.5 ± 0.13mm), weight

variation (314 ± 1.06mg), friability (0.53 ± 0.14%), floating lag time (102 ± 0.71sec.), swelling index (129.5 ± 0.37%), lag time (4.2±0.18hrs), *In-vitro* studies showed lower initial release after the lag time, 83±0.20% drug release was seen at the end of 7th hour. Model-dependent kinetics studies indicated F4 follows zero-order release kinetics and korsemeyer-peppas release mechanism. Based on 'n' value drug release mechanism was identified as anomalous transport. The release process is swelling-controlled. Stability studies for one month indicated no significant difference in floating property, lag time, drug content and % drug release.

Acknowledgements

The authors acknowledge G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad, India for the provision of appropriate facilities for the conduct of the research work

Conflict of Interest

The authors have declared that no conflict of interest exists. All products utilised for the research are normally and predominantly used products in the area of research and country. Also, the research was funded by the personal efforts of the authors and the educational institute (G. Pulla Reddy College of Pharmacy, Hyderabad, India).

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