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Formulation and evaluation of matrix tablets of Famotidine using hydrophilic polymer

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Abstract

Famotidine is a potent H_2 receptor antagonist used in the management of benign gastric and duodenal ulceration, zollinger-Ellison syndrome and gastro esophageal reflux disease.Famotidine is incompletely absorbed from the GI tract following oral administration. The low bioavailability (40-45%) and short biological half-life (2.5 - 4 hrs) of famotidine following oral administration favors development of a controlled release formulation. Controlled release matrix tablets of famotidine were prepared using a hydrophilic polymer Hydroxypropyl methylcellulose K100M (HPMC K100M) with three concentrations (Drug: polymers 1:0.5, 1:0.75 and 1:1) by wet granulation method. The granules were evaluated for angle of repose, bulk density, tapped density, bulkiness, compressibility index and Hausners ratio. The tablets were subjected to weight variation, hardness, friability and drug content test. Invitro release studies revealed that famotidine formulation with high proportion of HPMC K100M (1:1) was able to sustain the drug release for 10 hours (84.1% ±1.85). Fitting the invitro drug release data to kinetic analysis, all the formulations followed the mechanism of both diffusion and erosion. All the formulations were stored at $45^0 \pm 2^0$C, 75 ± 5%RH and subjected to stability studies upto 45 days. It showed that all the formulations are physically and chemically stable.

Keywords: Bioavailability, Controlled release, Famotidine, Hydrophilic polymer, Wet granulation.

INTRODUCTION

Famotidine is a potent H_2 receptor antagonist used in the management of benign gastric and duodenal ulceration, zollinger-Ellison syndrome and gastro esophageal reflux disease. Conventional oral formulations of famotidine are administered multiple times a day. Treatment of gastric acid secretion using conventional formulations of famotidine is found to have many drawbacks, such as adverse side effects resulting from accumulation of drug in multidose therapy and poor patient compliance. Controlled release formulations of famotidine can overcome some of these problems. The matrix tablets can be prepared by wet granulation method. Among many polymers used in the formulation of matrix based CR drug delivery systems, hydrophilic polymer matrix systems are widely used because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance [1]. Hydroxypropyl methylcellulose (HPMC K100M) is the first choice for formulation of hydrophilic matrix system, providing robust mechanism, choice of viscosity grades, nonionic nature, consistent reproducible release profile, cost effectiveness and utilization of existing conventional equipment and methods [2]. Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from dosage form is controlled by the hydration of HPMC, which forms the gel barrier through which the drug diffuses [3].

MATERIALS AND METHODS

Materials

Famotidine was Kind gift from Fourrts India Pvt Ltd, Chennai, India. HPMC K100M, Talc and Magnesium stearate were procured from Loba Chemie Pvt Ltd; Mumbai, India. Ethyl cellulose, Lactose, PolyvinylPyrollidone and Isopropyl alcohol were procured from S.d fine chem. Pvt Ltd; Mumbai, India. All other chemicals and reagents used were of analytical grade.

2.1. Preparation of Famotidine CR tablets

Three formulations of controlled release tablets of famotidine using HPMC K100M with three ratios (1:0.5, 1:0.75, 1:1) were prepared by wet granulation method [4]. The details of composition of each formulation are shown in Table-I.

Famotidine and HPMC K100M were mixed separately. Lactose and ethyl cellulose were added to the drug polymer mixture and blended thoroughly for 5 minutes. PolyvinylPyrollidone (PVP) was dissolved in sufficient quantity of isopropyl alcohol (IPA) until it forms a solution and this was added to the drug mixture and mixed thoroughly to form a coherent mass. Then the coherent mass was passed through Sieve No: 16 to form granules and the collected granules were dried at 40°C±2°C for 2 hours. The dried granules were passed through sieve No: 22. The granules retained on sieve No: 22 were evaluated for bulk density, tapped density; bulkiness, angle of repose, compressibility index and Hausners ratio (Table- II). Then the granules were mixed with magnesium stearate, talc and finally compressed into tablets. The same procedure was followed to prepare famotidine tablets without polymer (Control).

Table-I Composition of matrix tablet formulations of Famotidine

Ingredients (mg)	HPMC K 100M			Control (without polymer)
	1:0.5 (H1)	1:0.75 (H2)	1:1 (H3)	
Famotidine	40	40	40	40
Ethyl cellulose	20	20	20	20
Hydroxypropyl Methylcellulose K 100M	20	30	40	-
Polyvinyl pyrrolidone (PVP K30)	3	3	3	3
Lactose Monohydrate	107	97	87	127
Talc	6	6	6	6
Magnesium Stearate	4	4	4	4
Isopropyl Alcohol	q.s	q.s	q.s	q.s
Weight of one tablet is 200mg				

2.2 IR spectral analysis

The drug and polymer must be compatible with one another to produce a stable product. Drug and polymer interactions were studied by using FTIR (Shimadzu, Japan, model-8400S) as per the method described by Sharma [5]. IR spectral analysis of pure famotidine, famotidine with HPMC K100M (1:1) were carried out. The peaks and patterns produced by the pure drug were compared with combination of polymer and pure drug.

2.3. Evaluation of tablets

2.3.1. Hardness

The tablets to be tested are held between a fixed and a moving jaw of hardness test apparatus (Monsanto) and reading of the indicator is adjusted to zero. The screw knob was moved forward until the tablet breaks and the force required to break the tablet was noted [6].

2.3.2. Friability

Friability test was performed using Roche friabilator. Ten tablets were weighed and placed in the friabilator, which was then operated for 25 revolutions per minute. After 100 revolutions the tablets were dusted and reweighed [7]. The percentage friability was determined using the formula,

$$\text{Percentage friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

2.3.3. Weight Variation

For weight variation test, twenty tablets were selected at random and weighed individually. The individual weights were compared with average weight for determination of weight variation [8].

2.3.4. Drug Content

Ten tablets were weighed and powdered [9]. Powder equivalent to 100mg of famotidine was dissolved in 10ml of 0.1M HCl, then make upto 100ml with phosphate buffer pH7.4 in 100ml standard flask. From this 10µg/ml, equivalent solution was prepared and analyzed at 265 nm using UV double beam spectrophotometer.

2.3.5. Dissolution Studies

Invitro release study was performed using USP apparatus type II at 50 rpm.The dissolution medium was 900ml of phosphate buffer PH 7.4. It was maintained at a temperature of 37±0.5^{o} C. The drug release was evaluated by taking 10ml sample (which was replaced with fresh medium) every one-hour interval upto 10 hours and suitably diluted with phosphate buffer pH7.4 and absorbance was measured at 265 nm using UV spectrophotometer [9].

2.4. Kinetic Analysis

To analyze the mechanism of drug release rate kinetics of all the formulations, the results of *invitro* release profiles were fitted into first order kinetic model, Higuchi model, zero order kinetic model and Korsmeyer model. The results of *invitro* release profiles were plotted in models of data treatment as follows:

1. Log cumulative percent drug remaining versus time (first order kinetic model) [10].
2. Cumulative percent drug release versus square root of time (Higuchi model) [11].
3. Log cumulative percent drug released versus time (zero order kinetic model) [12].
4. Log cumulative percent drug released versus log time (korsmeyers model) [13].

2.5. Stability Studies

Stability studies were carried out to assess the stability of all formulated controlled release famotidine tablets [14]. The prepared tablets were kept at 45^{o}±2^{o}C, 75±5% RH for 45 days. At 15 days intervals the tablets were evaluated for all physical parameters. The percentage of famotidine content and *invitro* drug release studies were also determined.

RESULTS AND DISCUSSION

Evaluation of Famotidine Granules and Tablets

The granules prepared for compression of matrix tablets were evaluated for their flow properties. The bulk density was within the range of 0.39 to 0.45 gm/cm^3. Tapped density ranged between 0.45-0.52 gm/cm^3. Bulkiness was found to be 2.22-2.52 cm^3/gm. Angle of repose was within the range of 27˙10 to 30˙96. Compressibility index was found to be 11.50-13.60 and Hausner ratio ranged from 1.13-1.18 for granules of different formulations (Table-II). These values indicate that the prepared granules exhibited good flow properties.

Table-II Evaluation of Famotidine Granules

Parameters	Famotidine : HPMC K100M			Control
	1:0.5	1:0.75	1:1	
Bulk density*(gm/cm^3)	0.45 ± 0.16	0.42 ± 0.12	0.39 ± 0.52	0.42 ± 0.76
Tapped density*(gm/ cm^3)	0.52 ± 0.84	0.47 ± 0.25	0.45 ± 0.42	0.48 ± 0.82
Bulkiness*(cm^3/gm)	2.22 ± 0.91	2.38 ± 0.84	2.52 ± 0.81	2.38 ± 1.02
Angle of repose*	30.96 ± 0.94	27.47 ± 0.91	27.10 ± 0.67	27.69 ± 1.04
Compressibility index*(%)	13.60 ± 1.05	12.0 ± 0.81	11.50 ± 0.82	11.98 ± 0.41
Hausners ratio*	1.15 ± 0.86	1.15 ± 0.74	1.13 ± 0.72	1.18 ± 0.48

*All values are expressed as mean ± standard deviation, n =5

Table-III Evaluation of Famotidine Tablets

Parameters	Famotidine : HPMC K100M			Control
	1:0.5	1.0.75	1:1	
Hardness* (kg/cm^2)	4.96 ± 0.14	4.98 ± 0.32	4.97 ± 0.32	4.92 ± 0.26
Friability* (%)	0.30 ± 0.04	0.24 ± 0.03	0.20 ± 0.07	0.18 ±0.09
Weight variation* (mg)	199.6 ± 4.2	199.5 ± 4.7	199.1 ± 3.3	199.2 ± 2.5
Content uniformity* (%)	97.92 ± 1.10	98.15 ± 0.60	99.46 ± 0.33	97.92 ± 0.26
Thickness * (mm)	4.2 ± 0.021	4.2 ± 0.04	4.1 ± 0.03	4.3 ± 0.03
Diameter* (mm)	6.1 ± 0.01	6.2 ± 0.03	6.1 ± 0.03	6.1 ± 0.05

*All values are expressed as mean ± standard deviation, n =5

All the prepared tablets showed good elegance in appearance. The hardness of the tablets of all formulations was within the range of 4.92 to 4.98 kg/cm^2, indicating satisfactory mechanical strength. The particle loss in the friability test was below 1% for all the formulations, which is an

indication of good mechanical resistance of the tablets. The variation in weight was within the range of ±7.5% complying with Pharmacopoeial specifications. The percentage of famotidine in all formulations was ranging from 97.92-99.46% indicating content uniformity was within the limits (±10%).The thickness and diameter of famotidine tablets was found to be in the range of 4.1 to 4.3 mm and 6.1 to 6.2 mm respectively, which showed uniform thickness and diameter. (Table-III).

IR spectral analysis

The IR spectral studies of pure Famotidine and combinations of famotidine with HPMC K100M (1:1) were carried out to study the interaction between the drug and polymer used. N-H stretching of primary amine, C-H stretching, C-S stretching, C-H deformation, N-H out of plain bending of pure famotidine and famotidine with polymer were almost in the same region of wave number ranging from 608 cm^{-1} to 3402 cm^{-1}. It showed that there was no significant interaction between the drug and polymer and they are compatible with each other.

Table-IV Percentage Drug Release of Famotidine Matrix Tablet Formulations

Time(hrs)	Cumulative percentage drug release *		
	H1 1:0.5	H2 1:0.75	H3 1:1
1	18.2 ± 1.49	15.5 ± 1.21	12.1 ± 1.53
2	27.8 ± 1.72	25.1 ± 1.45	21.7 ± 1.75
3	34.9 ± 1.60	32.3 ± 1.63	28.8 ± 1.29
4	42.9 ± 1.24	40.1 ± 1.78	36.7 ± 1.43
5	51.5 ± 1.83	49 ± 1.20	45.4 ± 1.19
6	61.3 ± 1.46	58.5 ± 1.92	55.1 ± 1.01
7	71.7 ± 1.04	69.2 ± 1.73	65.6 ± 1.73
8	79.7 ± 1.61	77.9 ± 1.90	73.6 ± 1.19
9	85.0 ± 1.35	83.1 ± 1.52	78.8 ± 1.85
10	90.2 ± 1.23	88.4 ± 1.39	84.1 ± 1.85

*All values are expressed as mean ± standard deviation, n = 5

Dissolution Studies

Invitro release studies were performed to determine the percentage of drug released from famotidine matrix tablet formulations with polymer, marketed tablet and famotidine tablet formulation without polymer (Control).Results of the *invitro* release studies of famotidine matrix tablet formulations with polymer are presented in (Table IV).

The percentage drug release of all formulations after 10 hours using HPMC K100M as polymer was found to be 90.2% (H1), 88.4% (H2) and 84.1%(H3).It was found that the cumulative percentage drug release of the formulation H1 was more than H2 and H3 . The cumulative percentage of drug release in the formulation H3 showed controlled release than H1 and H2.The polymer concentration played a major role in drug release. At higher concentration of the polymer, the drug release was prolonged than the lower concentration of the polymer. The graphical representation data of the famotidine matrix tablet formulations with polymer is shown in (Figure I).

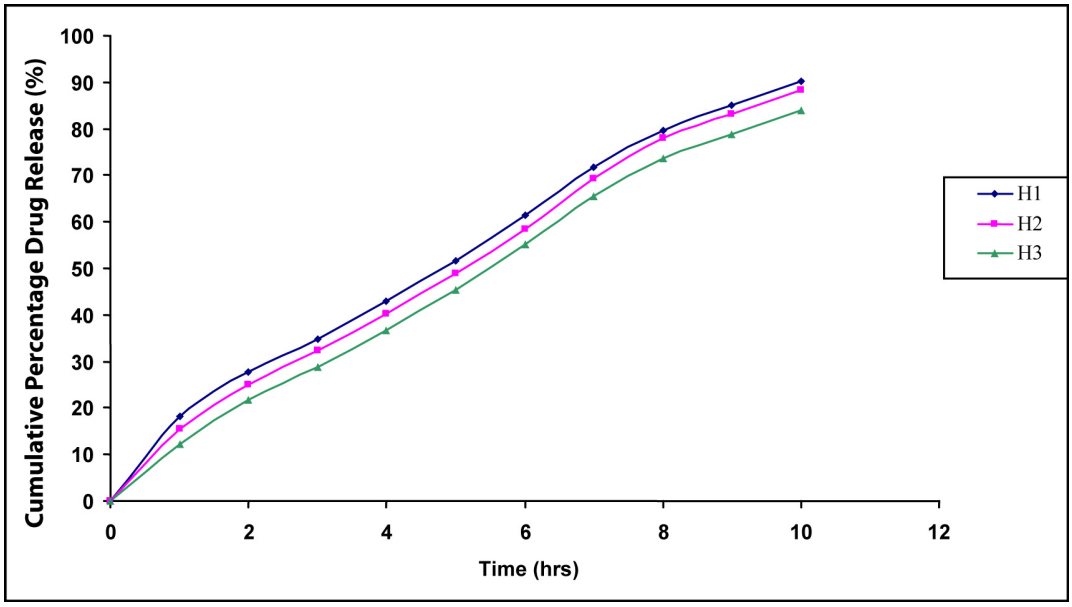

Figure-I: percentage drug release of Famotidine matrix tablet formulations

Invitro release of famotidine from the tablet formulation without polymer (Control) was found to be 96.7% where as the famotidine release from marketed tablet was 90.3% in 30 minutes.

Kinetic Analysis

The release rate kinetic data for all the formulations were shown in Table-V. When the data were plotted according to zero order, the formulations showed a high linearity, with regression co-efficient values (R^2) between 0.9873-0.9945. Diffusion is related to transport of drug from the dosage matrix into the *invitro* study fluid depending on the concentration. This is explained by Higuchi's model. The release profiles of drug from all the formulations could be best expressed by Higuchi's equations, as the plot showed high linearity with regression co-efficient values (R^2) between 0.9494-0.980.By using korsmeyer model, if n = less than 0.45 it is Fickian diffusion, if

n = 0.45-0.89 it is non-Fickian transport[13]. The result of all the formulations showed 'n' values between 0.611-0.843. It showed that all the formulations follow non- Fickian transport mechanism and also follow the mechanism of both diffusion and erosion (Table-V).

Table-V Curve fitting analysis for Famotidine formulations

Formulation Code	Regression Coefficient (R^2)			Korsmeyer's plot	
	Zero order Plot	First order Plot	Higuchi's Plot	R^2	Slope (n)
H1	0.9873	0.9515	0.980	0.6898	0.611
H2	0.9917	0.9545	0.9494	0.7231	0.694
H3	0.9945	0.9662	0.9523	0.7657	0.843

Stability Studies

Famotidine matrix tablets from all the formulations were stored at 45° ± 2°C, 75 ± 5% RH upto 45 days. Tablet evaluation tests were carried out at every 15 days intervals. All the formulations are physically stable. There were no deviations found in the tests and all are within the limits. There were no significant change in the drug content and *invitro* drug release profiles. It showed that all the formulations are chemically stable.

CONCLUSION

The results of experimental studies of famotidine matrix tablets proved that the granules of famotidine showed good flow properties, tablet evaluation tests are within the acceptable limits, IR spectral analysis proved that there was no drug- polymer interaction, the kinetic studies revealed that all the formulations followed zero order drug release and stability studies revealed that all the formulations were found to be stable after storing at 45° ± 2°C, 75 ± 5% RH for 45 days. The drawbacks of the conventional dosage forms of famotidine can be minimized by Famotidine CR tablets. Thus the results of the above study clearly indicated that famotidine may be formulated as controlled release tablets using HPMC K 100M as polymer by wet granulation method, which will provide continuous release of drug at a predetermined rate and for a predetermined time.

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Abbreviations

HPMC = Hydroxy Propyl Methyl Cellulose, CR = Controlled Release, RH = Relative Humidity, UV = Ultra Violet, GI = Gastro Intestine.

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