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Formulation and Evaluation of Floating Tablets of Cimetidine

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Abstract : The aim of present work was to develop and evaluate the floating tablets of cimetidine. The effect of polymer concentration and type of polymer were examined. The floating drug delivery system (tablets) were prepared by direct compression method using HPMC (K4M & K15M) as polymer and sodium bicarbonates as gas generating agent. All formulations were evaluated for the pre compression and post compression, *In vitro* buoyancy, *In vitro* dissolution studies, and short term stability study. Pre-compression studies revealed that there was no sign of any interaction between drug and polymers and all formulation showed good flow properties. Results of post compression parameters were found within the limits for all formulations. Among all the formulation F3 showed better buoyancy and drug release profile. The release of drug from the prepared formulations (F3) was found to follow zero order and mechanism was non-fickian. Stability studies showed that there were no significant changes in the buoyancy, drug release rate and physical appearance. It was concluded that drug release rate was increased as the concentration of polymer decreased. HPMC K4M showed greater drug release rate as compared to HPMC K15M.
Keywords: cimetidine, floating drug delivery system, HPMC, buoyancy, in-vitro evaluation, stability.

Introduction

The main motive of any drug delivery system is to deliver a sufficient concentration of drug to the specific target (cell, organ, tissue) in the body to achieve therapeutic concentration and maintain optimum concentration. Oral drug delivery system is the most commonly used system for drug delivery because of its several advantage like easy administration , easy to formulate and high patient compliance.[1] Oral controlled – release drug delivery system deliver the drug at a predetermined and controlled rate hence maintain optimum therapeutics concentration .oral controlled release drug delivery system have a several merit : enhancement of activity of duration for short half-life drug, elimination of side effect , reducing frequency of dosing and wastage of drug and high patient compliance.[2]

Oral-controlled drug delivery system has the ability of being retained in stomach and is said to be Gastro-retentive drug delivery system (GRDDS). Gastro-retentive drug delivery system are designed to control and prolong gastro-intestinal residence time and improve the systemic bioavailability of drug which are absorbed in stomach or in upper part of small intestine , locally active in stomach , unstable in the intestinal and colonic environment and show low solubility at high pH value [4,5]

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Gastro- retentive drug delivery system may be achieved by: high density system, floating system, mucoadhesive system, swellable system, magnetic system and superporous hydrogel system. [6,7]

Floading System (FDDS) are also known as hydro dynamically balanced system has a bulk density less than that of gastric fluid and so remains floating in the stomach without affecting gastric emptying rate for longer time [8] . During floating period drug is slowly released at desired rate from the system [9]. Floating system can be divided in to two types: effervescent and non –effervescent system[4]

Cimetidine is a histamine H_2 receptor antagonist. It is a specific competitive antagonist of histamine H_2 receptor at the parietel cell[10]. It is widely used in condition where inhibition of gastric acid secretion may be beneficial such as heart burn associated with acid reflux , duodenal and gastric ulcer , gastroesophagal reflux diseases and hyper-secretory syndrome such as Zollinger –Ellision's[11] . Literature show that cimetidine is poorly absorbed from the lower gastrointestinal tract and has a short elimination half-life.

Material and Methods

Material

Cimetidine was used as the API and purchased from Sigma-Aldrich. HPMC K4M and HPMC K15M were purchased from Bangalore fine chemicals and used as polymer. Sodium bicarbonate was used as gas generating agent and purchased from Anicare pharmaceutical. Dibasic calcium phosphate was purchased from Numex Chemical. Microcrystalline cellulose, Magnesium stearate, Talc and other chemical were purchased from Central drug house .All the reagent; chemical and solvent used were of analytical grade

Method

❖ Preformulation Study[12,13]

Preformulation studies is the type of study that focus on the various physicochemical properties of drug sample that may affect the performance of drug and development of dosage form. It is the first step in dosage development process. The main purpose of preformulation studies is to develop the stable, effective and safe dosage form by establishing kinetic rate profile and compatibility with other excipients

Physicochemical properties and identification of drug

Identification of drug by IR Spectroscopy

For the identification of given drug the IR spectra of drug samples (cimetidine) was compared with the standard IR spectra of pure drug

Physicochemical properties of drug

General appearance: Drug was tested for colour, odour and taste

Solubility of drug: Solubility test was conducted to determine its solubility in the dissolution medium and other solvent

Drug –excipient compatibility

IR spectroscopy method was used for carried out drug –excipient compatibility study .FT-IR spectra of pure drug and drug + HPMC were recorded .Characteristic peaks of pure drug were compared with peaks of drug + HPMC.

Precompression parameters of powder blends[14,15]

1. Bulk and Tapped density

10gm of powder was weighed. Weighed amount of given powder was introduced into 100ml measuring cylinder .After transferred of powder into a measuring cylinder the initial volume was observed for bulk density and then cylinder was tapped continuously until no further change in volume was observed . Record the final volume for tapped density. Then bulk and tapped density were calculated by using the given formula

BULK DENSITY = WEIGHT OF POWDER / INITIAL VOLUME

TAPPED DENSITY = WEIGHT OF POWDER / TAPPED VOLUME

2 . Carr's index

Carr's index is also known as compressibility index. It is significant number that can be obtained from bulk and tapped density. The compressibility of raw material and blend was determined by Carr's compressibility index by using given formula

Carr's index (%) = {(tapped density)- (bulk density)/ (tapped density}×100

3. Hausner's ratio

The Hausner's ratio is a number that indicates flowability of a powder. Hausner's ratio is calculated by given equation -

Hausner's ratio = Tapped density / Bulk density

4. Angle of repose

Maximum angle possible between the surface of a pile of powder and the horizontal plane are refer as angle of repose. Angle of repose used to measured frictional force leads to improper flow. Funnel stand method was used for determined the angle of repose. The average value is taken and angle of repose was calculated by using the given equation

$$\tan \theta = h/r$$

$$\theta = \tan^{-1}(h/r)$$

Where θ = Angle of repose
h = height of the heap
r = radius of the heap

❖ Compression of Tablet

FLOATING tablets of cimetidine were prepared by direct compression method using different ingredient. Cimetidine and other ingredient were passed through sieve no# 80 individually. According to different formulation required amount of ingredient was weighed by using digital balance. Drug ,HPMC K4M ,HPMC K15M, MCC, Dibasic calcium phosphate and sodium bicarbonate were blended geometrically in mortor and pestle and then powder blends were lubricated with talc and magnesium stearate .Final mixing was done by using poly bag .The punching machine dye was adjusted to get 300mg tablet with hardness 4-6 kg/cm$^{2.}$ Tablets were collected and evaluated.6 formulations of (F_1 to F_6) floating tablets of cimetidine were prepared using variable concentration of HPMC K4M & HPMC K15M as shown in table

Table 1: Composition (mg/tablet) of different floating tablet

INGREDIENTS	F_1	F_2	F_3	F_4	F_5	F_6
CIMETIDINE	40	40	40	40	40	40
HPMC K4M	90	75	60	-------	--------	-------
HPMC K15M	--------	------	-------	90	75	60
MCC	47	63	77	47	63	77
SODIUM BICARBONATE	78	78	78	78	78	78
DCP	35	35	35	35	35	35
MAGNESIUM STEARATE	7	7	7	7	7	7
TALC	3	3	3	3	3	3

❖ Post Compression Parameter (Evaluation)

The prepared floating tablets were evaluated for **general apparance**, **thickness, hardness, friability, weight variation, *In vitro* buoyancy ,*In vitro* dissolution studies ,** and **short term stability study.**[16-19]

General appearance

Organoleptic properties (General appearance) of tablet is the first most important quality for the acceptance of tablet. Its play a major role for the consumer acceptance. Prepared tablets was evaluated for organoleptic properties (colour, odour, taste and shape)

Thickness

6 tablets from each formulation were randomly selected and thickness was measured by using vernier calipers and then average value was calculated

Hardness

Hardness of tablet refer to the ability of a tablet to withstand for mechanical shocks. Hardness testing is used to test the breaking point of tablet. 6 tablets were taken from each formulation .Hardness of tablet was determined by using Pfizer hardness tester. Hardness was expressed in Kg/cm^2.

Friability

Roche friabilator was used for the determination of friability and it is expressed in percentage. 20 tablets were taken, initially weighed (W initial). Preweighed selected tablets were placed in the friabilator which revolves at 25 rpm (100 revolutions) for 4 min. Then tablets were removed from the chamber de-dusted and weighed again (W final). The % friability was then calculated by

F= {(W initial)- (W final)/ (W initial)}×100

Weight variation

20 tablets were taken from each formulation randomly and weighed individually. Average weight was calculated and percentage deviation from the average weight was determined by using given formula.

% deviation ={(Average weight – initial weight) /Average weight} X 100

Table 2: Percentage deviation in weight variation

Average weight of tablet	Percentage deviation
130 or less	10
130-324	7.5
More than 324	5

***In vitro* buoyancy/ floating study**

In-vitro buoyancy studies were performed for all the formulations. The randomly selected tablets from each formulation were kept in a 100 ml beaker containing 0.1N HCL pH 1.2. The time taken for the tablet to rise to the surface and float was floating lag time and the duration of time the dosage form constantly remained on the surface of medium was determined as total floating time (TFT)

In vitro dissolution studies

In vitro dissolution studies of cimetidine floating tablets were carried out by using USP type II apparatus (paddle type). Dissolution vessel was filled with 900ml 0.1 N HCL pH 1.2 and then temperature of the medium was adjusted to 37 ± 0.5^0C. Rotational speed of paddle was set at 50 rpm and then one tablet was introduced in each dissolution vessel .10ml solution were withdrawn from the dissolution vessels at every hour for 8 hrs and the samples were replaced with 10ml fresh dissolution medium. Absorbance of this solution was measured at 218 nm using a UV spectrophotometer.

Drug release kinetics

In order to understand the exact mechanism of drug release from the dosage form, result of *in-vitro* dissolution study of formulation which show good parameters was analysed according to various kinetics equation (zero order, first order , Higuchi model and korsmeyer Peppas)

Short term stability study

Ideal formulation for stability studies was selected on the basis of cumulative % drug release and floating time. Stability studies was performed according to ICH guideline at 40^0 C and 75% RH. The formulation was sealed in aluminum packing and introduced in humidity chamber maintained at 40^0C/75% RH for three months. After 3 months formulation was analysed for various parameters.

Results and Discussion

Cimetidine is a histamine H_2 receptor antagonist. It is widely used in condition where inhibition of gastric acid secreation may be beneficial such as heart burn associated with acid reflux , duodenal and gastric ulcer, gastroesophagal reflux diseases and hyper-secretory syndrome such as Zollinger –Ellision's. Floating tablets of cimetidine were developed to increase the gastric residence time of the drug, hence they could be retained in stomach for prolong time and drug is releases lowly at the desired rate .

Preformulation studies were conducted for drug and concluded that cimetidine is white to pale yellow crystalline powder, bitter in taste ,odourless and soluble in water ,0.1N HCL but not in organic solvents .FTIR spectra obtained indicated that there is no interaction between drug and polymer and sample is also identify by the characteristic peak of Cimetidine.

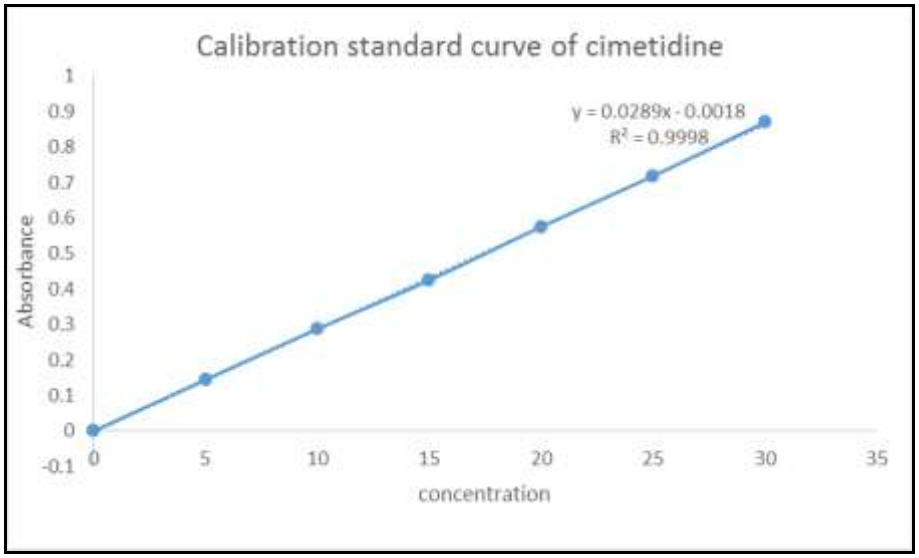

Fig 1 : calibration standard curve of cimetidine

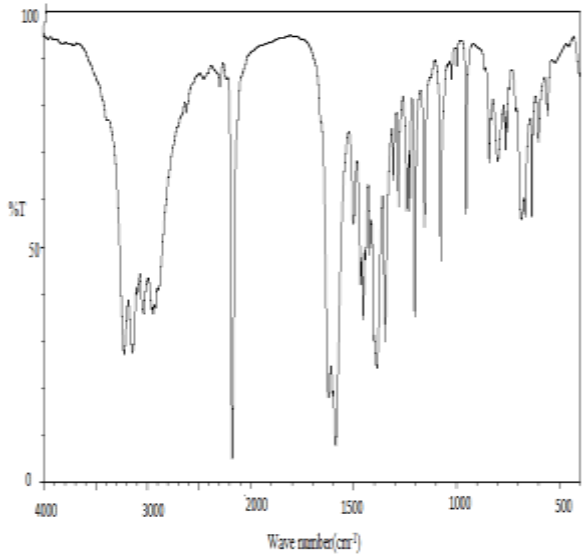

Fig 2: FTIR of Cimetidine

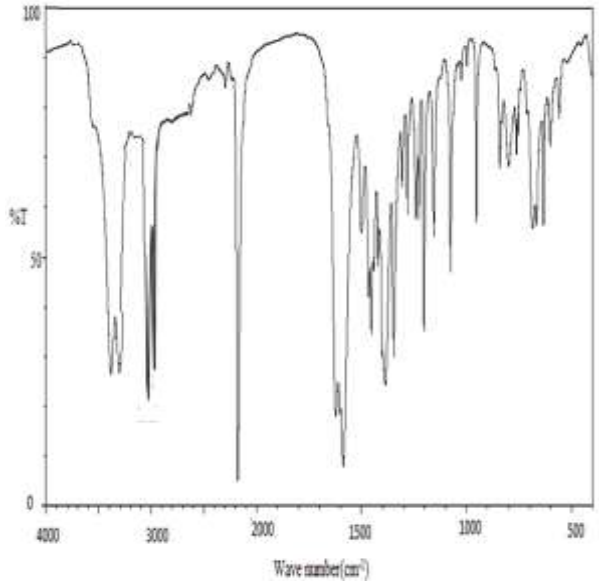

Fig 3: FTIR of Cimetidine + HPMC

Table 3: **Physicochemical properties of cimetidine**

Colour	White to pale yellow crystalline powder
Taste	Bitter
Odour	Odourless
Solubility	Soluble in water, 0.1N HCL but not soluble in organic solvent.

Raw materials and prepared powder blend of all formulations were evaluated for their flow properties such as the angle of repose, bulk density, tapped bulk density, Hausner's ratio and Carr's index. The Carr's index, Hausner's ratio and angle of repose were ranged between 13.26±1.05 to 14.76±1.5, 1.15±0.03 to 1.17±0.01 and 21.25±1.15 to 21.78±1.36 respectively. It could be concluded from the result that the powder blend with different formulations components were having good flow properties, good compressibility, which allow these formulations to be directly compressed into tablets. The results are shown in table no 4

Table 4: **Results of precompression parameters**

Formulation	**Bulk density**	**Tapped density**	**Carr's index**	**Hausner's ratio**	**Angle of repose**
F_1	0.450±0.02	0.530±0.06	14.31±1.03	1.17±0.02	22.26±1.23
F_2	0.440±0.02	0.514±0.03	14.39±1.11	1.168±0.02	21.25±1.15
F_3	0.451±0.03	0.520±0.05	13.26±1.05	1.152±0.03	21.39±1.09
F_4	0.456±0.05	535±0.02	14.76±1.15	1.173±0.01	21.78±1.36
F_5	0.480.33±0.02	0.559.33±0.05	14.12±0.02	1.16±0.02	21.53±1.28
F_6	0.437±0.04	0.512±0.01	14.64±0.98	1.17±0.01	21.68±1.22

All values are expressed as mean ± SD (n=3).

The prepared floating tablets of cimetidine were evaluated for various post compression parameters like general appearance, average weight, thickness, hardness, friability, buoyancy parameters and drug content. The results are shown in table no 5.

Table 5: Results of post-compression parameters

formulations	Hardness (kg/cm^2)	Thickness (mm)	Weight variation	Drug content %	Friability (%)
F_1	4.5±0.22	3.5±0.04	304.8±0.22	96.94±0.47	0.67±0.18
F_2	4.2±0.32	3.4±0.12	302.5±0.19	95.02±0.21	0.72±0.29
F_3	4.6±0.18	3.6±0.09	302.4±0.11	97.75±0.28	0.61±0.22
F_4	4.4±0.36	3.5±0.14	304.5±0.26	97.68±0.39	0.75±0.31
F_5	4.3±0.18	3.3±0.08	303.4±0.46	94.12±0.31	0.62±0.25
F_6	4.1±0.16	3.5±0.22	302.4±0.18	97.82±0.45	0.69±0.12

All values are expressed as mean ± SD (n=5).

All the post compression parameters of all the formulations are within the acceptance limit. **General appearance**: The prepared tablets of all formulations remained off white, smooth, flat faced circular with no visible cracks.

Thickness: The thickness of tablets was measured by vernier calipers and was ranged between 3.3 ± 0.08 to 3.6± 0.09,

Hardness: The hardness obtained was in the range of 4.1 ± 0.16 to 4.6± 0.18 kg/cm2.

Average weight: The values was obtained in the range of 302.4± 0.18 to 304.8±0.22 mg for weight variation.

Friability: All the tablets passed friability test and was found to be 0.66±0.22 to 0.75±0.29 %

Buoyancy: All the formulation showed good buoyancy parameters, floating lag time was found to be 13.35±0.3 to 15.57±0.12 sec and total floating time was between 11 to 13 hr. The formulations containing HPMC 4KM showed good buoyancy parameters when compared to formulations containing HPMC15KM. Among all the formulation F3 showed better result.

Table 6: buoyancy study results

Formulations	Floating lag time(sec)*	Total floating time(h)
F_1	14.22±0.5	12
F_2	14.20±0.9	12
F_3	13.35±0.3	11
F_4	15.57±0.12	13
F_5	14.44±0.6	12
F_6	13.54±0.2	12

*All values are expressed as mean ± SD (n=3).

***In vitro* dissolution**: From the *in vitro* dissolution result it can be concluded that floating tablets prepared with HPMC K4M showed better sustained drug release than floating tablets prepared with HPMC K15M.. Formulation containing HPMC K4M showed drug release within the range 77.50% to 93.03% on other hand formulations containing HPMC K15M was found between 76.42% to 90.69%. HPMCK4M containing gastroretentive formulation F3 exhibited 93.03% cumulative drug release and good buoyancy and was chosen for drug release kinetic studies. F3 follow zero order kinetics and mechanism of release is non-fickian diffusion

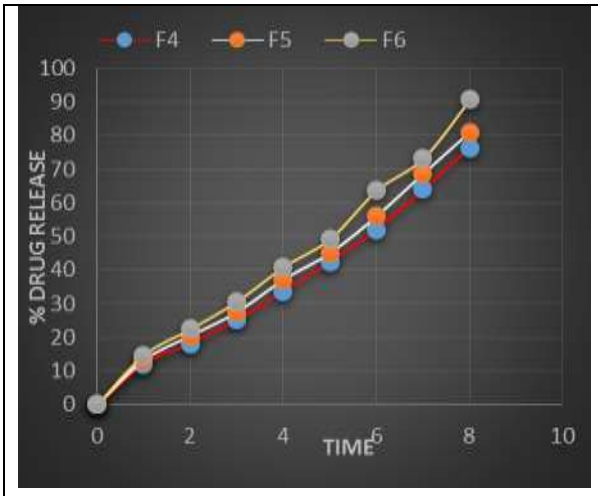

Fig 4:% drug release of F4, F5 and F6

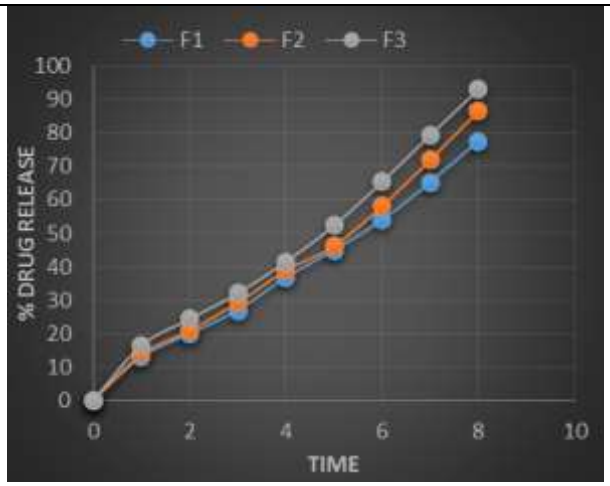

Fig 5:% drug release of F1, F2 and F3

Fig 6 : Zero order F3

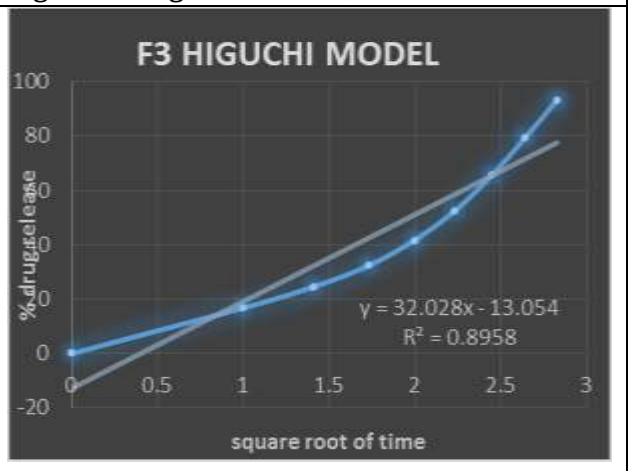

Fig 7 : Higuchi model F3

Fig 8 : First order F3

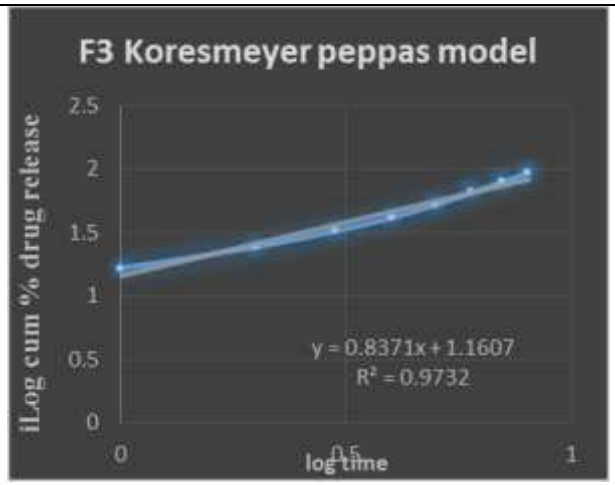

Fig 9 :Koresmeyer peppas model F3

Table 7: **Kinetic release data of F3**

Formulation	Correlation Coefficient (r2) Values				
	Zero order	First order	Higuchi's	Peppas's	
				r2	N
F3	0.990	0.825	0.895	0.973	0.83

F3 was finally selected for stability study on the basis of *in vitro* buoyancy and *in vitro* drug dissolution studies. The F3 formulation of cimetidine floating tablets were stable under 40°C/75% RH storage conditions for 90 days.

Table 8: **Stability study of F3**

Parameters	**1st month 40°C ± 2°C/ 75% RH ± 5%**	**2nd month 40°C ± 2°C/ 75% RH ± 5%**	**3nd month 40°C ± 2°C/ 75% RH ± 5%**
Physical appearance	Off white, flat faced	Off white, flat faced	Off white, flat faced
Hardness (kg/cm2)	4.6±0.18	4.6±0.18	4.6±0.17
Weight variation (mg)	302.4±0.11	302.35±0.12	302.33±0.16
Friability	0.61±0.22	0.61±0.20	0.607±0.17
Drug content (%)	97.75±0.28	97.73±0.20	97.73±0.23
Floating lag time (sec)	13.35	13.40	13.58
In-vitro release (%)	93.02%	93.02%	92.85%

Conclusion

The floating drug delivery system (tablets) of cimetidine were successfully prepared by direct compression method. Preformulation studies revealed that there was no sign of any interaction between drug and polymers and all formulation showed good flow properties. All formulations were evaluated for physiochemical properties and result was found within the limit. Among all the formulation F3 showed better buoyancy and drug release profile. The release of drug from the prepared formulations was found to follow zero order and mechanism was non-fickian. In vitro dissolution revealed that drug release rate was increased as the concentration of polymer decreased. HPMC K4M showed greater drug release rate as compared to HPMC K15M. Stability studies showed that there were no significant changes in the buoyancy, drug release rate and physical appearance. The results of present study suggested further investigations for F3 on evaluation of long term stability studies, and investigations on *in vivo* performance using animal models.

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