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RESEARCH ARTICLE

Formulation and Evaluation of Chronomodulated Floating Drug Delivery System of Famotidine

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Formulation and Evaluation of Chronomodulated Floating Drug Delivery System of Famotidine

Summary

Chronomodulated floating drug delivery system for famotidine was successfully prepared, evaluated and optimized for their desired effect. By using present drug delivery system, one can deliver famotidine locally to the stomach with certain period of lag time. Different levels of percentage weight ratio of ethyl cellulose to hydroxypropyl cellulose and different coating levels were successfully optimized by using statistical analysis. Combining 32 factorial design and response surface methodology %weight ratio of polymers and coating levels were optimized for desired lag time of off release and cumulative drug release. Response surface methodology represents combined effect of both independent variables on dependent variables. So, we can predict optimum levels of independent variables for desired responses. For the present study of formulating chronomodulated floating drug delivery system optimized coating level/%weight gain was 7.50% and percentage weight ratio of ethyl cellulose to hydroxypropyl methyl cellulose was 78.50% that can give observed lag time of 218 minute and percentage cumulative drug release 88.21% with minimum percentage error with predicted values from the software.

Chronomodulated floating drug delivery of famotidine can effectively give night time relief from nocturnal acid breakthrough (pH<4 at 2-4 am) in patients with peptic ulcer, duodenum ulcer and Gastro esophageal reflux disease.

Key Words: *Chronomodulated floating drug delivery system, Famotidine, Nocturnal gastric acid.*

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Famotidin İçeren Zaman Ayarlı Yüzen İlaç Taşıyıcı Sistemlerin Formülasyonu ve Değerlendirilmesi

Özet

Famotidin içeren zaman ayarlı yüzen ilaç taşıyıcı bir sistem başarılı bir şekilde hazırlanmış, değerlendirilmiş ve istenen etkiler için optimize edilmiştir. Bu ilaç taşıyıcı sistem kullanılarak, famotidin lokal olarak mideye belirli bir geceikme zamanı ile taşınmaktadır. İstatistiksel analiz kullanılarak, farklı kaplama seviyeleri ve hidroksipropil selülozdan etil selüloza kadar yüzde cinsinden farklı ağırlık oranları başarılı bir şekilde optimize edilmiştir. 32 faktöriyel tasarım ve yüzey cevap metodolojisi kullanılarak, polimerlerin % ağırlık oranı ve kaplama seviyeleri kümülatif ilaç salımı ve salım öncesi gecikme zamanı açısından optimize edilmiştir. Yüzey cevap yöntemi bağımsız ve bağımlı değişkenlerin kombine etkisini göstermektedir. Böylece, istenen yanıtlar için bağımsız değişkenlerin optimum seviyeleri hakkında öngörüde bulunulabilmektedir. Formüle edilen zaman ayarlı yüzen ilaç taşıyıcı bir sistem için, optimize kaplama seviyesi / % ağırlık kazanımı oranı %7,5 ve hidroksipropil selülozdan etil selüloza kadar yüzde cinsinden farklı ağırlık oranları %78,5 olup gecikme zamanı 218 dakika olarak gözlenmiş, minimum yüzde hata ile programdan öngörülen değerlerle kümülatif ilaç salımı yüzdesi %88,210 bulunmuştur. Famotidinin zaman ayarlı yüzen ilaç taşınımı ile etkili bir şekilde gastroözofageal reflü hastalığı, düedonum ülseri ve peptik ülseri olan hastalardaki (pH<4 sabaha karşı 2-4 arası) gece asidi durumunda etkin bir gece rahatlaması sağlanır.

Anahtar Kelimeler: *Zaman ayarlı yüzen ilaç taşıyıcı sistem, Famotidin, nokturnal gastrik asit.*

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INTRODUCTION

In the field of modified release, there has been a growing interest in time specific oral delivery, which generally refers to the pre-programmed release of drugs following administration to achieve improved therapeutic efficacy. These systems constitute a relatively new class of devices, the importance of which is especially connected with the recent advances in chronopharmacology (1). Particular rhythms in the onset and extent of symptoms were observed in diseases such as, bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, diabetes, attention deficit syndrome, hypercholesterolemia, and hypertension (2). Numerous studies conducted in the last decade on animals as well as clinical trials have provided convincing evidences, that the pharmacokinetics and the drug's effects can be modified by the circadian timing of drug application within 24h of a day (3,4). All these acted as push for the development of pulsatile drug delivery system which is based on the principle of rapid drug release matching the circadian pathophysiology after a predetermined off-release period, lag time (5). The viscous contents of lower part of GI tract cause hindrance to the drug diffusion and also enzymatic degradation of some drugs makes it an unfavorable site for drug release (6) .

On the contrary, gastro-retentive dosage forms reside in stomach only and are not affected by variability of pH, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in the stomach. These considerations led to the development of pulsatile release dosage forms possessing gastric retention capabilities (7, 8). Of the numerous approaches to prolong gastric retention, floating drug delivery system is the most widely used technique and offers a simple practical approach to increased gastric residency through inherent buoyancy (9) .

So, by using both these approaches, pulsatile delivery system with gastro retention by floating approach comes up with a delivery system, which locally delivers the drug to the stomach in a chronopharmaceutical manner. Drugs, indicated in diseases which follows circadian rhythm in their onset and extent, if required local delivery in the stomach then the chronomodulated floating delivery system is the best system for treatment.

The aim of the study was to develop a chronomodulated floating drug delivery system for Famotidine to release the drug in the stomach after a predetermined time period. Famotidine is a histamine H_2 receptor antagonist. It is widely prescribed in gastric ulcer, duodenal ulcer, zolinger-ellison syndromes and gastroesophageal reflux diseases. In the management of benign gastric and duodenal ulceration, the dose is 40 mg daily by mouth at bed time, for 4 to 8 weeks. In gastroesophageal reflux disease, the recommended dose is 20 mg by mouth twice daily for 6 to 12 weeks; whereas if the gastroesophageal disease is associated with esophegeal ulceration, then the recommended dosage is 40 mg twice daily for a similar period.

Nocturnal gastric acid breakthrough is defined as the appearance of gastric acid in the antrum of pH < 4 overnight for periods of longer than one hour during the administration of proton pump inhibitors (PPIs). Nocturnal acid breakthrough typically appears in the second 6- hour period (2 to 4 am), after the evening dose of a PPI when patients are sleeping. Some investigators have proposed that this surge in gastric acidity in patients taking PPI therapy is related to the high nocturnal histamine concentration. Famotidine is a histamine H_2 receptor antagonist with elimination half life 3 hours. Taking conventional tablets of Famotidine after evening meals can not overcome the nocturnal acid break through effectively. Chronomodulated tablets of Famotidine with local delivery to stomach, having ability for off release followed by burst release, can effectively suppress nocturnal histamine level and hence suppress high nocturnal acid release.

MATERIALS AND METHODS

Materials

The active ingredient Famotidine was gifted from Zydus Cadila Healthare Ltd., Gujarat (India). Glyceryl behenate was gifted from Colorcon Asia Pvt Ltd.. HPMC E 6 and 15 were gifted form Zydus Cadilla Healthcare Ltd., Gujarat, Avicel PH-102, Sodium

Starch Glycolate, PEG 4000, and Ethylcellulose 10 cps were purchased from S.D Fine Ltd, Mumbai. All other chemicals used in the study were of analytical grade.

Method

Drug-excipient compatibility study

The drug-excipient compatibility study was carried out by using Differential Scanning Calorimetric (DSC) and Fourier Transform Infrared (FT-IR) spectroscopy

Formulation of Chronomodulated Floating Tablet

Preparation of Floating Core for Burst Release by Direct Compression

The core tablets containing famotidine, glyceryl behenate, hydroxypropyl methyl cellulose E 6, sodium starch glycolate, microcrystalline cellulose (Avicel® PH102) were prepared by direct compression. Composition of the core is presented in table 1. The core tablets (diameter, 10.3 mm; biconvex; hardness, 4-5 kg/cm^2; average tablet weight, 200 mg) were compressed using a twelve station single rotary tablet compression machine (Rimek Minipress-II, Karnavati, Ahmedabad, India). In each batch 100 tablets were prepared.

Selection of the Batch for Time Lagged Coating

Selection of the batch for time lagged coating is based on the floating ability of tablet. Tablets which can float in 0.1 N HCL for more then 6 hours were selected. 15% coating (%weight gain) was given to each batch F1 to F6 by using water insoluble polymer ethylcellulose 10 cps.

Each above batch was evaluated for their floating ability as per method described by Rosa et al., the tablets were placed in a 100 ml beaker containing 0.1 N hydrochloric acid. The duration of which the dosage form constantly remained on the surface of medium was determined as the total floating time. The batch with more than 6 h of floating ability was selected for further time lagged coating (10) .

Coating was made in standard coating pan by simple pan-pour method. Pan pour methods have been used for many years for film coating. Coating composition used in the earlier pan-pour methods was usually too viscous to be sprayed effectively. Tablet coated by pan-pour methods were subjected to alternate solution application, mixing and drying steps similar to pan-pour sugar coating. Tablets coated by pan-pour processes were subjected to an additional drying step to remove latent solvents. Aqueous based coatings are not suitable for this method of application as the localized over wetting inherent with the pan-pour process causes numerous problems ranging from surface erosion to product instability due to unacceptably high latent moisture content in the cores (11) .

Table 1. Composition of the tablet core

S. No.	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
1	Famotidine	40	40	40	40	40	40
2	Glyceryl Behenate	10	20	30	40	50	60
3	HPMC E6 (15%)	30	30	30	30	30	30
4	Sodium starch glycolate (4%)	8	8	8	8	8	8
5	Mg. Stearate (1%)	2	2	2	2	2	2
6	Colloidal Silicon Dioxide (0.5%)	1	1	1	1	1	1
7	Microcrystalline Cellulose	109	99	89	79	69	59
Total core weight		200	200	200	200	200	200

Time-Lagged Coating of Floating Core Tablets for Pulsatile Release of Famotidine

A full factorial 3^2 design was used for optimization procedure. It is suitable for investigating the quadratic response surfaces and for constructing a second-order polynomial model, thus enabling optimization of the time-lagged coating process. Mathematical modeling and response surface modeling were performed with employing Design-Expert® software (Version 7.1.6, Stat-Ease Inc., Minneapolis, MN). The studied factors (independent variables) were %weight gain/ coating level (*A*) and percentage weight ratios of ethyl cellulose to hydroxypropyl methyl cellulose (*B*). Preliminary studies provided a setting of levels for each of the formulation variables. The responses (dependent variables) studied were lag time (the time required for drug release) (*Y*1) and cumulative percentage drug release at 0.1N HCL (pH 1.2) in 7 h (*Y*2). Table 2 summarizes the independent and dependent variables along with their relevant levels. Results of the formulations (testing runs) are listed in Table 3.

Formula for Time Lagged Coating, (5% coating solution was prepared)

5% (w/w) coating solutions of ethyl cellulose 10 cps (rupturable polymer) combined with hydroxypropyl methyl cellulose E 15 (erodible polymer) were prepared in ethanol and dichloro methane (4:1). The coating solution was plasticized with polyethylene glycol (5%, w/w, with respect to dry polymer), and then talc was added as glidant (5%, w/w, related to dry polymer). The coating was made by the simple pan ladling method. In that, the coating solution was poured on the tablets in coating pan with ladle. Coating process was continued until the desired weight gain (5%, 10% and 15%) was achieved. At each stage the coated tablets were further air dried in the coating pan for 15min. The tablets were then placed in the oven at 40°C for 2h to remove the residual solvent.

Evaluation of the powder blend

Blend was evaluated for bulk density, tapped density, angle of repose, compressibility index and the Hausner's ratio (Wells, 1988) .

Table 2. Independent and dependent variables

Independent variables	Level			Response (dependent variables)
	-1	0	1	
A = %weight gain/coating level	5	10	15	Y1 = lag time prior to drug release
B = %weight ratio of ethyl cellulose to HPMC E15	60:40	75:25	90:10	Y2 = % cumulative drug release in 7 hr

Table 3. Formula for time lagged coating solution

Item no	Variables	Fp1	Fp2	Fp3	Fp4	Fp5	Fp6	Fp7	Fp8	Fp9
1	Ethyl cellulose (60%)	3.0g	3.0g	3.0g	3.75g	3.75g	3.75g	4.5g	4.5g	4.5g
2	HPMC E15 (40%)	2.0	2.0g	2.0g	1.25g	1.25g	1.25g	0.5g	0.5g	0.5g
3	PEG 4000 (5%)	0.25g	0.25g	0.25g	0.25g	0.25g	0.25g	0.25g	0.25g	0.25g
4	Talc (5%)	0.25g	0.25g	0.25g	0.25g	0.25g	0.25g	0.25g	0.25g	0.25g
5	ethanol and dichloromethane combination (4:1)	q.s to 100ml	q.s to 100ml	q.s to 100ml	q.s to 100ml	q.s to 100ml	q.s to 100ml	q.s to 100ml	q.s to 100ml	q.s to 100ml
6	Coating level (%weight gain)	5	10	15	5	10	15	5	10	15

Evaluation of the Floating Core and Coated Tablets (12, 13)

a) General Appearance

The general appearance of a tablet, its visual identification and over all 'elegance' is essential for consumer acceptance. This includes tablet's size, shape, color, presence or absence of an odor, taste, surface texture.

b) Tablet Thickness

Tablet thickness is an important characteristic in reproducing appearance, ten tablets were taken and their thicknesses were recorded using a vernier caliper.

c) Weight variation

Weight variation was calculated as per method descried in the Indian Pharmacopoeia.

d) Hardness Test

Five tablets from each batch were selected and their hardness were measured using a Pfizer hardness tester, in order to determine the average tablet hardness.

e) Friability (%F)

20 tablets from each batch were selected randomly and weighed. These tablets were subjected to friability testing using a Roche friabilator for 100 revolutions.

f) Uniformity of the drug content

Uniformity of the drug content was determined by using a UV spectrophotometer (UV-1800, Shimadzu) at 265 nm, according to USP .

g) Total Floating Time

Floating time of the tablets were determined before coating and after coating of the tablets. Floating lag time and total floating time were determined as per the method described by Rosa et al (10) .

h) In Vitro Dissolution Study

Dissolution test was carried out using the USP Type II dissolution test apparatus at 37 ±0.5°C and 50 rpm speed. Famotidine released from the tablets was determined by taking the absorbance at 265 nm, using a double beam spectrophotometer. (UV-1800, spectrophotometer SHIMADZU) (USP, 2006) .

i) Lag time determination

The lag time was determined by intersecting the time axis as part of the straight line of the dissolution curve extended to the time axis (14) .

Experimental design

To develop a system with the time-lagged coating of rupturable polymer combined with erodible polymer, the coating composition and the coating level are important parameters, affecting the drug release profile, regardless of the core composition. A multivariate optimization strategy was carried out with the aim of finding the optimum coating composition and coating level to achieve a pulsatile release pattern from a time-lagged coated floating tablet.

Independent variables set for 3^2 full factorial experimental design were A (%weight gain/coating level) and B (%weight ratio of ethyl cellulose to HPMC E 15). Response data determined as per 3^2 full factorial experimental design were response Y1 (lag time, min) and response Y2 (cumulative drug release in 7 h, %)

Scanning electron microscopy

Scanning electron microscopy (SEM) study was carried at VNIT, Nagpur (M.S.). Scanning electron microscopy study was carried out for fulfilling the purpose of finding out whether coating was done uniformly or not.

RESULT AND DISCUSSION

Evaluation of physical properties of tablet blends

Six tablet blends were prepared and analyzed for various micromeritic and flow properties (Table 4). Values of Carr's index were between 13.95 and 15.31. The Hausner ratio was between 1.162 and 1.180. The angle of repose was between 26.767° and 30.759°. The Carr's index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials, because all of these can influence the

Table 4. Evaluation of physical properties of tablet blends

Code	Angle of Repose ±SD	Bulk Density (gm/ml) ±SD	Tapped Density (gm/ml) ±SD	Hausner Ratio (H R)	Carr's Index (IC)
F-1	26.767 ±0.544°	0.571 ±0.013	0.673 ±0.010	1.178	15.15
F-2	29.304 ±0.864°	0.555 ±0.012	0.645 ±0.017	1.162	13.95
F-3	30.759 ±1.247°	0.523 ±0.023	0.612 ±0.008	1.170	14.54
F-4	27.632 ±1.564°	0.503 ±0.011	0.594 ±0.008	1.180	15.31
F-5	28.198 ±0.789°	0.480 ±0.014	0.560 ±0.014	1.167	14.28
F-6	27.555 ±0.287°	0.476 ±0.009	0.556 ±0.012	1.168	14.38
Broad range	26.767-30.759	0.476-0.571	0.556-0.673	1.162-1.180	13.95-15.15

n = 3

observed compressibility index. The outcomes of these parameters indicated good flow properties and the blends were suitable for direct compression.

For formulation of chronomodulated drug delivery system with floating characteristic, glyceryl behenate, a low density wax, was used in concentration 5, 10, 15, 20, 25 and 30% in batches F-1, F-2, F-3, F-4, F-5 and F-6 respectively. Bulk density and tapped density of the formulation blends were increased from batch F-1 to F-6 as the concentration of glyceryl behenate increased from F-1 to F-6 by 5%.

Evaluation of the Tablets

a) Physical evaluation:

Tablets were evaluated for their physical parameters and the results are summarized in Table 5. Thickness of the table was 3.7 mm. Diameter of a tablet was 10.6 mm. Tablets were within limits of weight variation allowed by I.P. 1996. Tablet hardness varied from 3.6 to 4.03 kg/cm^2. Tablets with hardness below 4 kg/cm^2 were prepared because tablet containing glyceryl behenate with low hardness can have low density, so can float easily.

The friability of all the formulations was found to be less than 1.0%. The results indicate resistance to loss of weight and ability to withstand abrasion in

Table 5. Evaluation of various parameters of the tablets.

Code	Thickness ±SD (mm)	Diameter ±SD (mm)	Hardness ±SD (kg/cm2)	Weight variation ±SD (mg)	Friability ±SD (%)	% Drug Content
F-1	3.7 ±0.00	10.6 ±0.00	3.6 ±0.163	200.15 ±1.90	0.4942	98.475
F-2	3.7 ±0.00	10.6 ±0.00	3.73 ±0.047	202.05 ±2.376	0.7519	96.341
F-3	3.7 ±0.00	10.6 ±0.00	3.76 ±0.188	201.85 ±2.264	0.8298	97.560
F-4	3.7 ±0.00	10.6 ±0.00	3.86 ±0.169	200.6 ±2.154	0.4844	99.390
F-5	3.7 ±0.00	10.6 ±0.00	4.03 ±0.124	199.7 ±2.123	0.75	96.646
F-6	3.7 ±0.00	10.6 ±0.00	3.87 ±0.094	199.05 ±1.657	0.6568	99.390

The mean weight of a tablet is 200 mg.

handling, packaging and during shipment.

b) Drug content:

All the formulation was found to be within the limit (85% to 115%) of % drug content allowed by I.P. 1996. (Table 5)

c) Total floating time:

From batches F-1 to F-6, only tablets of batch F-6 float on 0.1 N HCL for 205 ±10.801 sec. Tablets from formulation F-6 floated for >6 hours after 15% ethyl cellulose (water insoluble polymer) coating. We can conclude that the tablets containing 30% of glyceryl behenate with low hardness can float in gastric fluid. So formulation F-6 was selected for further time lagged coating.

Formulation of Timed Lagged Coating

Tablets having floating ability for >6 hour were selected for further time lagged coating. F-6 batch was selected for time lagged coating. To develop a system with time-lagged coating of rupturable polymer combined with erodible polymer, the coating composition and coating level are important parameters affecting the drug release profile, regardless of the core composition. 3^2 Factorial optimization strategy was carried out with the aim of finding the optimum coating composition and coating level to achieve a pulsatile release pattern from a time-lagged coated floating tablet. Nine batches of coating were prepared based on of 3^2 Factorial design.

Physical Evaluation of Coated Tablets

Thickness and diameter of the tablets before the time lagged coating was 3.7 mm. and 10.6mm respectively. The tablet thickness and diameter were increased to 3.83 mm-3.86 mm and 10.73 mm-10.76 mm respectively for 5%weight gain (Fp-1, Fp-4 and Fp-7). For 10%weight gain, the thickness and the diameter were increased to 3.86 mm-3.93 mm and 10.8 mm-10.83 mm respectively (Fp-2, Fp-5 and Fp-8). For 15%weight gain, the thickness and the diameter were increased to 3.96 mm-4.00 mm and 10.86 mm-10.96 mm respectively (Fp-3, Fp-6 and Fp-9). (Table 6)

The mean weight of a tablet is 200 mg. After time lagged coating with 5%, 10% and 15%weight gain, a tablet should weigh 210 mg, 220 mg and 230 mg, respectively. Observation showed the weights of the tablets after time lagged coating as 211 mg for 5%weight gain, 218 mg-221 mg for 10%weight gain, 230 mg for 15%weight gain. ±SD was also small. It was finally concluded that the uniform time lagged coating was achieved. (Table 6)

***In Vitro* Dissolution Study**

In vitro dissolution study was carried out for nine batches Fp-1 to Fp-9 in 0.1 N HCl to mimic the gastric condition. The test was carried out for 7 hrs. The %

Table 6. Physical evaluation of coated tablets

Code	Thickness ±SD (mm)	Diameter ±SD (mm)	Weight after coating ±SD (mg)
Fp-1	3.83 ±0.047	10.73 ±0.047	211.00 ±0.816
Fp-2	3.90 ±0.00	10.8 ±0.00	218.66 ±0.470
Fp-3	3.96 ±0.047	10.86 ±0.047	230.33 ±1.247
Fp-4	3.86 ±0.047	10.76 ±0.047	211.33 ±1.247
Fp-5	3.93 ±0.047	10.83 ±0.047	221.66 ±1.247
Fp-6	3.96 ±0.047	10.9 ±0.081	230.33 ±2.054
Fp-7	3.83 ±0.047	10.73 ±0.047	211.00 ±1.414
Fp-8	3.86 ±0.047	10.83 ±0.047	221.66 ±1.247
Fp-9	4.00 ±0.00	10.96 ±0.047	230.66 ±2.054
Range	3.83-4.00	10.73-10.96	211-230

Table 7. *In Vitro* dissolution study of chronomodulated floating tablet of famotidine

Time (min)	% Cumulative Drug Release								
	Fp-1	Fp-2	Fp-3	Fp-4	Fp-5	Fp-6	Fp-7	Fp-8	Fp-9
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
60	1.932	2.209	1.377	1.377	1.644	1.100	1.377	1.100	1.100
120	64.316	5.264	3.598	3.321	1.658	1.657	1.380	1.103	1.380
180	86.916	51.575	5.824	4.715	2.494	2.770	1.661	1.937	2.492
240	94.040	71.929	31.898	48.530	3.608	4.162	6.932	3.882	2.775
300	95.634	89.555	48.604	69.708	29.123	10.825	23.028	7.772	3.890
360	96.677	92.803	78.377	84.557	66.338	43.564	41.654	28.028	21.642
420	97.168	93.840	89.363	92.230	88.110	68.336	78.343	57.201	37.770

Fp = Formulation code

cumulative drug releases (%CDR) of all the batches are given in Table 7.

In vitro dissolution study showed that after 7 hrs, the % CDR was 97.168 to 37.770 for batches Fp-1 to Fp-9. The graphical representation of drug release profile is presented in Figure 1.

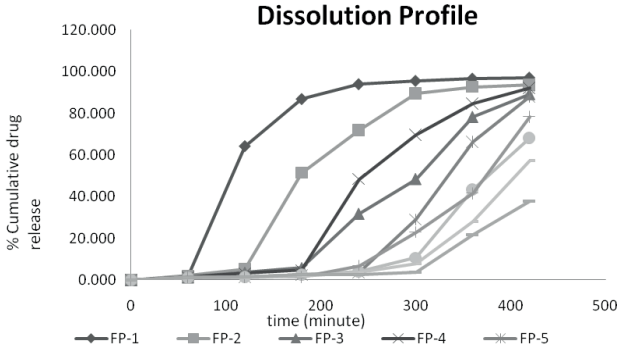


Figure 1. Dissolution profile of all the formulation Fp-1 to Fp-9 in 0.1 N HCl.

All the formulation shows burst release after certain lag time of off release. The change in their lag time was due to the variation in coating level and also coating composition. In coating composition ethyl cellulose and hydroxypropyl methyl cellulose, rupturable and erodible polymers respectively were used in varied ratio to attain maximum lag time of off release with maximum drug release within 7 h.

Lag Time Determination

The lag time was determined by intersecting the time axis as part of the straight line of the dissolution curve extended to the time axis. The lag time for all the formulation is presented in Table 8. Fp- 9 (288 min) shows the maximum lag time where as Fp-1 shows the lowest lag time (58 min). The lag time was increased proportionally to the coating level and also increase in %weight ratio of ethyl cellulose 10 cps to HPMC E15.

Effect of %weight ratio of Ethylcellulose to HPMC E 15 on lag time and drug release

Ethyl cellulose is water insoluble polymer. It is widely used in sustaining the release coating formulation. HPMC is a hydrophilic polymer so erode slowly in

Table 8. Lag time for burst release

Code	Fp-1	Fp-2	Fp-3	Fp-4	Fp-5	Fp-6	Fp-7	Fp-8	Fp-9
Lag time (min)	58	113	169	175	233	280	223	277	288

0.1 N HCL. Ethyl cellulose and HPMC E 15 were used as rupturable and erodible polymers respectively. HPMC erode slowly and allow water to enter the core. As superdisintegrants and swellable polymers were used in the core, in presence of water, the outward pressure is created, which breaks the coat and leads to burst release of famotidine from the core.

In Fp-1, Fp-4 and Fp-7, formulation level of coating or %weight gain is same, but here, %weight ratio of ethyl cellulose to HPMC E 15 is varied like 60:40, 75:25 and 90:20, respectively. That is why the % cumulative drug release of formulation Fp1 is greater than Fp-4, and drug release from Fp-4 is greater than Fp-7. As we have discussed above, ethyl cellulose is a water insoluble polymer and so it retards drug release more. Due to erosion of HPMC E 15 pore formed in coating of all the formulation, due to low ratio of HPMC E 15 in formulation Fp-7 <Fp-4 <Fp-1 they show different lag time in drug release. The lag time of the drug release is greater in Fp-7 than Fp-4, and than Fp-1.

Formulation Fp-2, Fp-5 and Fp-8; also have the same coating level (10%), but the %weight ratio of ethyl celulose to HPMC E 15 vary like 60:40, 75:25 and 90:10. So %, cumulative drug release of formulation Fp-2 >Fp-5 >Fp-8 and the lag time for drug release for formulation Fp-2 <Fp-5 <Fp-8.

Formulation Fp-3, Fp-6 and Fp-9 have the same coating level too (15%), but the %weight ratio of ethyl celulose to HPMC E 15 vary like 60:40, 75:25 and 90:10. So, the %cumulative drug release of formulation Fp-3 >Fp-6 >Fp-9 and lag time for drug release for formulation Fp-3 <Fp-6 <Fp-9.

Effect of %weight gain on lag time and drug release

As there is increase in the %weight gain/coating level on core tablet, there is an increase in the thickness of coating. Due to the increase in the thickness of coating, its too hard for the water to penetrate through the coating. For the same concetration of ethylcellulose and HPMC E 15, higher the coating level, more time is require for the drug release. Higher coating level requires more time for erosion of HPMC and so more time for pore formation in the coat. Ultimately we will get low drug release with higher lag time for drug release in predetermined time period.

Formulation Fp-1, Fp-2 and Fp-3 having the same %weight ratio of ethyl cellulose to HPMC E 15 (60:40) in their coating, but vary in the %weight gain/coating level by 5%, 10% and 15% respectively. Therefore, the %cumulative drug release for formulation Fp-1 >Fp-2 >Fp-3, where as the lag time of drug release for formulation Fp-1 <Fp-2 <Fp-3.

Formulation Fp-4, Fp-5 and Fp-6 having the same %weight ratio of ethyl cellulose to HPMC E 15 (75:25) in their coating, but vary in the %weight gain/coating level by 5%, 10% and 15% respectively. Therefore, the % cumulative drug release for formulation Fp-4 >Fp-5 >Fp-6, where as the lag time of drug release for formulation Fp-4 <Fp-5 <Fp-6.

Formulation Fp-7, Fp-8 and Fp-9 having the same %weight ratio of ethyl cellulose to HPMC E 15 (90:10) in their coating but vary in the %weight gain/coating level 5%, 10% and 15% respectively. Therefore, the % cumulative drug release for formulation Fp-7 >Fp-8 >Fp-9, where as the lag time of drug release for formulation Fp-7 <Fp-8 <Fp-9.

Experimental Design: 3^2 Factorial Design

To develop a system with time-lagged coating of rupturable polymer combined with erodible polymer, the coating composition and coating level are important parameters affecting the drug release profile, regardless of the core composition. A multivariate optimization strategy was carried out with the aim of finding the optimum coating composition and coating level to achieve a pulsatile release pattern from a time-lagged coated floating tablet.

The independent variables set for 3^2 full factorial experimental design were A (%weight gain/coating level) and B (%weight ratio of ethyl cellulose to HPMC E 15). Response data determined as per 3^2 full factorial experimental design were response Y_1 (lag time, min) and response Y_2 (cumulative drug release in 7 h, %) are presented in Table 9.

Table 9. Formulation runs with various levels of variables with responses.

Formulation Run	Variables		Responses	
	A (%weight gain)	*B* (%weight ratio of Ethyl cellulose to HPMC E 15)	Y_1 (Lag time in min)	Y_2 (% CDR)
1	5	60:40	58	97.168
2	10	60:40	113	93.840
3	15	60:40	169	89.363
4	5	75:25	175	92.230
5	10	75:25	233	88.110
6	15	75:25	280	68.336
7	5	90:10	223	78.343
8	10	90:10	277	57.201
9	15	90:10	288	37.770

The response parameters were statistically analyzed by applying ANOVA (analysis of variance), at 5% significance level and the significance of the model was estimated using the statistical package Design-Expert 7.1.6.

The individual parameters were evaluated using *F*-test and the mathematical relationship was generated between the dependent variables and independent variables (responses), using multiple linear regression analysis, for determining the levels of factors which yield optimum dissolution responses. A second-order polynomial regression equation that fitted to the data is as follows:

$$Y = b_0 + b_1*A + b_2*B + b_3*A*B + b_4* A^2 + b_5B^2$$

Where b_0 is the intercept representing the arithmetic averages of all the quantitative outcomes of 9 runs; b_1, b_2, b_3, b_4 and b_5 are the coefficients obtained from the observed experimental values of Y; and A and B stand for the main effects. The term A*B represents interaction, and A^2 and B^2 represent quadratic terms. The factor is considered to influence the response if the effect shifts from zero and p-value is less than 0.05. Table shows effect of factor on response and p-value. The polynomial equations for the final response are as shown below

1) $Y_1 = +235.22 + 46.83 * A + 74.67 * B - 11.50 * A * B - 8.83 * A^2 - 41.33 * B^2$

2) $Y_2 = +84.57 - 12.05 * A - 17.84 * B - 8.19 * A * B - 2.52 * A^2 - 7.28 * B^2$

Equation suggests the quantitative effect of variables on the responses. A*B suggests the simultaneous effect of both variables by interaction. A2 and B2 suggest quadratic effect on responses. Positive sign indicate the synergistic effect and negative sign indicate antagonistic effect.

Table 10: Summary of factor effect and p-value.

Factor	Y_1 (Lag Time)		Y_2 (% Cumulative Drug Release in 7 hrs)	
	Factor effect	p-value	Factor effect	p-value
A	+ 46.83	0.0012	- 12.05	0.0025
B	+ 74.67	0.0003	- 17.84	0.0008
A * B	- 11.50	0.0933	- 8.19	0.0133
A^2	- 8.83	0.2786	- 2.52	0.3351
B^2	- 41.33	0.085	- 7.28	0.0452

As represented in the Table 31 the variable A (%weight gain) gives positive effect on lag time means, as there is an increase in the coating level/%weight gain, there will be increase in lag time for drug release. Same variable shows negative effect on % cumulative drug release. Variable B (%weight ratio of ethyl cellulose to HPMC E 15) shows positive effect on lag time and

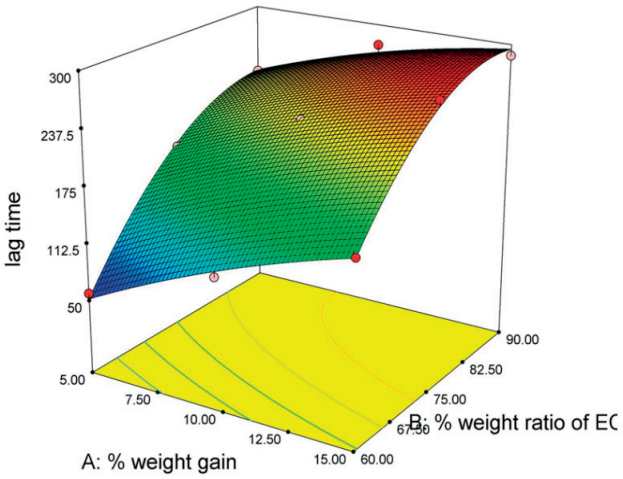


Figure 2. Response surface plot showing the effect of variables %weight gain (A) and %weight ratio of ethyl cellulose to HPMC E 15 (B) on response Y1 (lag time in min.)

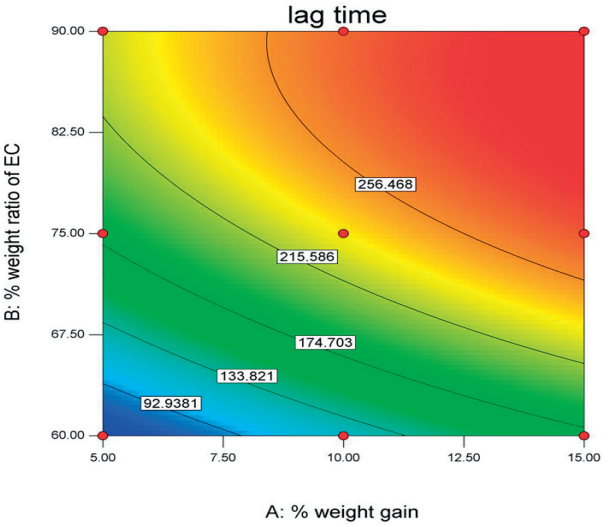


Figure 3. Contour plot showing the effect of variables %weight gain (A) and %weight ratio of ethyl cellulose to HPMC E 15 (B) on response Y1 (lag time in min.

negative effect on % cumulative drug release i.e. as we increase ethyl cellulose concentration in coating composition the lag time will increase and the % cumulative drug release will decrease.

Response Surface Methodology

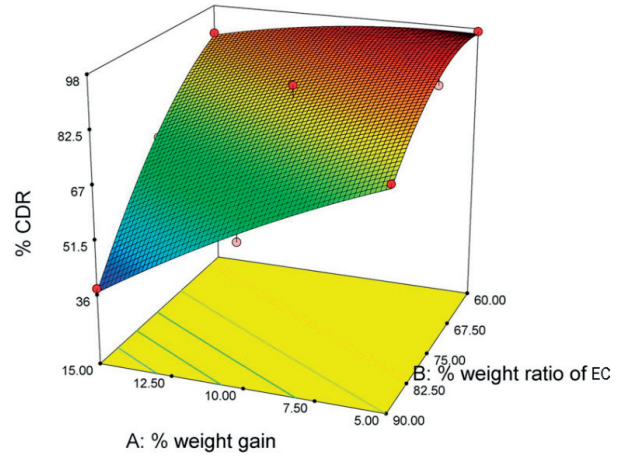
Response surface graph was plotted by using software design expert 7.1.6. In the plot curve surface represents the response value (Y) as a function of independent variables (A and B)

Response Y_1 (Lag time)

Figure 2 and 3 showing synergistic effects of the two independent variables on lag time. This increase in lag time was due to the decreased permeability and increased hydrophobicity of the coating membrane, because of the higher concentration of insoluble polymer (ethyl cellulose) as well as the increased coating thickness.

Figure 4 showing the antagonistic effect of the two independent variables on % cumulative drug release.

Response Y_2 (% cumulative drug release)



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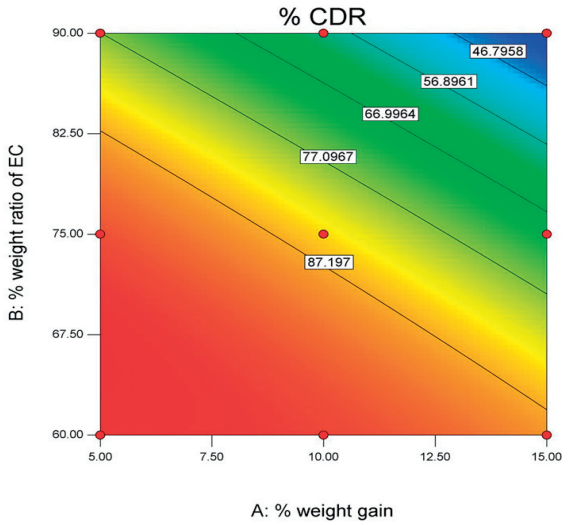


(b)

Figure 4. Response surface plot (a) and Contour (b) showing the effect of variables %weight gain (A) and %weight ratio of ethyl cellulose to HPMC E 15 (B) on response Y2 (% cumulative drug release)

Table 11: % cumulative drug release of final optimized formulation

Sr. no	Time (minute)	% CDR
1	0	0.000
2	60	1.100
3	120	2.766
4	180	5.267
5	240	18.310
6	300	50.788
7	360	71.417
8	420	88.210

This decrease in % cumulative drug release was due to the decreased permeability and increased hydrophobicity of the coating membrane because of the higher concentration of insoluble polymer (ethyl cellulose), as well as the increased coating thickness.

Optimization

Numerical optimization was carried out with desirability approach for finding out the optimum formulation with desirability response. The constrains were 225 min <lag time (Y_1) <275 min for lag time and 85% <% cumulative drug release (Y_2) <95% for % cumulative drug release. The optimal calculated independent variables were:

- %weight gain/coating level, A = 7.56%
- Percentage weight ratio of ethyl cellulose to HPMC, B = 78.50%

Table 11 and Figure 5 represents the % cumulative drug release of final optimized formulation with 7.56% coating level and 78.50% weight ratio of ethyl cellulose to hydroxypropyl methyl cellulose. The lag time was determined by intersecting the time axis as part of the straight line of the dissolution curve extended to the time axis. The lag time (Y_1) found was 218 min.

The predicted values for the lag time and the % cumulative drug release were 226.716 min and 86.228% respectively. The percentage prediction error was very negligible. Table 12 represents the

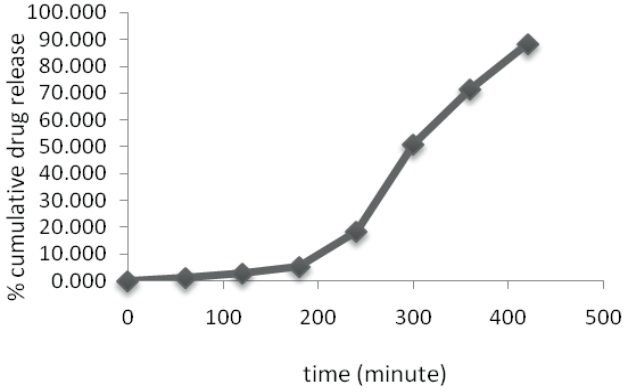


Figure 5. % cumulative drug release of final optimized formulation

Table 12. Predicted and observed values for responses Y1 and Y2 with percentage prediction error

Sr. no.	Responses	Predicted values	Observed values	% prediction error
1	Lag time, Y_1 (min)	226.716	218	-3.84
2	% cumulative drug release, Y_2	86.228	88.210	+2.29

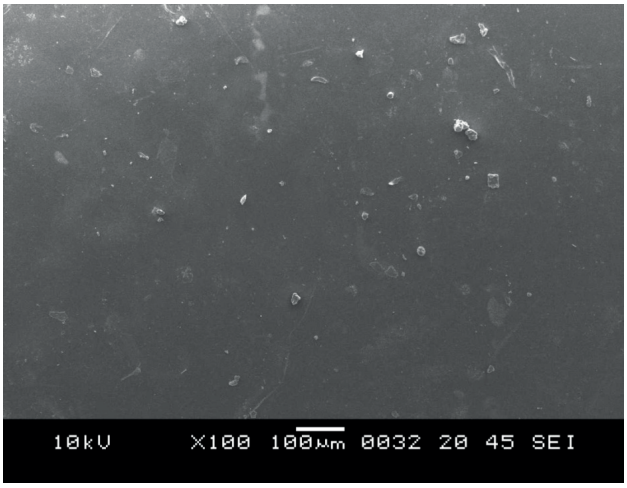
predicted and observed values of the lag time and the percentage cumulative drug release.

Scanning Electron Micrograph of Final Optimized Formulation

Scanning electron microscopy study was carried out to observe uniformity of the time lagged coating. Final optimized formulation was formulated with 7.56%weight gain/coating level. The obtained scanning electron micrograph of time lagged coating shows uniformity of coating. Figure represents the scanning electron micrograph of surface and cross sectional view of final Chronomodulated Floating tablet of famotidine.

REFERENCES

1. Sangalli ME, Maroni A, Zema L, Busetti CJ. In vitro and in vivo evaluation of an oral system for time and/or site-specific drug delivery. *Control Release* .73: 103–110, 2001.



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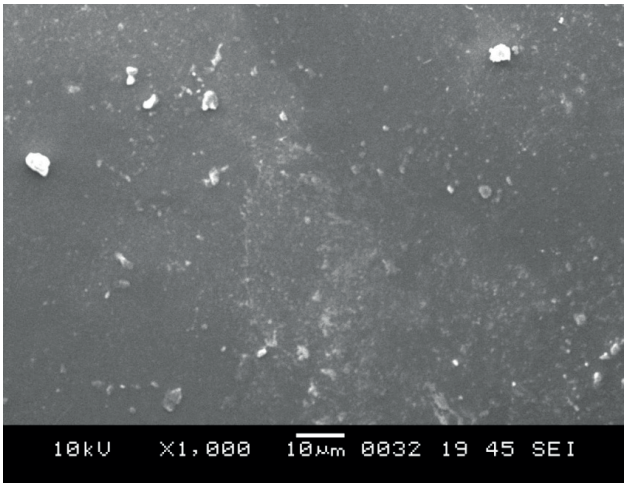

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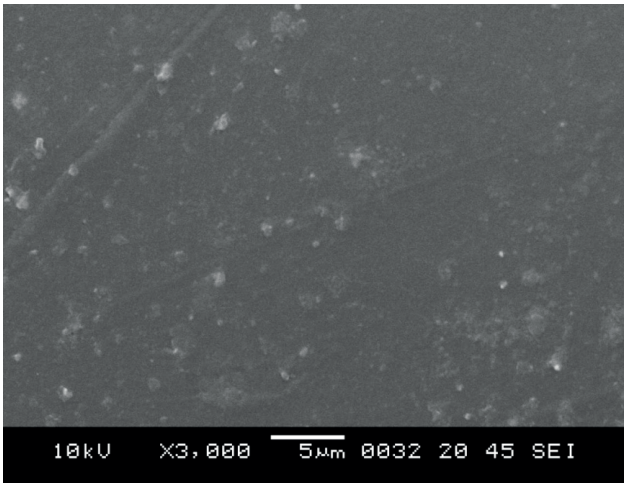

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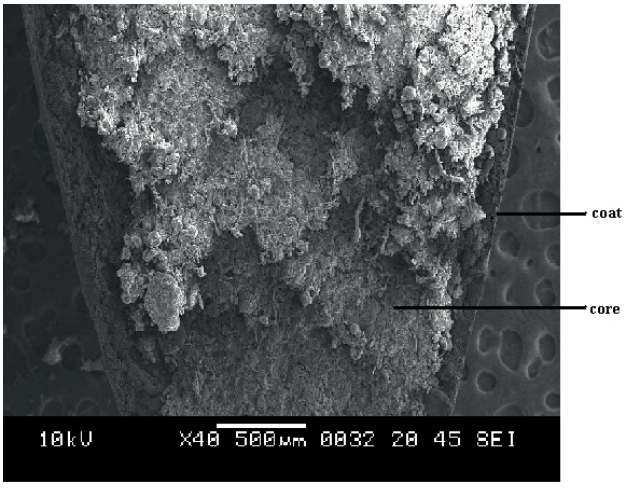

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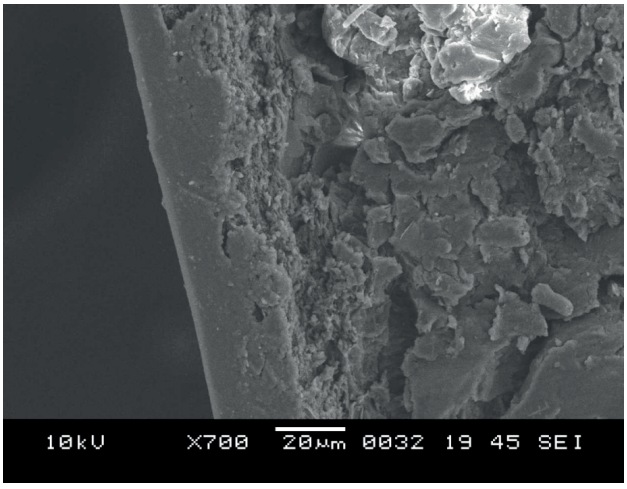

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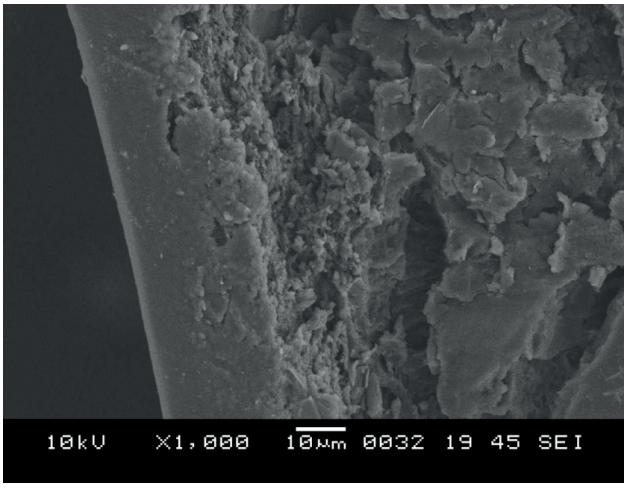

(a)

Figure 6. A. Scanning Electron Micrograph X 100 (surface view) **B.** Scanning Electron Micrograph X 1000 (surface view) **C.** Scanning Electron Micrograph X 3000 (surface view) **D.** Scanning Electron Micrograph X 40 (cross sectional view) **E.** Scanning Electron Micrograph X 700 (cross sectional view) **F.** Scanning Electron Micrograph X 1000 (cross sectional view)

2. Lemmer B. Circadian rhythms and drug delivery. *J. Control. Release.*16: 63-74, 1991.
3. Lemmer B. Chronopharmacokinetics: implications for drug treatment. *J. Pharm. Pharmacol.* 51: 887–890, 1999.
4. Bjorn L. The clinical relevance of chronopharmacology in therapeutics. Pharmacol. Res. 33: 107–115, 1996.
5. Kikuchi A, Okano T. Pulsatile drug release control using hydrogels. *Adv. Drug Del. Rev.*54: 53–77, 2002.
6. Hoffman A, Stepensky D, Lavy E, Eyal S, Klausner E, Friedman M. Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms. *Int. J. Pharm.* 277: 141–153, 2004.
7. Badve SS, Sher P, Korde A, Pawar AP. Development of hollow/porous calcium pectinate beads for floating-pulsatile drug delivery. *Eur. J. Pharm. Biopharm*. 65: 85–93, 2007.
8. Krögel I, Bodmeier R. Floating or pulsatile drug delivery systems based on coated effervescent cores. *Int. J. Pharm.*187: 175–184, 1999.
9. Singh BN, Kim KH. Floating drug delivery system: an approach to oral controlled drug delivery via gastric retention. *J. Control. Release*. 63: 235– 259, 2000.
10. Rosa M, Zia H, Rhodes T. Design and testing invitro of bioadhesive and floating drug delivery system for oral application. *Int. J. Pharma.* 105, 65-70, 1994.
11. Lachman L. Lieberman HA, Kanig J L. The theory and practice of industrial pharmacy. In: Fiese EF and Hagen TA, editor. Preformulation, Bombay; Varghese Pub. House: 2003, p. 179.
12. The Indian Pharmacopoeia. Ministry of Health and Family Welfare, Govt. of India. The Controller of publication: New Delhi,1996; pp 736.
13. United States Pharmacopoeia 29-NF 24. The Official Compendia of Standards. Asian ed. Rockville, MD: United States Pharmacopoeial Convention Inc.2006; 2679-2681.
14. Fukui E, Uemura K, Kobayashi M. Studies on applicability of press-coated tablets using hydroxypropylcellulose (HPC) in the outer shell for timed-release preparations J. Control. Release. 68: 215–223, 2000.