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Research Article

DESIGN, DEVELOPMENT AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM USING FAMOTIDINE FOR THE TREATMENT OF DUODENAL ULCER

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ABSTRACT

In the present work, floating gastro retentive formulation of Famotidine was formulated to sustained release of Famotidine above its site of absorption.Famotidine is histamine H_2 receptor antagonist in treating gastric ulcer, duodenal ulcer, Zollinger Ellison syndrome, gastroesophegal reflux disease and erosive esophagitis. It inhibits acid production by reversibly competing with histamine for binding to H_2 receptors on the basolateral membrane of parietal cells. It competitively inhibits histamine action at all H_2 receptors but their main clinical use is as inhibition of gastric acid secretion. It inhibited histamine stimulation and gastrin stimulated acid secretion. It decreases both basal and food stimulated acid secretion by 90% or more, but promote healing of duodenal ulcer. The swelling of the polymers used (HPMC K15M, Ethyl cellulose, Xanthan Gum) were determined by water uptake of the tablet. The percent swelling of the tablet was determined for 12 h at different time intervals. Increase in percent swelling was found with increasing concentration of polymers.

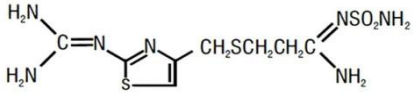
Key words: Famotidine, Zollinger Ellison syndrome, duodenal ulcer, gastrin, histamine.

INTRODUCTION

Famotidine is histamine H_2 receptor antagonist in treating gastric ulcer, duodenal ulcer, Zollinger Ellison syndrome, gastroesophegal reflux disease and erosive esophagitis. It inhibits acid production by reversibly competing with histamine for binding to H_2 receptors on the basolateral membrane of parietal cells. It competitively inhibits histamine action at all H_2 receptors but their main clinical use is as inhibition of gastric acid secretion. It inhibited histamine

stimulation and gastrin stimulated acid secretion. It decreases both basal and food stimulated acid secretion by 90% or more, but promote healing of duodenal ulcer. The chemical name of famotidine is Propanimidamide, N-(aminosulfonyl)-3 [[[2-[(diaminomethylene)-amino]-4- thiazolyl] methyl] thio]- [1-amino-3- [[[2- [(diaminomethylene) amino]-4- [thiazolyl]-methyl] thio] propylidene] sulfamide. The molecular formula and molecular weight of famotidine are $C_8H_{15}N_7O_2S_3$ and 337.445 respectively. It is a white or Yellowish- white, crystalline powder or crystals having melting point is 163-169^oC. It is freely Soluble in Dimethyl Formamide and in Glacial Acetic Acid, slightly soluble in Methyl Alcohol, very slightly soluble in water and in Dehydrated Alcohol, Practically insoluble in ether and in Ethyl Acetate. It is preserve in well closed container, Protected from light. The structure of famotidine is given below (figure 1)

Figure 1: The structure of Famotidine



The major therapeutic use of famotidine is promoting healing for gastric and duodenal ulcer, treatment of uncomplicated Gastroesophageal reflux disease (GERD) and for prophylactic treatment of stress ulcer. In addition, it employed in combination with antibiotics to treat infection with Helicobector pylori i.e in treatment of Gastritis.

Pharmacokinetics

Table 1: Pharmacokinetics of Famotidine

Bioavailability	40-45%
Plasma Half Life	2.5h-3.5hrs.
Plasma Protein Binding	15- 20%
Peak Plasma Concentration (Cmax)	1- 3 hours
Excretion	Renal Excretion (65-70%) Metabolic Excretion (30-35%)
Renal Clearance	250-450ml/min
Drug Interaction	It does not inhibit hepatic microsomal enzyme CYTP450 system and hence does not interact with drugs which are substrate for CYTP450 systems like Warfarin, Pheytoin, Quinidine, Caffiene etc. It does not block androgen receptors and do not causeGynaecomastia and impotence like Cimetidine.

MATERIAL AND METHODS

Famotidine was received as a gift sample from BelcoPharma, Bahadurgarh, Haryana, India. Hypromellose (HPMC), Xanthan Gum, Ethyl Cellulose, Microcrystalline Cellulose, and Dibasic Calcium Phosphate were received as a gift from Central Drug House, Mumbai. Povidone and HCl were received as a gift sample from Merck SpecialitiesPvt Ltd, Mumbai. Isopropyl Alcohol was perchased from Nice Chemicals Pvt Ltd, Cochin.

Magnesium stearate and talc were perchased as a gift from Qualikems Fine Chemicals Pvt Ltd, Delhi. Lactose was perchased from Central Drug House (P) Ltd. New Delhi, India.All other ingredients used were of analytical grade.

Experimental methods

Preparation of Floating Tablets of Famotidine

The composition of different formulations of Famotidine floating tablets was shown in table 2. The ingredients were weighed accurately and mixed thoroughly.Tablets of Famotidine were prepared by direct compression& wet compression method and their release profiles were compared to select the manufacturing process for further studies.

Selection of manufacturing process

Batches were prepared with HPMC K15M using wet granulation method and direct compression method and their release profiles were compared. Formula is given in Table 2.

Table 2: Formulation of Famotidine using HPMC K15M with direct compression and wet granulation methods

Batch No.	**F1 (Wet Granulation)**	**F2 (Direct Compression)**
Ingredients Name	**mg/tab**	**mg/tab**
Famotidine	80	80
HPMC K15M	90	90
Sodium bicarbonate	70	70
Citric Acid	30	30
Lactose	109	-
Microcrystalline Cellulose	-	124
Povidone	15	-
Isopropyl Alcohol	q.s.	-
Magnesium Stearate	3	3
Talc	3	3
Total	400	400

Formulation of batches with different ratio of Sodium bicarbonate and Citric acid

Batches were prepared with HPMC K15M using wet granulation method to select the proportion of Sodium bicarbonate and Citric Acid and their release profiles were compared. Formula is given in Table 3

Table 3: Formulation of batch with different ratio of Sodium bicarbonate and Citric acid

Batch No.	**F1**	**F3**	**F4**
Ingredients	**mg/tab**	**mg/tab**	**Mg/tab**
Famotidine	80	80	80
HPMC K15M	90	90	90
Sodium bicarbonate	70	80	90
Citric Acid	30	20	10

Lactose	109	109	109
Povidone	15	15	15
Isopropyl Alcohol	q.s.	q.s.	q.s.
Talc	3	3	3
Magnesium Stearate	3	3	3
Total	400	400	400

Preparation of trial batches with different polymers with different concentration

Formulation batches were prepared using different polymers (HPMC K15M, Xanthan gum, and Ethyl Cellulose). Formula is given in Table 4

Table 4: Formulation of different batches with different polymer concentration

Batch no.	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Ingredients	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**Mg/tab**	**mg/tab**	**mg/tab**
Famotidine	80	80	80	80	80	80	80
HPMC K15M	90	110	130	90	90	90	90
Ethyl Cellulose	-	-	-	-	-	25	40
Xanthan Gum	-	-	-	25	40	-	-
Sodium bicarbonate	90	90	90	90	90	90	90
Citric Acid	10	10	10	10	10	10	10
DCP	-	-	-	84	69	84	-
Lactose	109	89	69	-	-	-	69
Povidone	15	15	15	15	15	15	15
Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Talc	3	3	3	3	3	3	3
Magesium Stearate	3	3	3	3	3	3	3
Total	400	400	400	400	400	400	400

Effect of various diluents with their elastic or plastic properties:

Formulations were prepared using different diluents such as Dibasic calcium phosphate and Lactose and compared to select the best diluent for further formulations. Formula is given in Table 5.

Table 5: Formulation of Famotidine by using different diluents with their elastic or plastic properties

Batch no.	**F8**	**F11**
Ingredients	**mg/tab**	**mg/tab**
Famotidine	80	80
HPMC K15M	90	90
Xanthum Gum	40	40
Sodium bicarbonate	90	90
Citric Acid	10	10
Lactose	69	-
DCP	-	69
Povidone	15	15
Isopropyl Alcohol	q.s.	q.s.
Talc	3	3
Magnesium Stearate	3	3
Total	400	400

In – Vitro evaluation

1. Evaluation of granules

Bulk Density (BD)

Bulk density was determined according to Method I as reported in USP XXXII. The drug powder was passed through BSS # 25 screens to break up agglomerates. The drug powder was introduced into a dry 100 ml tarred measuring cylinder. The powder was then carefully labeled, if necessary, without the application of force and the unsettled volume (bulk volume) was noted. The weight of the powder was also noted and the bulk density was calculated as:

Bulk density (g/ml) = Weight of powder (g) / Bulk volume (ml)

Tapped density (TD)

After the initial volume $V_a$was observed, the cylinder containing the sample was mechanically tapped by raising the cylinder and allowing it to drop under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further changes was observed in volume was noted and tapped volume V_b was noted. The tapped density was calculated from the formula given below:

Tapped Density (g/ml) = Weight (g) / Tapped volume (ml)

The flow properties of granules before compression were characterized in terms of angle of repose, Carr's index and Hausner ratio. For determination of angle of repose, the granules were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0cm above hard surface. The granules were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The $\tan^{-1}$ of the (height of the pile/ radius of its base) gave the angle of repose. Granules were poured gently through a glass funnel into a graduated cylinder cut exactly to 10ml mark. Excess granules were removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0cm until the time when there

was no more decrease in the volume. Bulk density and tapped density were calculated.

Hausner's Ratio = Tapped density / Bulk density

Carr's Index (%Compressibility Index) = [100× (TD-BD)]/TD

Table 6: Results of flow properties of granules

Batch No.	Bulk Density	Tapped Density	Angle of Repose	Hausner's ratio	Carr's index
F1	0.392	0.542	37.8,(fair)	1.38,(poor)	27.67,(poor)
F2	0.388	0.573	35.6, (fair)	1.47, (poor)	32.28, (poor)
F3	0.390	0.593	38.2, (fair)	1.52, (poor)	34.23, (poor)
F4	0.398	0.485	39.4, (fair)	1.21, (fair)	17.9, (fair)
F5	0.372	0.492	36.3, (fair)	1.32, (passable)	24.3, (passable)
F6	0.380	0.511	34.2, (good)	1.34, (passable)	25.6, (poor)
F7	0.386	0.495	37.3, (fair)	1.28, (passable)	22.02, (passable)
F8	0.394	0.482	33.5, (good)	1.22, (fair)	18.25, (fair)
F9	0.381	0.493	33.8, (good)	1.29, (passable)	22.7, (passable)
F10	0.376	0.532	36.2, (fair)	1.41, (poor)	29.32, (poor)
F11	0.385	0.480	37.7, (fair)	1.24, (fair)	19.7, (fair)

2. Evaluation of colon targeted matrix tablets

(1) Weight variation tests of tablets

Weight variation of the formulation was performed as per USP. 20 tablets were weighed using a Scale-Tec electronic balance individually and compared with the average weight of the twenty tablets.

(2) Hardness of the tablets

The hardness of five tablets was determined using Pfizer type hardness tester and the average values were calculated.

(3) Friability of tablets

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W_0) or a sample of tablets were dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1% w/w.

$$\% \text{ Friability} = (W_0\text{-}W)/W0 \times 100$$

(4) Thickness Test:

The Thickness of the tablets was determined by using verniercalliper. Five tablets were used, and average values were calculated.

(5) Assay:

Five tablets were weighed and triturated, from that transfer an accurately weighed portion of the powder equivalent to about 80 mg of Famotidine to a 100 ml volumetric flask

containing 0.1 N HCl and then concentration is measured at λ_{max}i.e. 265 nm.

(6) In vitro buoyancy studies

On immersion in 0.1 N HCl solutions (pH 1.2) at 37° C, all the tablets first sank in the release medium and then they float to the surface. All the tablets remained buoyant up to 24 h.

Table 7: Results of evaluation of parameters of tablets from different batches

Batch no.	Average weight(mg)	Thickness (mm)	Friability %	Hardness (kp)	Assay	Floating lag time (sec)s	Floating Duration (h)
F1	403	3.7	0.04	5	97.62	120	24 h
F2	398	4.2	0.06	6	98.87	135	24 h
F3	402.3	4.0	0.03	4	97.37	110	24 h
F4	399	3.8	0.06	6	99.65	90	24 h
F5	397	3.5	0.02	5	101.25	120	24 h
F6	401	3.6	0.07	6	98.72	240	24 h
F7	399	3.7	0.05	6	99.56	90	24 h
F8	399.6	3.8	0.03	5	101.12	60	24 h
F9	401	4.2	0.01	4	97.89	40	24 h
F10	402	3.5	0.04	5	102.67	120	24 h
F11	401.3	3.7	0.02	4	98.52	30	24 h

(7) Swelling Behavior studies

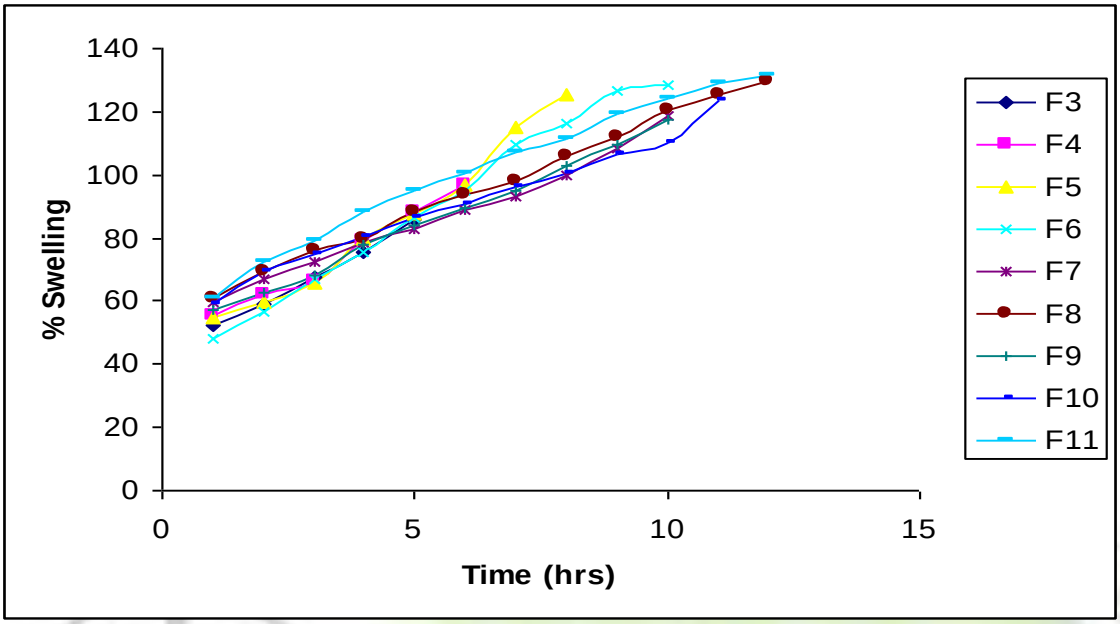
The swelling of the polymers used (HPMC K15M, Ethyl cellulose, Xanthan Gum) were determined by water uptake of the tablet. The percent swelling of the tablet was determined for 12 h at different time intervals. Increase in percent swelling was found with increasing concentration of polymers. The percent swelling of F11 was found to be higher (131.20%) than that of other formulations (Fig. 2). The percent swelling increased gradually up to 12 h. Results of swelling index shown in Table 8

Table 8: Results of swelling index

Time (hr)	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	52.11	55.47	54.87	47.79	59.66	60.65	57.32	59.21	60.65
2	59.17	62.20	59.60	56.89	67.25	69.52	62.58	69.52	72.56
3	67.81	66.54	66.03	67.08	72.44	76.12	67.96	75.01	79.32
4	75.63	79.28	79.8	75.44	78.32	80.01	77.63	80.35	88.01
5	86.06	88.06	87.70	86.66	83.05	88.47	84.01	86.22	95.09
6	-	96.50	96.80	95.05	89.12	93.94	89.52	90.56	100.51
7	-	-	115.02	109.44	93.26	98.20	95.02	96.04	106.84
8	-	-	125.54	116.6	99.54	106.21	103.12	100.55	111.36
9	-	-	-	126.52	108.56	112.05	109.75	106.51	119.20

10	-	-	-	128.60	118.62	120.61	117.26	110.24	124.25
11	-	-	-	-	-	125.41	-	123.42	129.05
12	-	-	-	-	-	129.50	-	-	131.20

Figure 2:Swelling indices of various batches Vs. Time



(8) Dissolution studies:

Dissolution studies were conducted to determine the release pattern of the product. Dissolution test for Famotidine was carried out as per USP method for dissolution test for tablets using apparatus-II.

Dissolution parameters

Medium : 0.1 N HCl (pH 1.2)

Volume : 900 ml

Apparatus : USP-II (Paddle)

RPM : 50 rpm

Time point : 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 hrs.

Temperature : 37°C ± 0.5°C

Volume of sample withdrawal: 10 ml

λ_{max} for absorbance : 265 nm

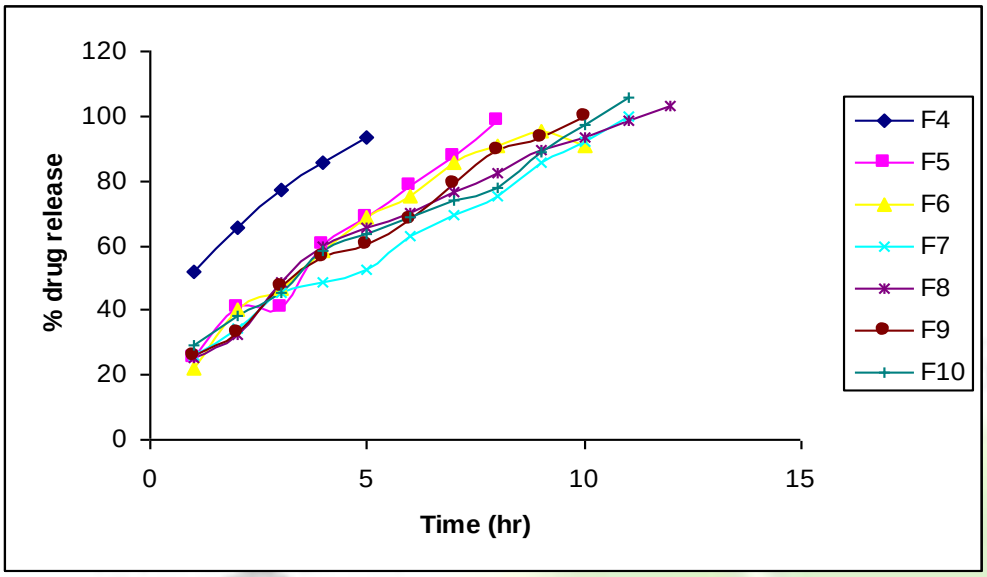
The drug release profiles obtained were fitted into several mathematical models and drug release mechanism was determined from the matrix tablet.

Table 9: Release profiles of formulations using different polymers in different concentrations

Time (hr)	% Drug release						
	F4	F5	F6	F7	F8	F9	F10
1	52.1	25.27	22.14	26.14	25.62	26.14	29.50
2	65.7	40.67	40.32	34.21	32.32	33.37	38.11
3	76.9	49.90	46.71	45.58	48.66	47.06	45.16
4	85.4	60.09	58.32	48.50	59.47	56.49	58.17
5	93.7	68.99	68.54	52.31	65.24	60.21	63.25
6	100.7	78.21	75.42	62.91	69.89	68.37	68.71
7	-	87.44	85.46	69.40	76.27	78.83	74.21
8	-	98.55	90.50	75.30	82.60	89.40	77.65
9	-	-	95.63	85.40	89.21	93.20	88.80

10	-	-	99.50	92.13	93.12	99.93	97.40
11	-	-	-	99.83	98.56	-	105.51
12	-	-	-	-	103.36	-	-

Fig 3: Dissolution profile of formulations with different Polymers



SUMMARY

Gastric ulcer, one of the most widespread, is believed to be due to an imbalance between aggressive and protective factors. The gastric mucosa is continuously exposed to potentially injurious agents such as acid, pepsin, bile acids, food ingredients, bacterial products (*Helicobacter pylori*) and drugs. These agents have been implicated in the pathogenesis of gastric ulcer, including enhanced gastric acid and pepsin secretion, inhibition of prostaglandin synthesis and cell proliferation growth, diminished gastric blood flow and gastric motility. Drug treatment of peptic ulcers is targeted at either counteracting aggressive factors (acid, pepsin, active oxidants, platelet aggravating factor "PAF", leukotrienes, endothelins, bile or exogenous factors including NSAIDs) or stimulating the mucosal defences (mucus, bicarbonate, normal blood flow, prostaglandins(PG), nitric oxide). The goals of treating peptic ulcer disease are to relieve pain, heal the ulcer and prevent ulcer recurrence.

Various types of treatment are available for the treatment of gastric ulcer Proton pump inhibitor, Anticholinergics, Antacids, Prostaglandin analogues and H2 Antihistamines. H2 antihistamines are widely used in the management of gastric ulcer, Zollinger- Ellison Syndrome and Gastroesophgeal reflux disease. Three types of histamine receptor are known H1, H2, and H3. H1 is located in smooth muscles and blood vessels. H2 receptors are located in gastric glands, heart and uterus. H3 receptors are located in brain, lungs and spleen.

Controlled release drug delivery systems are developed to modulate the apparent absorption or alter the site of release of drugs, in order to

achieve specific clinical objectives that cannot be attained with conventional dosage forms. Unlike immediate-release preparations, in which the total amount of drug is rapidly available after ingestion, controlled-release formulations are designed to release specific amounts of drug over a certain time period. The major benefits include improved pharmacokinetics (e.g., less variation between peaks and troughs), less frequent dosing, and improved patient adherence optimized performance, a greater selectivity of activity or new indications.

In present work an attempt was made to prepare the Floating Tablet of Famotidine using different polymers by wet granulation and direct compression method with Lactose, DCP and MCC as diluents, citric acid and Sodium bicarbonate as gas generating agent.

It was found that wet granulation method facilitated greater efficiency in controlling Famotidine release behavior from the matrices. Hence, all further formulations were prepared with wet granulation technique. FTIR studies shows that there was no incompatibility between drug, polymer and co-excipients. All the prepared formulations were evaluated for hardness, friability, uniformity of weight, thickness, in vitro buoyancy study, assay and in vitro release. Batches were prepared by HPMC and HPMC K15M+ EC, HPMC K15M+Xanthum gum. Ratio of polymers in formulation played major role in controlling the release rate of Famotidine, which is evident from the prolongation in release of Famotidine with HPMC: Xanthum gum. Concentration of sodium bicarbonate and citric acid affect the floating lag time and all the formulation float upto 24 hours. Effect of diluent on drug release was also studied by comparing lactose and dibasic calcium phosphate. Dibasic calcium phosphate had maximum retarding capacity followed by lactose. The release kinetics of all the batches were carried out and it was found final batch followed Higuchi kinetic model. The optimized formulation has drug release profile up to 12 hours.

CONCLUSION

1. The absorbance maxima of Famotidine were found as 265 nm which was selected for UV analysis.
2. The physical compatibility study at 40^{o}C/75% RH showed that Famotidine and excipients used found to be physically compatible.
3. FTIR spectra data showed that Famotidine and excipients used found to be compatible.
4. Melting point of Famotidine was found to be 165^{o}C.
5. Formulation was prepared with two processes i.e. direct compression and wet granulation; it was found that wet granulation method facilitated greater efficiency in controlling Famotidine release behaviour from the matrices as compared to direct compression.

6. Characterization of granules prepared by selected manufacturing processes like bulk density, tapped density, Carr's index, Hausner's ratio, Angle of repose was done and found to have good flow and compressibility.
7. The tablets prepared were found to be within the limits with respect to hardness, average weight, %friability and thickness.
8. From the different polymers used in polymer selection batches, combination of HPMC and Xanthum gum were found to be satisfactory.
9. Dibasic calcium phosphate was found to be the best diluent in controlling the release rate of drug and thus helps in extending the release profile.
10. Under the study of kinetic models, five models have been studied namely Zero Order, First Order, Higuchi, Hixon-Crowell, Korsmeyer-Peppas model. It was found that the drug release model of final batch followed Higuchi kinetic model (having maximum R^2 value of 0.9966).

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