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Research Article

FORMULATION AND EVALUATION OF CIMETIDINE FLOATING MATRIX TABLETS

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ABSTRACT

Floating Drug Delivery System (FDDS) appears to be one of the promising GRDS. FDDS is beneficial which shows a better gastric retention and increase the efficiency of the medical treatment. Oral dosage has really progressed from immediate release to delayed release to sustained release and site-specific delivery. The design of oral drug delivery systems (DDS) should be primarily aimed to achieve more expectable and increased bioavailability. This is achieved by better control of plasma drug levels with less frequent self-administered dosing yielding constant infusion of drug. The present study deals with the formulation and evaluation of cimetidine floating matrix tablets. Gastric floating drug delivery systems (GFDDS) offer numerous advantages over other gastric retention systems. Multiple dosing of Cimetidine is required for effective treatment leading to therapeutic fluctuations; thus a sustained release dosage form of Cimetidine is suitable. The absolute bioavailability of the Cimetidine is found to be 35% due to site specific absorption. Different polymers have been evaluated in the design of gastric floating drug delivery. In the present investigation two different polymers are used for the matrix formation, HPMC is a very good vehicle for floating tablets design and Guar gum is also selected as it is a natural vegetable gum which is considered as GRAS (generally regarded as safe) by FDA they selected for design of effervescent gastric floating matrix tablets of Cimetidine. The concentration of sodium bicarbonate and its effect on the floating behaviour and drug release was studied on polymer concentration. Effervescent gastric floating matrix tablets were prepared by wet granulation method. The tablets were designed to release the total dose of the drug over a period of 12±1 hours. Uniformity of weight hardness, friability and % assay of all the prepared ten formulation were found within the official and fixed limits. Floating lag time of the table's decreases which increase in sodium bicarbonate, concentration helps to produce carbon dioxide gas which is entrapped within the hydrophilic matrices leading to increases in volume of dosage form resulting in lowering the density which helps the table to float. Due to the high viscosity of HPMC and Guar gum prevent the entry of media into the matrix and prolongs the total floating time up to 12 hour for all the batches. F5 formulation show shortest floating lag time when compared to other formulation.

Keywords: Cimetidine**,** HPMC, Guar gum, Hydrophilic matrices, Floating matrix tablets.

INTRODUCTION

Orally administered CRDDS encounters a wide range of highly variable conditions, such as pH, agitation intensity and composition of the gastrointestinal tract (GIT). Considerable efforts have been made to design oral CRDDS that produce more predictable and increased bioavailability of drugs.It is apparent that for a drug having such an "absorption window", the effective oral CRDDS should be designed not only to deliver the drug at a controlled rate, but also to retain the drug in the stomach for a long

period of time. For such type of drugs, increased or more predictable availability would result in controlled release system and thus the drug could be retained in the stomach for extended periods of time.

Stomach

The main function of stomach is to store food temporarily grind it and then release it gradually into the duodenum. The stomach is the important site of enzyme production. Compare to small intestine the absorption from stomach is low due to its small surface which acts as a barrier for the delivery of drug to small intestine.Gastrointestinal motility is based on fasted and fed state of the stomach, two distinct patterns of gastrointestinal (GI) motility and secretions have been identified. The bioavailability of orally administered drugs will vary depending on the state of feeding. The fasted state is associated with various cyclic contractile events, commonly known as migration myoelectric complex (MMC), which is further divided into four consecutive phases[8, 9].

Phase I

It is an inactivity period lasting from 30 to 60 min with no contractions and is characterized by absence of secretory, electrical and contractile activity. It is also called basal phase.

Phase II

It is also called as pre-burst phase it consists of intermittent active contractions that gradually increase in intensity and frequency as the phase progresses and it lasts about 20 to 40 min.

Phase III

This is a short period of intense distal and proximal gastric contractions this is 4-5 contractions per min due to this contraction all the undigested material is cleared out of the stomach down the small intestine.it is also known as “house-keeper waves”.

Phase IV

This is the short period of about 0 to 5 min and contractions dissipate between the last part of the phase III and quiescence of phase I.

Formulation development

For the optimum design of a GFDDS, the key step is to understand the principles of GI dynamics such as gastric emptying, small intestinal transit, colonic transit etc. acquiring knowledge about the rate and extent of drug absorption from different sites of GIT and factors that can alter or limit the absorption further aid in designing the type of dosage from needed for a particular drug. For instance, with drug such as sulpiride, furosemide, theophylline and albuterol, which are predominantly, absorbed form the upper part of the GIT, designing a gastric retention dosage form is a logical strategy for improving and extending their limited oral bioavailability.

MATERIALS AND METHODS

Cimetidine is obtaines as gift sample from MSN Labs Pvt Ltd, Hyderabad. HPMCK4M, Guar gum, Meglumine were obtained from SD Fine chemicals. All the other excipients were procured from Otto chemicals, Mumbai.

Table 1: Formulation Chart of Cimetidine Floating Matrix Tablets

S.No	INGREDIENTS mg	Formulations									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Cimetidine	40	40	40	40	40	40	40	40	40	40
2	HPMC K4M	72.5	82.5	105	122.5	120	--	--	--	--	--
3	Guar Gum	--	--	--	--	--	70	82.5	107.5	120	122.5
4	Sodium bicarbonate	50	57.5	52.5	50	72.5	52.5	57.5	50	55	70
5	Microcrystalline cellulose	172.5	155	137.5	122.5	102.5	172.5	155	137.5	120	102.5
6	Meglumine	5	5	5	5	5	5	5	5	5	5
7	IPA	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
8	Magnesium Stearate	3	3	3	3	3	3	3	3	3	3
9	Talc	3	3	3	3	3	3	3	3	3	3
Total mg		350	350	350	350	350	350	350	350	350	350

METHODOLOGY

Preparation of Tablets by wet granulation

The gastro retentive tablets were prepared by wet granulation method using polymers as described in Table No. 7 Megluminewas used as granulating agent and sodium bicarbonate were used as gas generating agent, microcrystalline cellulose was used as diluent. Drug and the Excipients except magnesium stearate and talc were bended geometrically in mortor and pestle and then IPA was added. Granules were obtained by passing the mass through sieve no. 22 the resulting granules were air dried at for 30 min. the dried granules were passed through sieve no. 12 and lubricated with Magnesiumstearate and talc. The granules so obtained were compressed into tablets of average weight 350 mg using 9 mm round punch. 10 formulations were prepared and coded as F1 to F10. F1 – F5 contains HPMC K4M and F6-F10 contains Guar Gum.

Preformulation study

Preformulation studies are an important component of drug development.it provides the scientific basis of formulation development. A comprehensive preformulation study helps in investigation of physic-chemical properties of a drug molecule it also gives the foundation for designed to determine the compatibility of initial excipients with the active substance for a biopharmaceutical, physicochemical, and analytical investigation in support of promising experimental formulations. Efforts spent on preformulation provide cost saving in the long run, by reducing challenges during formulation development.

Preparation of standard calibration curve of Cimetidine

I stock solution

A weighed amount of the Cimetidine (100mg) was taken and dissolved in 50 ml of 0.1 N hydrochloric acid in a volumetric flasks and the volume was made up with 100 ml of 0.1 HCl.

II stock solution

From the Istock solution 1 ml was withdrawn and diluted to 100 ml with 0.1 NHCl to get a concentration of 100µg/ml. From standard stock solution samples of 0.5, 1, 1.5, 2, 2.5,3 ml were pipetted into 10 ml volumetric flasks. The volume was made up with 0.1 N HCl to get the final concentration ranging from 5-30 respectively. The absorbance of each concentration was measured at 265 nm.

Drugs-excipient compatibility study

The drug and the excipients chosen for the formulation were screened for compatibility study.

Compatibility study using FT-IR

Drug excipients interaction was checked by comparing the FT-IR spectra of pure drug Cimetidine and FT-IR spectra of the physical mixture of drug and excipients. The IR spectra were taken from FT-IR-8400S (Shimadzu Corporation, Tokyo, Japan). In the present study, potassium bromide (KBr) pellet method was employed. The samples were thoroughly blended with dry powdered KBr crystals. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectrum was recorded.

Precompression studies

Angle of repose (θ)

Frictional force leads to improper flow these forces are measured by using angle of repose. Angle of repose is defined as the maximum angle possible between the surfaces of a pile of the powder on the horizontal plane. The angle of repose experiment is determined by using funnel and burette stand. The funnel is fixed at height on the burette stand and the powder was passed through the funnel which from a pile .this region is encircled to measure radius of the pile. The process is done for multiple times, the average value is taken.

The angle of repose is calculated using the equation

$$\text{Angleofrepose } (\theta) = \text{Tan}^{-1}(h/r)$$

Bulk density

The bulk density of a powder is the ratio of the mass of an untapped powder sample (W) is taken in a graduated measuring cylinder and volume (V_0) including the contribution of the interparticulate void volume. Hence the bulk density depends on both density of powder particles and the spatial arrangement of particles in the powder bed. The bulk density can be expressed in grams per millilitre (g/ml).

Bulk density is calculated using the equation

$$\text{Bulkdensity (BD)} = \frac{\text{weightofthepowder}}{\text{Volumeofpowder}}$$

Tapped density

The tapped density is obtained by tapping a measuring cylinder containing a powder sample and the volume is measured as initial volume. Measuring cylinder was fixed in the 'TAPPED DENSITOMETER' and tapped for 750-1250 times until the difference between succeeding measurements is less than 2%. The final reading

was denoted by (V_f). The Tapped density can be expressed in grams per millilitre (g/ml)

$$\text{Tappeddensity (TD)} = \frac{W}{V_f}$$

Carr's index

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 to 30% is defined as the free flowing material.

Carr's index was calculated by using the formula:

$$\text{Carr's index} = \frac{(\text{TappedDensity} - \text{BulkDensity})}{\text{TappedDensity}} \times 100$$

Hausner ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

Hausner ratio was calculated by using the formula.

$$\text{Hausnerratio} = (\text{Tappeddensity})/(\text{bulkdensity})$$

EVALUATION PARAMETERS[48, 49]

Thickness and Dimension

Six tablets from each batch were selected and measured for thickness and diameter using digital vernier calipers. The extent to which the thickness of each tablet deviated from±5% of the standard value was determined.

Weight variation

Twenty tablets were selected at random and weighed individually and the average weight was determined in a digital balance. Then percentage deviation for the average weight was calculated.

Friability

Friability can be performed by picking five to ten preweighed tablets from each formulation were placed in to the Roche friabilator operated 100 revolutions. Tablets were removed de dusted and weighted again. Conventional compressed tablets that loss<0.5-1.0% of their weight are considered acceptable.

Hardness

Tablet hardness of each formulation was determined using a Monsanto hardness tester. The tablet was placed in between a fixed and moving jaw. The scale was adjusted to zero. Load was slowly increased until the tablet broken the value of the load at that point given a measure of hardness of the tablet. Hardness was expressed in Kg/cm^2.

% Assay of Cimetidine tablets

Twenty tablets were selected randomly from each batch and powdered in a mortar and accurately weighed powder was placed in 50 ml volumetric flask. The drug was extracted into 25 ml 0.1N HCl with vigorous shaking on a mechanical shaker for few min. And the volume made up to the mark with 0.1N HCl. The solution was filtered through "Whatman filter paper" and appropriate dilutions were further made with 0.1N HCl. The dilutions sample were measured for the absorbance at 256nm against blank (0.1N HCl) and drug content was calculated.

***In vitro* Buoyancy studies**

In vitro buoyancy studies were performed from all the ten formulations and 5 tablets are randomly selected from each formulation were introduced in a 100ml glass beaker containing simulated gastric fluid pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT) the time for which the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

***In vitro* Dissolution studies**

Dissolution of the tablet of each batch was carried out using USP type II apparatus using paddle. 900 ml of 0.1 N HCl was filled in a dissolution vessel and temperature of the medium were set at 37±0.5^{0}C. One tablet was placed in each dissolution vessel and the paddle rotational speed was set at 50 rpm.10 ml of sample was withdrawn from the dissolution apparatus at every hour for 12 hours and same volume of fresh medium was replaced into the dissolution flask every time. Absorbance of this solution was measured at 265.5 nm using a UV spectrophotometer.

Release kinetics

The release kinetics methods are based on different mathematical functions, which describe the dissolution profile. Once a suitable function has been selected the dissolution profiles are evaluated depending on the derived model parameters. In order to determine the suitable drug release kinetic model describing the dissolution profile.

Zero-order model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q_0 - Q_1 = k_0 t$$

Rearrangement of above equation

$$Q_t = Q_0 + K_0 t$$

Where:

Q_t = the amount of drug dissolved in time t

Q_0= the initial amount of drug in the solution (most times, $Q_0 = 0$)

K_0= the zero order release constant

It is expressed in units of concentration / time. The release kinetics data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released *vs.* time.

Application

This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drug in coated forms, osmotic systems etc. the pharmaceutical dosage forms following this profile release thesame amount of drug by unit of time and it is the ideal method of drug release in order to achieve a prolonged pharmacological action.

First order model

This model has also been used to describe adsorption or elimination of some drugs although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by equation.

$$\frac{dC}{dt} = -Kc$$

Where K is first order rate constant expressed in units of time.

RESULTS AND DISCUSSION

Table 2: Standard calibration curve of Cimetidine using 0.1 N HCl

S.No	Concentration	Absorbance
1	5	0.146
2	10	0.287
3	15	0.428
4	20	0.576
5	25	0.719
6	30	0.872

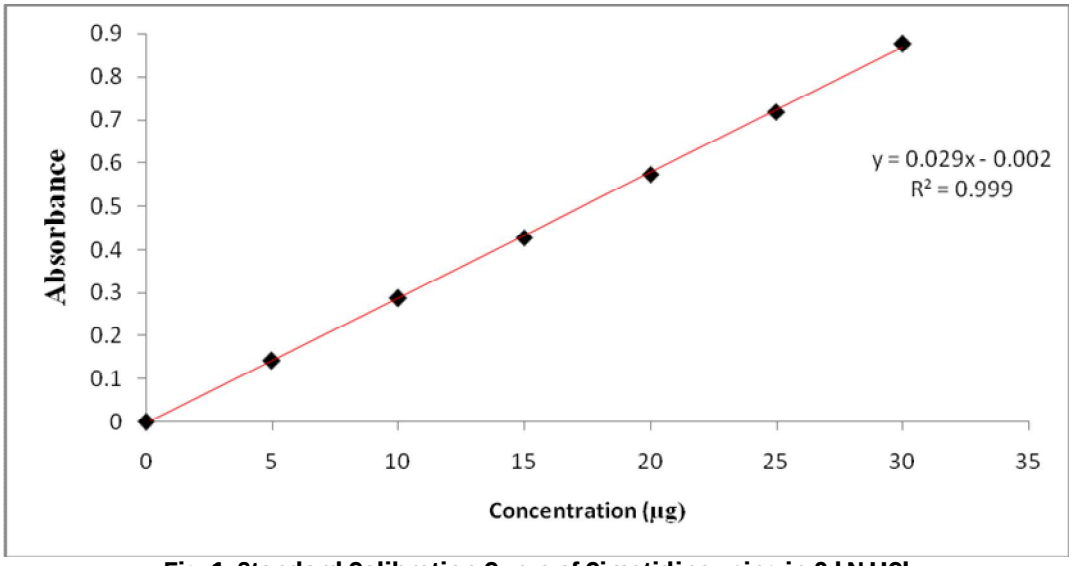

Fig. 1: Standard Calibration Curve of Cimetidine using in 0.l N HCl

Drug excipient compatibility studies

FTIR spectrum of Cimetidine

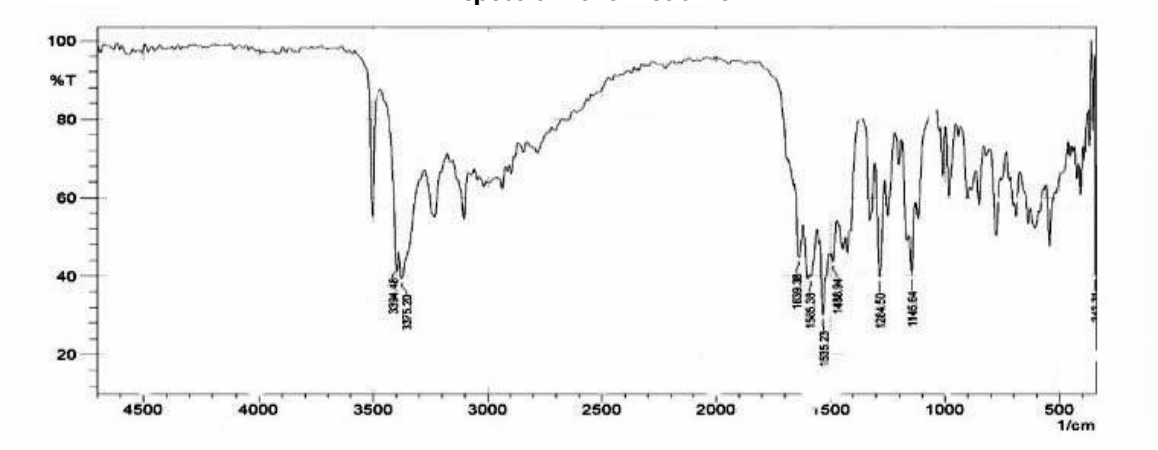

Fig. 2: IR spectrum of Cimetidine

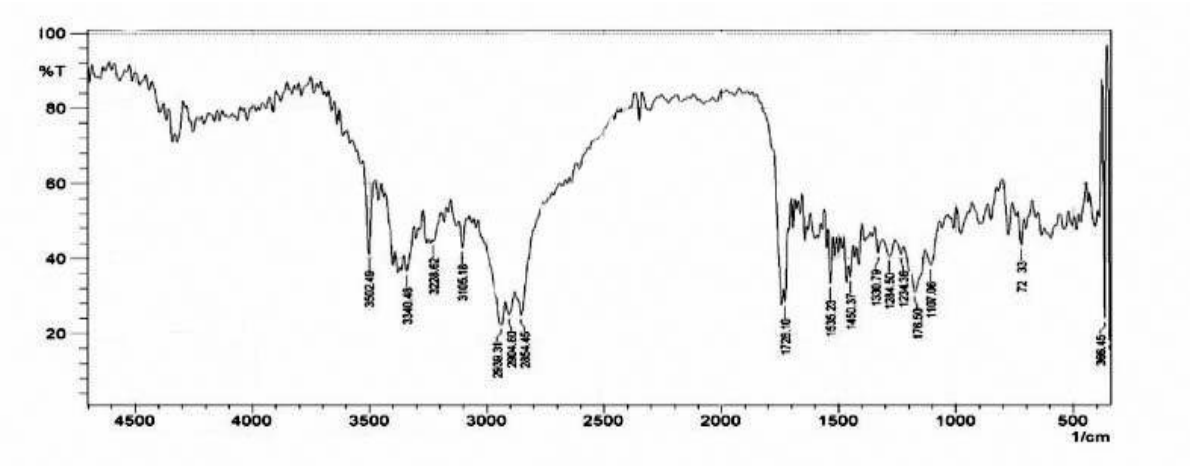

Fig. 3: IR spectrum of Cimetidine and HPMC K4M

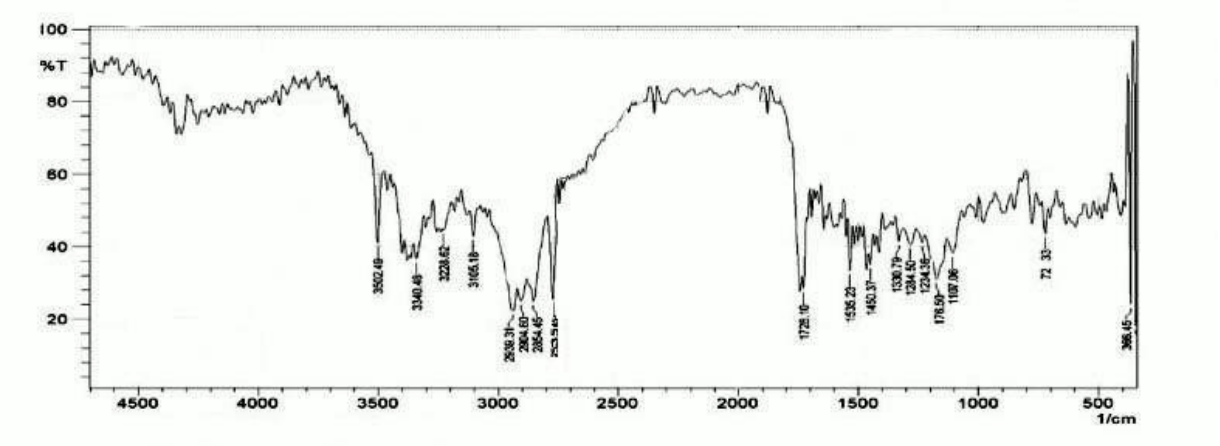

Fig. 4: IR spectrum of Cimetidine and Guar gum

Flow properties

Table 3: Evaluation of percompressed granules of Cimetidine

Formulation	Bulk density (gm/m)	Tapped density (gm/m)	Compressibility index (%)	Hausner's ratio	Angle of repose(Θ)
F1	0.323±0.02	0.436±0.05	27.5±0.1	1.32±0.02	32.15±0.1
F2	0.362±0.01	0.517±0.009	29.4±0.2	1.36±0.01	29.42±0.4
F3	0.315±0.01	0.488±0.01	25.6±0.3	1.53±0.05	31.20±0.3
F4	0.363±0.03	0.471±0.01	23.5±0.3	1.31±0.02	30.21±0.2
F5	0.357±0.02	0.458±0.03	21.6±0.4	1.28±0.04	29.10±0.1
F6	0.330±0.03	0.451±0.04	26.6±0.1	1.35±0.01	30.19±0.4
F7	0.346±0.01	0.465±0.01	25.8±0.3	1.35±0.01	29.09±0.3
F8	0.325±0.04	0.432±0.03	24.5±0.2	1.30±0.02	32.16±0.3
F9	0.349±0.05	0.478±0.02	26.5±0.3	1.38±0.01	34.35±0.2
F10	0.327±0.03	0.461±0.01	28.6±0.1	1.45±0.02	31.05±0.1

Note: All values are expressed as mean± SD, n = 3

Table 4: Evaluation of compressed granules of Cimetidine

S.No	Batch code	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Weight variation (mg)	% Assay	Floating lag time(min)	Total Floating time (hours)
1	F1	6.4±0.23	3.53±0.03	0.25±0.15	346±0.22	98.9±0.2	4.23±0.1	≥12
2	F2	6.6±0.34	3.41±0.14	0.42±0.03	346±0.13	98.7±0.3	5.12±0.02	≥12
3	F3	5.9±0.17	3.67±0.19	0.45±0.06	352±0.34	99.2±0.1	5.32±0.09	≥12
4	F4	6.1±0.38	3.62±0.12	0.27±0.082	349±0.12	98.2±0.3	5.48±0.01	≥12
5	F5	6.2±0.14	3.51±.0.9	0.20±0.15	349±0.15	99.3±0.1	1.46±0.09	≥12
6	F6	6.2±0.17	3.52±0.15	0.19±0.19	347±0.24	99.5±0,2	5.43±0.08	≥12
7	F7	6.8±0.34	3.61±0.20	0.25±0.09	347±0.16	101.4±0.5	5.56±0.04	≥12
8	F8	6.4±0.05	3.43±0.17	0.43±0.08	352±0.13	96.1±0.7	6.81±0.04	≥12
9	F9	6.0±0.01	3.66±0.13	0.32±0.018	350±0.12	98.5±0.2	6.42±0.06	≥12
10	F10	6.1±0.13	3.62±0.5	0.22±0.017	347±0.14	99.2±0.1	3.46±0.23	≥12

Note: All values are expressed as mean± SD, n = 3

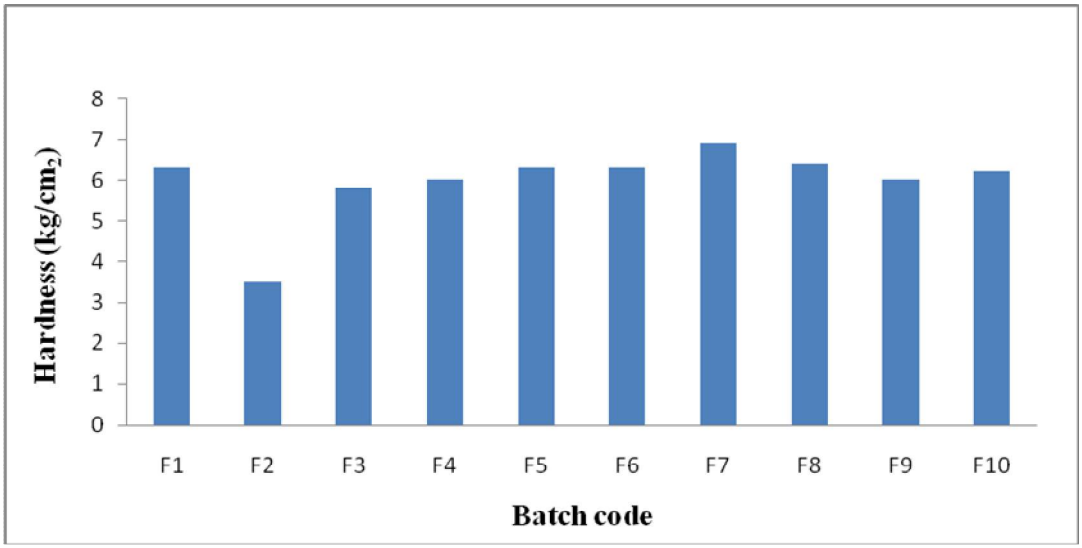

Fig. 5: Hardness profile

Fig. 6: Thickness profile

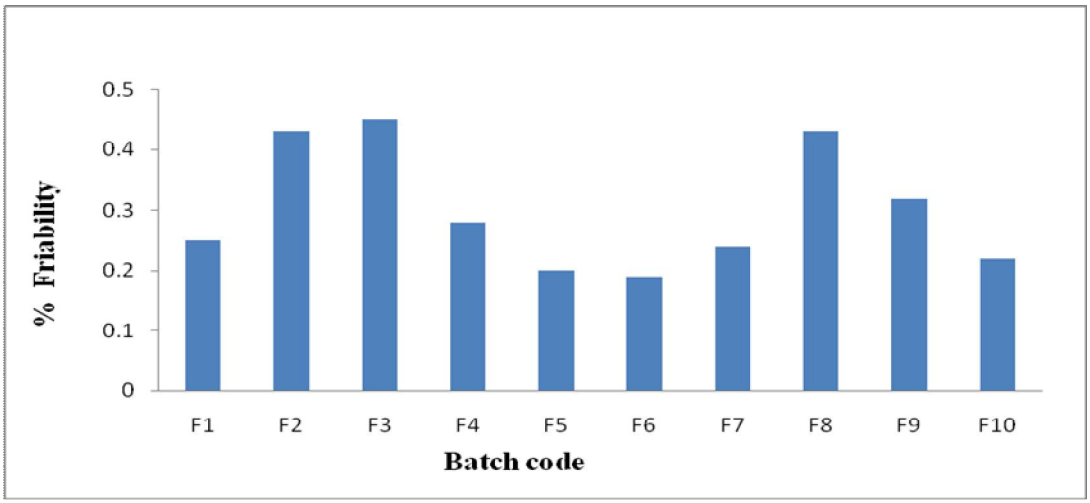

Fig. 7: Friability profile

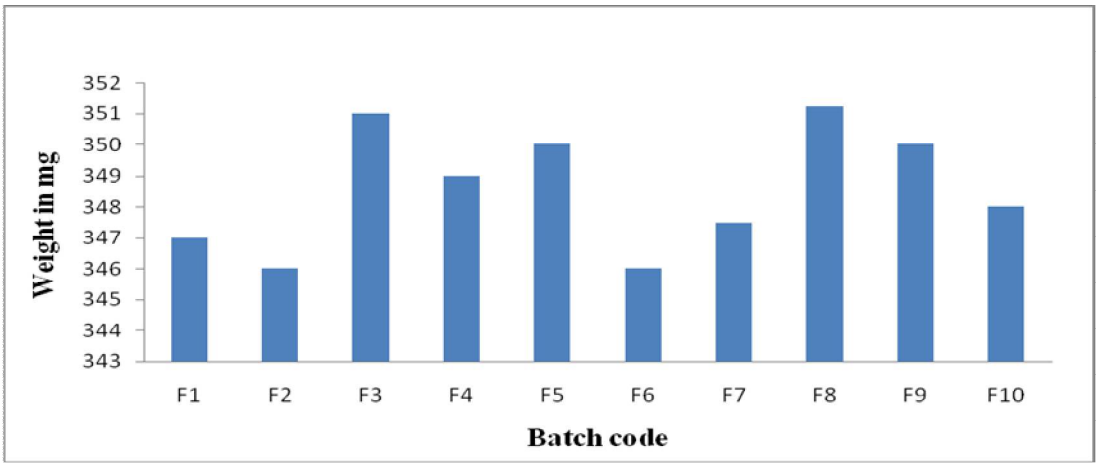

Fig. 8: Weight variation profile

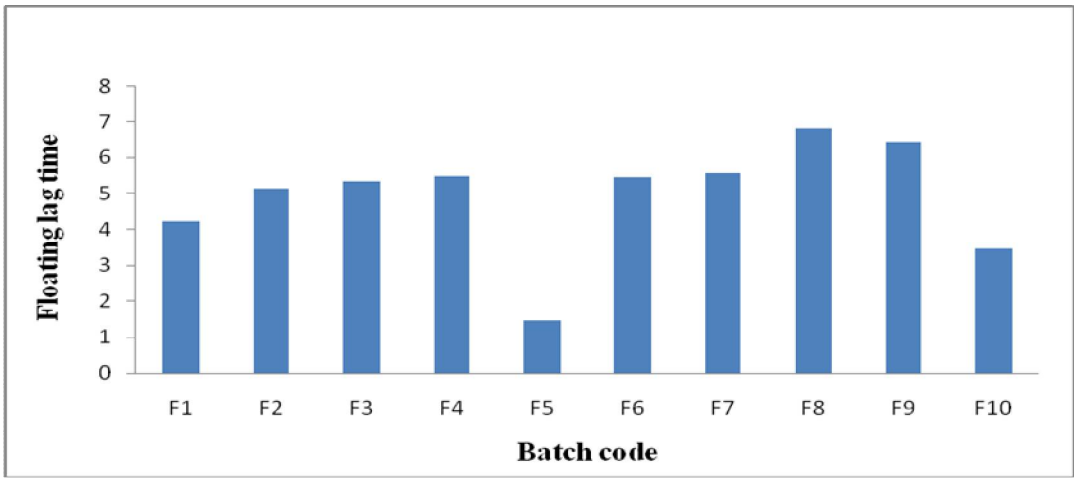

Fig. 9: Floating lag time profile

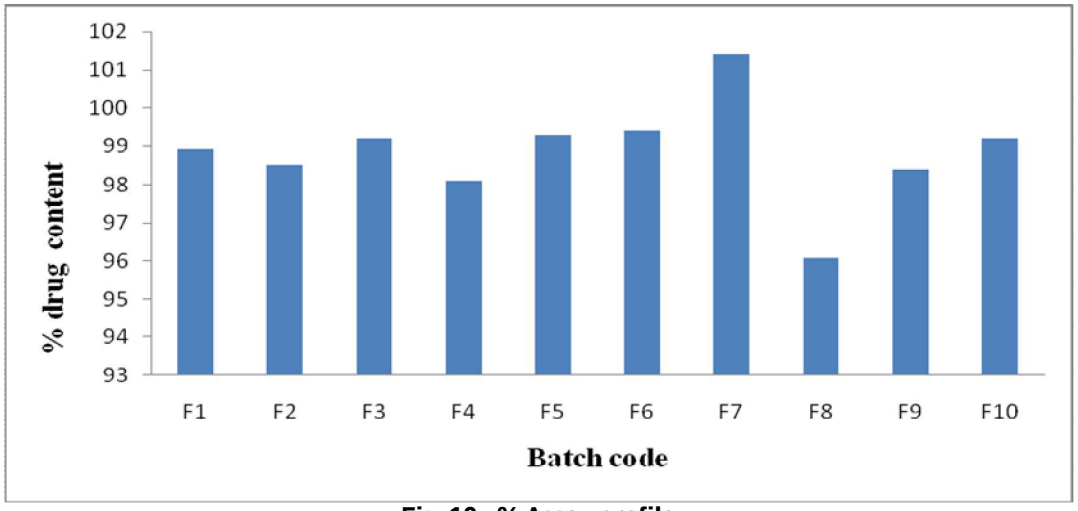

Fig. 10: % Assay profile

Table 5: % Drug Release of Cimetidine from F1 to F10

S.No	Time (hr)	% Drug Release									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	1	31.4 ±0.4	28.5 ±0.3	23.2 ±0.3	16.8 ±0.1	17.4 ±0.3	28.2 ±0.	25.9 ±0.	21.3 ±0.	16.7 ±0.3	24.8 ±0.
2	2	44.5 ±0.2	36.3 ±0.5	31.6 ±0.3	28.7 ±0.2	31.8 ±0.1	38.7 ±0.2	31.5 ±0.4	29.6 ±0.1	23.2 ±0..2	31.5 ±0.
3	3	51.2 ±0.5	47.1 ±0.8	42.1 ±0.8	39.8 ±0.1	44.7 ±0.2	48.2 ±0.7	44.6 ±0.2	41.9 ±0.1	37.7 ±0.2	40.3 ±0.3
4	4	68.3 ±0.2	60.9 ±0.1	56.6 ±0.3	52.7 ±0.2	52.4 ±0.5	63.8 ±0.1	58.7 ±0.1	54.8 ±0.2	49.8 ±0.1	56.8 ±0.1
5	6	80.4 ±0.4	72.6 ±0.4	68.4 ±0.5	60.6 ±0.3	61.7 ±0.2	75.4 ±0.4	71.4 ±0.4	62.6 ±0.3	58.9 ±0.1	68.5 ±0.4
6	8	97.3 ±0.1	82.7 ±0.2	76.7 ±0.2	71.2 ±0..7	78.4 ±0.3	87.3 ±0.6	81.6 ±0.2	73.2 ±0.8	66.3 ±0.3	79.3 ±0.6
7	10		98.9 ±0.1	90.8 ±0.1	84.3 ±0.6	84.6 ±0.2	96.3 ±0.2	91.8 ±0.1	87.6 ±0.3	72.5 ±0.2	91.7 ±0.3
8	12			95.7 ±0.3	97.9 ±0.1	99.3 ±0.1		93.6 ±0.3	94.1 ±0.7	81.5 ±0.2	96.7 ±0.1

Note: All values are expressed as mean± SD, n = 3

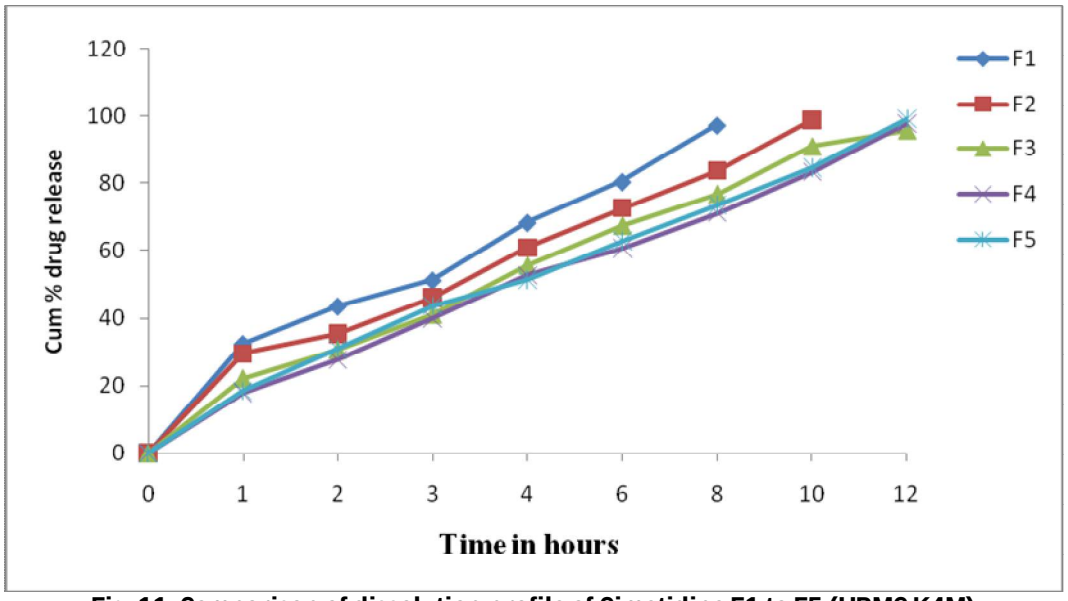

Fig. 11: Comparison of dissolution profile of Cimetidine F1 to F5 (HPMC K4M)

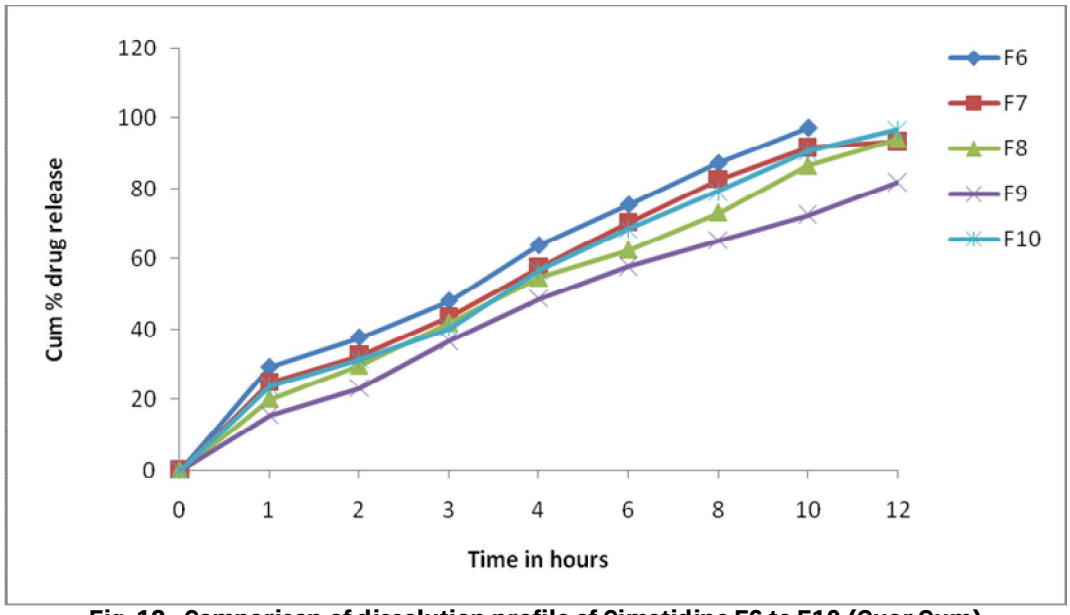

Fig. 12: Comparison of dissolution profile of Cimetidine F6 to F10 (Guar Gum)

Table 6: Determination of release kinetics

S.No	Time (hours)	Square root of time	Log time	Cum %drug release	Log cum % drug release	Cum % drug remaining	Log cum % drug remaining
1	**1**	1.000	0.000	18.5	1.256	82	1.924
2	**2**	1.414	0.302	30.9	1.497	69.1	1.849
3	**3**	1.732	0.478	43.8	1.630	56.3	1.721
4	**4**	2.000	0.603	52.4	1.721	48.6	1.677
5	**6**	2.449	0.779	61.7	1.767	37.3	1.572
6	**8**	2.828	0.904	74.4	1.876	26.6	1.435
7	**10**	3.162	1.000	84.7	1.937	15.3	1.188
8	**12**	3.464	1.078	99	1.976	1	0.000

Table 7: Coefficient of Correlation for kinetic drug release

	Zero order	First order	Higuchi modal	Peppas modal
Slope	6.7137	0.1481	28.475	0.7626
r2	0.9869	0.7822	0.8631	0.8922

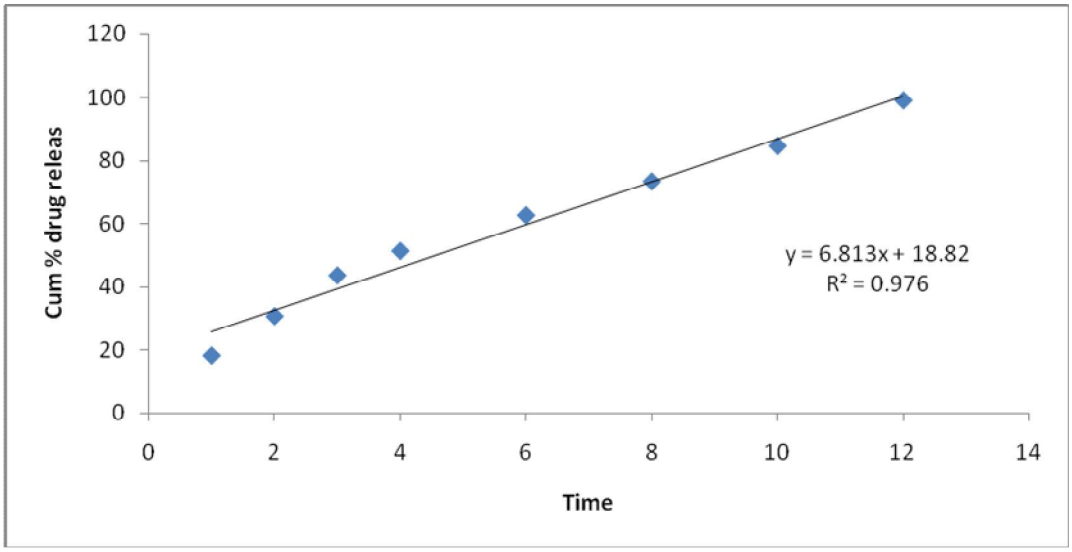

Fig. 13: Formulation of F5 – Zero order kinetics

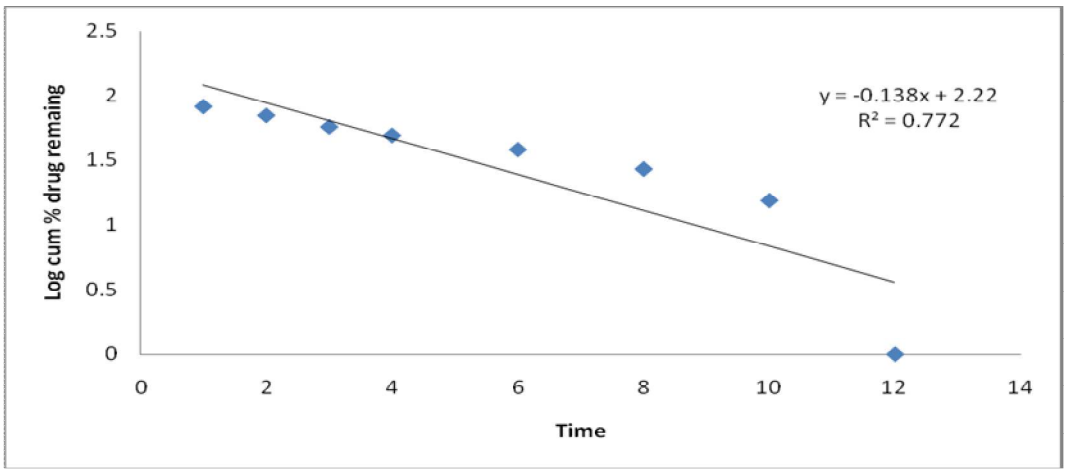

Fig. 14: Formulation of F5 –First order kinetics

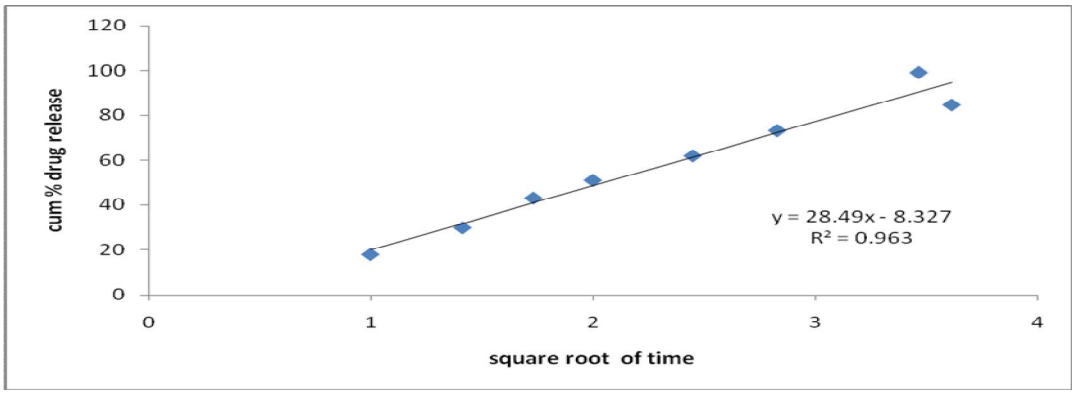

Fig. 15: Formulation of F5 – Higuchi model

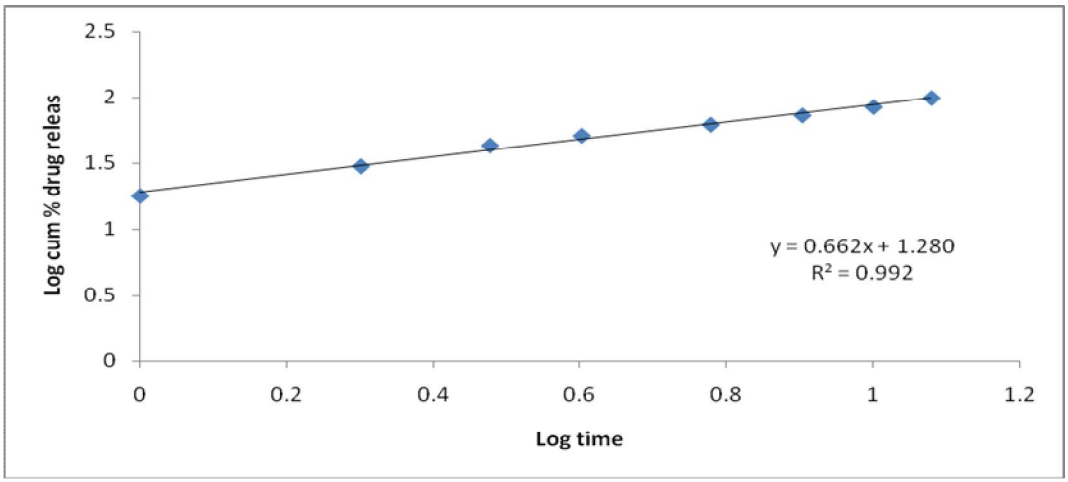

Fig. 16: Formulation of F5 –KoresmeyerPeppas model

Table 8: Accelerated stability studies data of best formulation (F5)

S.No	Test	Initial	Period in months		
			1	2	3
1	Physical appearance	Brownish white, smooth, flat	Brownish white, smooth, flat	Brownish white, smooth, flat	Brownish white, smooth, flat
2	Hardness (kg/cm²)	7.3±0.13	6.3±0.11	6.0±0.10	6.2±0.14
3	Friability (%)	0.10±0.03	0.17±0.02	0.28±0.01	0.18±0.01
4	Assay (%)	99.4±0.4	99.6±0.2	99.2±0.1	99.3±0.4
5	Buoyancy Lag time (min)	1.56±0.8	1.36±0.6	1.48±0.6	1.46±0.5
6	Total floating time (h)	>12	>12	>12	>12
7	*In vitro* release (%) (at 12 hour)	99.3±0.2	98.5±0.3	98.9±0.2	99.3±0.3

Note: All values are expressed as mean± SD, n = 3.

DISCUSSION

Standard calibration curve for Cimetidine

The calibration curve of Cimetidine in 0.1 N HCL was derived from the concentration and corresponding absorbance. Values of linear regression analysis gave the equation for the line of best fit as Y= 0.029x-0.0029. Linearity was observed in the concentration range between 5 to 30µg/ml.

Drug excipient compatibility studies

The compatibility study was performedusing FTIR for drug-polymer mixtures.

The peaks of the Pure drug were found to be 3505.69 =N-H stretching (amides), 3376.67 = N-H asymmetric (sulfonamide), 3237.06 = symmetric vibration, 3103.86= C-H stretching vibration. From the FTIR graphs of drug-polymer mixture, it was found that the same peaks of the drug are available. Since it proves that there is no incompatibility with the polymers.

Preparation of tablets

The tablets were prepared by wet granulation method. Two different matrix forming agents were used to compare which one shows better prolonged drug release when the concentration of polymers was increased. All the tablets were prepared by effervescent approach using sodium bicarbonate as an effervescent agent to make the tablet float and some binders and lubricant are used in this formulation.

Flow properties

The prepared granules of all the 10 formulation are taken to study the flow properties. The flow properties of each formulation such as bulk density, angle of repose, tapped density, compressibility index and haunsers ratio are determined and flow properties of all the 10 formulation are found to be unsatisfactory.

Evaluation of tablets

The floating matrix tablets are evaluated for weight variation, thickness, hardness, frability,

floating lag time, total floating time andassay. The values are in the range of 347 to 350 mg for weight variation for all formulation except F3 and F8 which show 351 mg. Thickness and hardness values range from 3.42to 3.67 mm and 5.8 to 6.9 kg/cm^2 .The range of friability are 0.53 to 0.75 respectively. Results are in the range of 98.4% to 101.4% for assay. Total floating time is more than 12 hours for all the formulations but the floating lag time varies for the each batch ranges from 1.46 to 6.81mins.

Floating lag time

In the present work an attempt is made to floating matrix tablets of Cimetidine. Form a review of previous studies on the floating properties of various polymers, it can be concluded that HPMC polymer is very good vehicle for floating tablets design. Guar gum was also selected as it is a natural vegetable gum which is considered as GRAS (generally regarded as safe) by FDA. For formulation F1-F4 four different concentrations of HPMC K4M was used ranging from 20, 25, 30,and 35% of the total weight of the tablet along with 15% of sodium bicarbonate. In case of formulation F5, 35% of HPMC was used but the concentration of sodium bicarbonate was increased to 20% of the total weight of the tablets. Similarly in the case of formulations with Guar gum, 20-30% of gum along with 15% of sodium bicarbonate was used F10 contains 35% of Guar gum and 20% of sodium bicarbonate the floating lag time increases which increase in sodium bicarbonate. Incorporation of sodium bicarbonate helps to produce carbon dioxide gas which is entrapped within the hydrophilic matrices leads to increase in volume of dosage form resulting in lowering of density which helps it to float. Sodium bicarbonate is the most common bicarbonate used in effervescent formulations because of its high water solubility and low coast.

Total floating time

The tablets of formulation exhibited a longer floating time due to the presence of sodium bicarbonate and polymers at high level. The high level of HPMC and Guar gum prevents the entry of media into the matrix and prolongs the floating time. All the batches of tablets were found to exhibit maximum floating time for more than 12 hours. The increase in concentration of HPMC and Guar gum did not have any significant effect on the total floating time.

Release profile of the drug

The total polymer concentrations were fixed between 20-30% which gave satisfactory floating behavior and drug behavior and drug release characteristics. For a matrix dosage form using a hydrophilic polymer the drug release follows three steps. First step is the penetration of the medium in the tablet matrix (hydration). Second step is the swelling with concomitant or subsequent dissolution or erosion of the matrix and third step is the transport of the dissolved drug either though the hydrated matrix or from the parts of the eroded tablet to the surrounding dissolution medium. Tablet no.13 and representedgraphically in the Fig numbers 16, 17shows that as the concentration of the polymer increased the rate of drug release was delayed. The increase in concentration of concentration of sodium bicarbonate showed an increase in drug release in case F5 as compared to F4 and F10 as compared to F9.

Drug release kinetic

F5 was chosen on the basis of the release parameters. The data obtained was used to study the release mechanisms and kinetics. The criteria for selection the most appropriate model was based on linearity (coefficient of correlation). The release of Cimetidine from developed tablets was found to be very close to zero-order kinetics indicating that the concentration was independent of drug release *In vitro* release mechanism was best explained by KorsmeyerPeppas equation indicated a good linearity (r2= 0.992). The release exponent n was0.6626 for F5 formulationand n indicates diffusion constant which is the general operating release mechanism.

It is know that the Peppas model is widely used to confirm whether the release mechanism is Fickian diffusion and Non- Fickian diffusion. The 'n' (release exponent of KorsmeyerPeppas model) value could be used to characterize different release mechanisms.

The mechanism of release is anomalous, that is both diffusion and erosion are involved.

Stability studies

Stability studies were conducted for the formulation F5. The stability study was performed at 40±2^{0}C /75±% RH for 1to 3 moths. The tablets were analyzed for appearance, moisture content, drug content impurities and *in vitro* drug release. The overall results showedthat the formulation is stable at the end of 1st 2nd 3rd months.

SUMMARY AND CONCLUSION

The controlled or sustained drug delivery systems in the stomach prolongs overall GI transit time thereby resulting in improved oral bioavailability of the drug and lead to the development of gastric retentive drug delivery system (GRDDS).

Various approaches have been developed to retain the dosage form in the stomach. Gastric floating drug delivery systems (GFDDS) offer numerous advantages over other gastric retention systems. Hence in the present investigation, matrix type of gastric floating drug delivery system of Cimetidine has been studied. Cimetidine, histamine H2 – receptor antagonist, is widely used to treat duodenal ulcer, gastric ulcers Zollinger – Ellison syndrome, gastro esophageal reflux disease. Multiple dosing of Cimetidine is required for effective treatment leading to therapeutic fluctuations; thus a sustained release dosage form of Cimetidine is suitable. The absolute bioavailability of the Cimetidine is found to be 35% due to site specific absorption. As it is mainly absorbed form the stomach and upper parts of the small intestine with short half -life, there is a need for the design of gastroretentive drug delivery system for Cimetidine to improve its bioavailability.

Different polymers have been evaluated in the design of gastric floating drug delivery. In the present investigation two different polymers are used for the matrix formation, HPMC is a very good vehicle for floating tablets design and Guar gum is also selected as it is a natural vegetable gum which is considered as GRAS (generally regarded as safe) by FDA they selected for design of effervescent gastric floating matrix tablets of Cimetidine. The concentration of sodium bicarbonate and its effect on the floating behavior and drug release was studied on polymer concentration. Effervescent gastric floating matrix tablets were prepared by wet granulation method. The tablets were designed to release the total dose of the drug over a period of 12±1 hours.

Uniformity of weight hardness, friability and % assay of all the prepared ten formulation were found within the official and fixed limits. Floating lag time of the table's decreases which increase in sodium bicarbonate, concentration helps to produce carbon dioxide gas which is entrapped within the hydrophilic matrices leading to increases in volume of dosage form resulting in lowering the density which helps the table to float. Due to the high viscosity of HPMC and Guar gum prevent the entry of media into the matrix and prolongs the total floating time up to 12 hour for all the batches. F5 formulation show shortest floating lag time when compared to other formulation.

Drug release studies were performed with the help of *in vitro* dissolution, based on the dissolution data the best formulation was selected. Further, accelerated stability studies were carried out for the best formulation for 3 months according to the ICH guidelines, which was found to have good stability.

Floating tablets of Cimetidine increases the therapeutic efficacy of the drug

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