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FORMULATION AND EVALUATION OF GASTRO-RETENTIVE FLOATING BILAYER TABLETS OF FAMOTIDINE FOR THE TREATMENT OF HYPERTENSION

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Abstract:
The aim of present investigation was to formulate and evaluate bilayer gastro retentive tablet of Famotidine. The floating system is intended to float in and over the gastric contents resulting in prolonged GRT. It is very difficult to release loading dose of drug from matrix of tablet within specified period of time, to overcome this difficulty bi-layer tablet of famotidine was prepared. In which one layer was made up of immediate release layer to provide loading dose of famotidine. Loading dose of famotidine released within 30 minutes due to action of super disintegrating agents. Another layer was made up of gastroretentive layer or sustained release layer to provide maintenance dose of famotidine, this layer released drug till 24 hrs due to floating mechanism of HPMC polymer. So there is need to develop a formulation which increase the gastric retention of famotidine so that it slowly available in the stomach and gives the maximum use of famotidine. Initially quantitative estimation of famotidine in formulation was carried out by UV/Visible spectrophotometry using 0.1 N HCl (pH-1.2) as solvent and measuring the absorbance at 266 nm. In phosphate buffer 7.4 pH observed λ max was found to be 286nm. Compatibility studies of drug with excipients were performed under different storage condition forone month. Drug excipient were mixed and divided in five parts, sealed in vials and kept under different temperature conditions. The control sample containing only drugs were sealed in vials and kept as such in low temperature conditions. After one month the sample were withdrawn and observed that there was no change observed in the physical characteristics of the drugs. This shows that there is no incompatibility between drug and excipient used. Physical mixture of drug and polymer was also used for the compatibility study and the samples were analyzed in IR spectrophotometer. For immediate release layer, it was found that all the batches gives release of more than 85 % of drug with in 30 minutes due to the high solubility of famotidine. For sustained release second layer, the use of hydrophilic polymer matrix is one of the most popula rapproaches in formulating an extended-release dosage form Formulation F1 was found to have lower erosion compared to F3 because HPMC K 100 M has higher viscosity as compared to HPMC K 15 M. It was concluded that HPMC K 100 M gave least erosion. Hence HPMC K 100 M is superior over the other it was selected for formulation. Gas generating agent increased swelling as well as erosion of polymers due to burst effect. Effect of channeling agent, Lactose is used as diluent as well as channeling agent in the floating delivery of the drug. To find out the mechanism of drug released from all the formulations of Famotidine floating tablets, the data was fitted to zero order, first order, Higuchi square root law and Korsmeyer's equation.Bi-layer tablet releases loading dose within 30 minutes and maintenances dose release till 24 hrs due togood floating & bio adhesive ability. To find out the mechanism of drug release from bilayer tablet, the data were subjected to kinetic modeling. Drug released from bi-layer tablet suggests that drug releases via diffusion mechanism. Thus, the Bi-layer gastro retentive tablet of famotidine can be successfully formulated with HPMC K100 M and super disintegrating agent povidone.

Keywords: *Superdisintegrants, fillers, disintegration, drug release, dosing frequency,*

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INTRODUCTION:

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract isa complex procedure and is subject to many variables. Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substance. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract and drugs that are less soluble in or are degraded by the alkaline pH may benefit from prolonged gastric retention. In addition, for local and sustained drug delivery to the stomach and proximal small intestine to treat certain conditions, prolonged gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability and therapeutic efficacy and possible reduction of dose size. It has been suggested that prolonged local availability of antibacterial agents may augment their effectiveness in treating H. Pylori related peptic ulcers. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of Mucoadhesion, flotation, sedimentation, expansion, modified shape systems or by the simultaneous administration of pharmacological agents that delay gastric emptying. Gastroretentive delivery systems (GRDS), however, are not suitable for drugs that may cause gastric lesions, e.g., non-steroidal anti-inflammatory agents. Also, the drug substances that are unstable in the strong acidic environment of the stomach are not the suitable candidates to be incorporated in such systems. In addition, these systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract. Floating systems have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Eventually, the residual system is emptied from the stomach. Gastric emptying is much more rapid in the fasting state and floating systems rely heavily on the presence of food to retard emptying and provide sufficient liquid for effective buoyancy.

MATERIALS AND METHODS:

Table No.: 1 List of Materials

S. No.	Name of Ingredients	Source/ Manufacturer
1.	FAMOTIDINE	ARISTO PHARMA
2.	Gelatin	CDH
3.	Methanol	CDH
4.	Glacial Acetic Acid	CDH
5.	Mannitol	CDH
6.	Dextrin	CDH
7.	Glycine	MERCK
8.	Lactose	ALFA ASER
9.	HPMCK4,K15,K100	CDH
10.	TALC	CDH
11.	MANNITOL SD 200 (PEARLITOL)	RANBAXY LABORATORY
12.	CROSPOVIDONE	RANBAXY LABORATORY
13.	MAGNESIUM STEARATE	CDH
14.	SODIUM SRARCH GLYCOLATE	-
15.	AEROSIL	CDH
16.	TALC	LOBA CHEMIE
17.	POTASSIUM DIHYDROGEN PHOSPHATE	CDH
18.	DISODIUM HYDROGEN PHOSPHATE	MERCK
19.	AMARANTH	CDH

FORMULATION AND DEVELOPMENT OF FAMOTIDINE TABLETS

Table No.: 2 Formula of Famotidine tablets

INGREDIENTS (in mg)	FORMULATION BATCHES							
	F1	F2	F3	F4	F5	F6	F7	F8
Famotidine	40	40	40	40	40	40	40	40
HPMC K4M	0	30	0	0	30	30	0	30
HPMC K15M	0	0	30	0	30	0	30	30
HPMC K100M	0	0	0	30	0	30	30	30
NaHCO3	20	20	20	20	20	20	20	20
Bees wax	30	30	30	30	30	30	30	30
Lactose	98	68	68	68	38	38	38	8
Magnesium sterate	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6
Average weight	200	200	200	200	200	200	200	200

RESULT AND DISCUSSION:

Organoleptic properties:

The tests were performed as per the procedure. The results were tabulated below.

Table. No. 3 Organoleptic properties

Test	Specifications/limits	Observations
Colour	White to pale yellow	White powder
Odour	Odourless	Odourless

The result complies as per specifications.

Physical Properties:

Angle of Repose:

It was determined as per procedure. The results were tabulated below.

Table.No. 4 Flow properties

Material	Angle of repose
Famotidine	27.14^0

Bulk density and tapped density:

It was determined as per procedure. The results were tabulated below.

Table No. 5 Bulk Density and Tapped Density

Material	Bulk density(gm/ml)	Tapped density(gm/ml)
Famotidine	0.48	0.44

Powder Compressibility:

It was determined as per procedure. The results were tabulated below.

Table No. 6 Powder Compressibility

Material	Compressibility index	Hausner's ratio
Famotidine	11.27	1.44

Melting point:
It was determined as per procedure. The results were tabulated below.

Table No. 7 Melting point

Material	Melting point range	Result
Famotidine	163.5 °C	163 ^{0}C

pH of the solution:

It was determined as per procedure. The results were tabulated below.

Table No. 8 PH of the solution

Material	Specification	Observation
Famotidine	5-6(1% aqueous solution)	6.22

The result indicates that the Famotidine drug was pure one.

Solubility:

It was determined as per procedure. The results were tabulated below.

Table No. 9 Solubility study of Famotidine

S. No.	Solvents	Solubility
1	Distilled water	Soluble
2	Ethanol	Insoluble
3	Methanol	Insoluble
4	Acetone	Insoluble
5	Chloroform	Insoluble
6	Dimethyl formamide	Soluble
7	Glacial acetic acid	Soluble
8	0.1 N NaOH	Insoluble
9	PBS (pH 7.4)	Soluble
10	Diethyl ether	Insoluble

The result complies as per specification.

Quantitative Estimation of Drug:
In Phosphate Buffer Saline (Pbs) Ph 7.4 The λ_{max} was found to be 286 nm

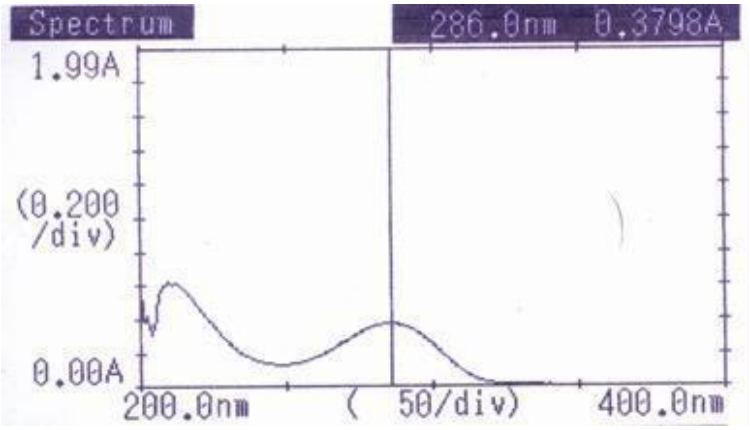

Fig. 1 UV absorption spectra of famotidine in PBS pH 7.4

Preparation of Standard Curve in PBS (pH 7.4)

Table No. 10 Standard curve of Famotidine in PBS (pH 7.4) at λ max (286 nm)

S. No.	Concentration	Absorbance
1	0	0.0000
2	8	0.3966
3	16	0.7870
4	24	1.1704
5	32	1.5650
6	40	1.8960

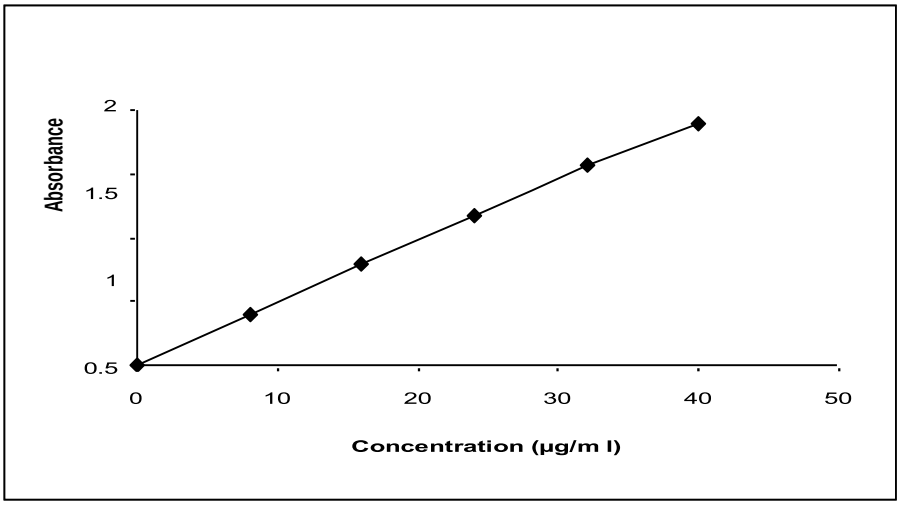

Fig. 2 Calibration curve of Famotidine in PBS (pH 7.4)

Drug-excipient compatibility studies:

The FT-IR peaks were observed that there is no change in the spectrum representing that there is no interaction between the drug and polymers and other excipients. These peaks play a vital role with respect to drug release.

Table No. 11 Drug-excipient compatibility

Drug + Excipients	Initial	After 1 month at		Compatible
		40^0C/75%RH	60^0C	
Drug	White powder	No change	No change	Yes
Drug + HPMC K4 M	White powder	No change	No change	Yes
Drug + HPMC K15 M	White powder	No change	No change	Yes
Drug + HPMC K100 M	White powder	No change	No change	Yes

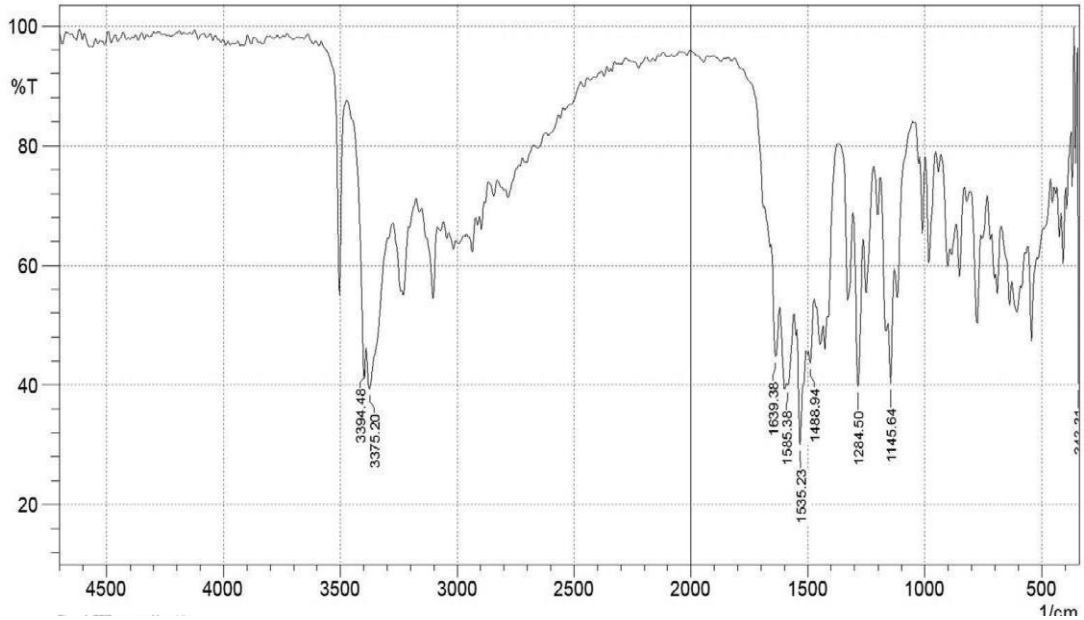

Fig. 3 FTIR of Famotidine

Table No. 12 Principle characteristic absorption bands of Famotidine (Sample)

S. No.	Wave Number(cm^{-1})	Characteristic absorption
1	3399.89	Asymmetrical N-H stretching
2	3376.75	symmetrical N-H stretching
3	1658.48	C=C stretching
4	1638.00	C=N stretching
5	1331.61	SO_2NH_2 absorption
6	1147.44	SO_2NH_2 absorption
7	1009.55	S=O absorption
8	777.01	C-H stretching vibration

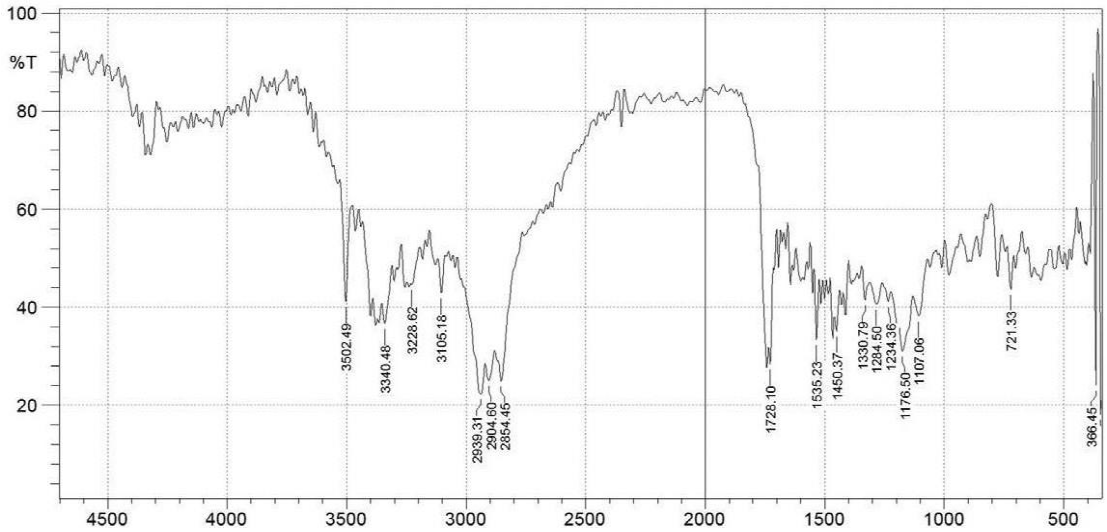

Fig. 4 FTIR of Famotidine + Excipients

Table No. 13 Principle characteristic absorption bands of Famotidine + Excipients

S. No.	Wave Number (cm^{-1})	Assignment
1	700	N-H deformation
2	700-800	C-H bending (Aromatic)
3	900	S-N stretching
4	1050-1400	S=O stretching
5	1500-1650	N-H bending
6	3399.89	Asymmetrical N-H stretching
7	3376.75	Symmetrical N-H stretching
8	1658.48	C=C stretching
9	1638.00	C=N stretching

Evaluation of granules:

Table. No. 14 Showing Results of Angle of Repose, Bulk and Tapped Density, Carr's Index, Hausner Ratio

Batch no.	Angle of repose (^{0})	Bulk density (gm/ml)	Tapped density (gm/ ml)	Carr's Index (%)	Hausner ratio
F1	26 º 32'	0.2891	0.3503	14.04	1.21
F2	24º 64'	0.2845	0.3394	15.68	1.22
F3	28º 59'	0.2924	0.3349	11.94	1.13
F4	26º12'	0.2875	0.3446	13.96	1.16
F5	23º 62'	0.2862	0.3420	15.13	1.19
F6	24º74'	0.2677	0.3214	13.92	1.15
F7	24 º 77'	0.2743	0.3242	15.42	1.19
F8	26 º 56'	0.2847	0.3177	10.38	1.11

Discussion:

The angle of repose for the formulations F1-F8 was found to be in the range 23^0.62' to 28^0.59' shows good flow compressibility index for the formulations F1-F8 found between 10.38% to 15.6% indicating that the blend has good flow property for compression.

CONCLUSION:

The floating system is intended to float in and over the gastric contents resulting in prolonged GRT. Furthermore, as the total gastrointestinal transit time of the dosage form is increased by prolonging the gastric residence time, these systems can also be used as sustained release devices with a reduced frequency of administration and therefore, improved patient compliance. It is very difficult to release loading dose of drug from matrix of tablet within specified period of time, to overcome this difficulty bi-layer tablet of famotidine was prepared. In which one layer was made up of immediate release layer to provide loading dose of famotidine. Loading dose of famotidine released within 30 minutes due to action of super disintegrating agents. Another layer was made up of gastroretentive layer or sustained release layer to provide maintenance dose of famotidine, this layer released drug till 24 hrs due to floating mechanism of HPMC polymer. Famotidine competitively inhibits the action of histamine on the H_2 receptors of parietal cells, reducinggastric acid secretion and concentration under daytime and nocturnal basal conditions and also when stimulated by food, histamine, or pentagastrin. The H_2-receptor antagonist activity of famotidine reportedly is slowly reversible, since the drug dissociates slowly from the H_2 receptor. So there is need to develop a formulation which increase the gastric retention of famotidine so that it slowly available in the stomach and gives the maximum use of famotidine. Famotidine are intended to give the immediate action. So we develop a bilayer formulation having one layer as immidiate release and other layer was made up of gastroretentive layer or sustained release layer to provide maintenance dose of famotidine so that it is available for longer duration for its pharmacological action. Initially quantitative estimation of famotidine in formulation was carried out by UV/Visible spectrophotometry using 0.1 N HCl (pH-1.2) as solvent and measuring the absorbance at 266 nm. In phosphate buffer 7.4 pH observed λmax was found to be 286nm. Compatibility studies of drug with excipients were performed under different storage condition forone month. Drug excipient were mixed and divided in five parts, sealed in vials and kept under different temperature conditions. The control sample containing only drugs were sealed in vials and kept as such in low temperature conditions. After one month the sample were withdrawn a n d observed that there was no change observed in the physical characteristics of the drugs. This shows that there is no incompatibility between drug and excipient used.

Physical mixture of drug and polymer was also used for the compatibility study and the samples were analyzed in IR spectrophotometer. From the study it is clear that no interaction was found in between them. The aim of present investigation was to formulate and evaluate bilayer gastro retentive tablet of Famotidine. In bi-layer tablet of famotidine, loading dose and maintenance dose was prepared based on pharmacokinetics data. For immediate release layer, it was found that all the batches gives release of more than 85 % ofdrug with in 30 minutes due to the high solubility of famotidine. Povidone is selected for the immediate release disintegrating agent for the reason that its was used in low quantity with less disintegration time (second) and having required physical properties i.e. hardness, friability, etc. For sustained release second layer, the use of hydrophilic polymer matrix is one of the most popularapproaches in formulating an extended-release dosage form. This is due to the fact that these formulations are relatively flexible and a well-designed system usually gives reproducible release profile. Among the various swellable polymers used for prolong drug release, hydroxypropyl methyl cellulose (HPMC) has been widely used due to its rapid hydration, good compression and gelling characteristic, its ease of use, availability and very low toxicity. HPMC alone could not give floating of the dosage form therefore, gas-generating agents were required to be added to produce CO_2 gas which, traps in the gel layer leading to floating of the dosage forms. Gas-generating agents sodium bicarbonate with citric acid was used in order to allow the tablet to float. Sodium bicarbonate in concentration range 10.45 % from showed least floating lag time when used with citric acid in concentration range from 4.8 %. Effect of various concentration of HPMC K 100 M was performed and it was found that as the concentration of HPMC increases the release of the drug from the matrix system was decreases. Since it is well known that due to viscosity of polymer itself that tends to decrease the release of the drug from the matrix. Formulation F1 was found to have lower erosion compared to F3 because HPMC K 100 M has higher viscosity as compared to HPMC K 15 M. It was concluded that HPMC K 100 M gave least erosion and good swelling. Hence HPMC K 100 M is superior over the other it was selected for formulation. Gas generating agent increased swelling as well as erosion of polymers due to burst effect. Effect of channeling agent, Lactose is

used as diluent as well as channeling agent in the floating delivery of the drug. The release profile of drug was observed and it was found that when the lactose was used at a concentration of 20 mg per tablet the release upto 89.37 % was observed and as the concentration of channeling agent i.e. lactose increases there is increase in the release was observed. While studying the effect of citric acid it was found that citric acid level greatly influenced the drug release, irrespective of methocel grade. The famotidine release from the floating tablet was found tobe 87.37 to 94.83 % with methocel K 100 M .It is evident from in vitro dissolution data that increased in citric acid concentration increased the release rate but reduced the floating time probably due to the excess of carbon dioxide, disturbing the monolithic tablet. To find out the mechanism of drug released from all the formulations of Famotidine floating tablets, the data was fitted to zero order, first order, Higuchi square root law and Korsmeyer's equationpattern. Release mechanisms of all the formulations have not followed zero order and first order kinetic but they strictly followed Higuchi's square root kinetics. So we considered the release mechanism is due to diffusion of drug from the polymer matrix. When the release data was plotted according to Korsmeyer's equation, the formulations showed linearity with exponential value (n) ranging from 0.37.This n value however, indicates the coupling of swelling and diffusion mechanism so called as Fickian diffusion. From the above observations we concluded that Famotidine may resides in the stomach for a longer period of time when it is administered in the form of floating tablets in comparison with the suspension or conventional system. This system has suggested that the floating tablets could serve as candidate for novel oral delivery that may improve the bioavailability of Famotidine and possibly of other drugs, which are aimed to produce a local action and specifically absorbed through the upper region of the GIT. Both optimized layer were used for the preparation of bi-layer tablet of Famotidine. First, immediate release formulation placed on cavity of die and compressed then finally sustained release layer (gastroretentive layer) were placed, and pressures were applied in, Rimek 12 station mini press tablet machine. Bi-layer tablet releases loading dose within 30 minutes and maintenances dose release till 24hrs due to good floating & bio adhesive ability. To find out the mechanism of drug release from bilayer tablet, the data were subjected to kinetic modeling. Drug released from bi-layer tablet suggests that drug releases via diffusion mechanism. Thus, the Bi-layer gastro retentive tablet of famotidine can be successfully formulated with HPMC K 100 M and super disintegrating agent povidone.

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