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DESIGN CHARACTERIZATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF FAMOTIDINE

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ABSTRACT

Famotidine has been the most widely used drug for the treatment of peptic ulcer for many decades.Sustained release matrix tablets of famotidine were prepared using wet granulation method.This study was related to thesustained release matrix tablets of Famotidine, a highly selective H_2 receptorantagonist.HydroxyPropyl Methyl Cellulose (HPMC) K100M was used as a rate retarding polymerwhereas lactose was used as diluent. The effects of the proportion of the polymer and the influence of co-excipients like lactose on the release rate of drug were investigated. The results of the present study detected that the rate ofFamotidine released from HPMC K100M matrices were mainly controlled by the Drug–HPMC ratio. When the influence of excipients on the release of drug was examined, the excipient, lactose enhanced the release rate of Famotidine. The prepared sustained release matrix tabletswere evaluated for various parameters like hardness, friability, uniformity of weight, uniformity of drugcontent,in-vitrodrug release and stability studies.

KEYWORDS

HPMC, Sustained-release, Wet granulation, Famotidine, Bioavailability

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INTRODUCTION

The basic goal of therapy is to achieve a steady state blood levelof Famotidine (histamine H_2-receptor antagonist) that is therapeuticallyeffective and non-toxic for an extended period of time. The design of proper dosage regimen is an important element in accomplishing this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drugdelivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. In the case of orally administered dosage forms, this period is measured in hours and critically depends on the residence time of the dosage form in the gastrointestinal tract.The term controlled release has become associated with those systems from which therapeutic agents may be automatically delivered at predetermined rates over a long period of time. Products of this type have been formulated for oral, injectable and topical use and inserts for placement in body cavities. Controlled release also denotes systems which can provide some control whether this is of a temporal or spatial nature or both for drug release in the body. The system attempts to control drug concentrations in the target tissues or cells. Prolonged or sustained release systems prolong therapeutic bloodor tissue levels of the drug for an extended period of time.Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled-release system. If it is unsuccessful at this but never the less extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged release system.The oral route of administration for sustainedrelease systems has received greater attention because of more flexibility in dosage form design. The design

of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of thedrug.One approach to the manufacture of sustainedrelease dosage forms is the direct compressionof blends of drug, retardant material andadditives to form a tablet in which drug isembedded in a matrix core of the retardant. Alternatively, retardant drug blends may be granulated prior to compression.The matrix tablets can be prepared by wet granulation method. Among many polymers used in the formulation hydrophilic polymer matrix systems are widely used in the formulation of matrix because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance [5]. 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 equipmentand methods [9]. 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]. Matrix tablets are considered to be the commercially feasible sustained action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug.

MATERIALS AND METHODS

Famotidine was received from Search Chemicals Mumbai,India. Ethyl Cellulose was supplied by LobaChemiePvt Ltd, India. HPMC was supplied by Himedia Laboratories Pvt Ltd, Mumbai, India. Poly Vinyl Pyrolydine was supplied by Qualikems Fine ChemPvt Ltd, Gujarat, India. Lactose was supplied by Thermo Fisher Scientific India Ltd, Mumbai, India. Talc was supplied by LobaChemiePvt Ltd, India. Magnesium Stearate was supplied by Central Drug House (P) Ltd., New Delhi, India,Iso Propyl Alcohol was supplied by Qualikems Fine ChemPvt Ltd, Gujarat, India.

Preparation Of Famotidine Matrix Tablets by Wet Granulation:

The ingredients were weighed accurately and mixed thoroughly. Granulation was done with a solution of PVPK-30 in sufficient isopropyl alcohol[1]. The granules (40mesh) were dried in conventional hot air oven at 45^0C. The dried granules were sized through 40/60mesh, lubricated with magnesium stearate (2 %w/w) and purified talc (1 %w/w) and then compressed on a single punch tablet machine (Cadmach Machinery Ltd., Ahmedabad, India). The tablets were off white, round and flat. The hardness of the tablets was kept constant. Four formulations were prepared and coded them from F1 to F4**.**Four different batches of famotidine tablets were prepared by wet granulation methodusing HPMC K100M with four ratios (1:**0.25**,1:**0.50**,1:**0.75**,1:**0**).The details ofcomposition of each formulation are shown in table-1

- **Table-1**

Ingredients(mg)	(F1)	(F2)	(F3)	(F4)
Famotidine	40mg	40mg	40mg	40mg
Ethyl cellulose	20mg	20mg	20mg	20mg
Hydroxypropyl Methylcellulose	10mg	20mg	30mg	-
Polyvinyl pyrrolidone (K30)	5mg	5mg	5mg	5mg
Lactose	115mg	105mg	95mg	125mg

Talc	5mg	5mg	5mg	5mg
Magnesium Stearate	5mg	5mg	5mg	5mg
Isopropyl Alcohol	qs	qs	qs	qs
Total wt	200mg	200mg	200mg	200mg

IR spectral analysis:

The drug and polymer must be compatible with one another to produce a stable product. Drugand polymer interactions were studiedby using FTIR (Shimadzu, Japan, model-8400S) as per the method described by Sharma [8]. IR spectral analysis of pure famotidine, famotidine withHPMC K100M were carried out. The peaks and patterns produced by the pure drug werecompared with combination of polymer and pure drug.

Evaluation of tablets:

All the formulations of Famotidine matrix tablets prepared were evaluated for the following parameters

a) Friabilitytest: Previously weighed 10tablets were taken in Roche friabilator andthe friability was checked at 25 rpm for 4minutes. Then the tablets were dusted and reweighed and the percentage of powdereroded during 4 minutes was recorded [10].The resulting tablets were weighed and thepercentage loss was calculated using the Formula:

Initial weight – Final weight X 100
Initial weight

b) Hardnesstest: Hardness of the tabletswas tested using "Monsanto" hardness tester In all the cases, means of six replicate determinations were taken [2].

c) Uniformityofweight: Average weight of the tablet was calculated by weighing 20 tablets individually and all together. The percent weight deviation of each tablet was computed as per official method [4][11].

d) Drugcontentuniformityofthetablets: Ten tablets were weighed and powdered. Powder equivalent to 100mg of famotidine wasdissolved in 10ml of 0.1M HCl, then make upto 100ml with phosphate buffer pH7.4 in 100mlstandard flask. From this 10µg/ml, equivalent solution was prepared and analyzed at 265 nm using UV spectrophotometer [7].

IN VITRODISSOLUTIONSTUDIES

In vitrodissolution studies of the prepared Famotidinetablets was determined up to 10 hour using U.S.P type II paddle type dissolution rate test apparatus (VEEGO, India). 900 ml of 0.1 N HCl(pH 1.2) was used as dissolution medium for first 2hrs and (pH 7.4) phosphate buffer for up to 24 hrs the test of the period as dissolution medium. The paddle was adjusted at 75rpm and the temperature of 37±0.5ºC was maintained throughout the experiment. Samples of 5 ml were withdrawn at known time intervals and were replaced with same volume of fresh dissolution media after each withdrawal [7][12]. The samples were analyzed for drug contents by measuring absorbances at 265 nm using UV-VIS double beam spectrophotometer thermo scientific, India.

STABILITY STUDIES

Short-term stability studies were performed at temperature 40± 2°Cover a period of 45 days on the matrix tablet formulations [6]. Sufficient number of tablets (10) were packed inamber colored screw capped bottles and kept in stability chamber maintained at 40±2°C. Samples were taken at 15 days intervals for drug content estimation .At the end of 45 days period, dissolution test was performed to determine the drug release profiles.

RESULTS AND DISCUSSION

In the present work, an attempt has been made to prepare sustained release matrix tablets of famotidine, ahistamine H_2-receptor antagonist using HPMC K100M with lactose as diluent , by wet granulation method with PVP K30 as binder. The prepared tablets were tested for physical parameters like hardness, weight variation, friability, drug content uniformity, invitrodrug release studies and short-term stability studies.

Evaluation of Famotidine Granules and Tablets

The bulk density was within the range of **0.40-0.70gm/cm3**. Tapped density ranged between**0.46-0.82 gm/cm3**. Angle of repose was within therange of **27.10-30.96^o**. Compressibility index was found to be **14-18**andHausner ratioranged from **1.11-1.18** for granules of different formulations. These values indicatethat the prepared granules exhibited good flow properties.The tablets of different formulation were evaluated for hardness, weight variation, friability and drug content. The result of tablets of formulation F1 to F4 where weight variation ranging from **199 - 203.6 mg**,hardness were maintained at **4.7-5kg/cm^2**, friability **0.30%**, drug content values ranging from **97.92 – 98%**.The results of tablets are concluded that all the parameters are within the acceptance range. The results of all these evaluations are given in Table-2 to 4

Table-2

Parameters	F1	F2	F3	F4
Bulk density (gm/cm^3)	0.45 - 0.68	0.40-0.62	0.40 - 0.56	0.42 - 0.70
Tapped density (gm/ cm3)	0.52 - 0.80	0.48- 0.81	0.46 - 0.79	0.50 - 0.82
Angle of repose	30 – 33	32 - 34	33 - 36	32 - 35
Compressibility index (%)	14– 16	14 - 19	15 - 20	15 - 19
Hausners ratio	1.15 - 1.18	1.14 - 1.20	1.11- 1.20	1.17 - 1.21

Table-3

Parameters	F1	F2	F3	F4
Hardness (kg/cm2)	4.96 – 5	4.7 - 5.2	4.7 - 4.9	4.9– 5
Friability (%)	0.30	0.31	0.30	0.27
Weight variation (mg)	199.6– 201	198 - 205	199 - 203.6	200.09 – 203
Content uniformity (%)	97.92 – 98	98.02 - 98.07	97.01 - 98.03	98 - 98.72
Thickness (mm)	4 - 4.2	4 - 4.1	4 - 4.2	4
Diameter (mm)	6	6	6	6

IR spectral analysis

The IR spectral studies of pure Famotidine and combinations of famotidine with HPMC K100M were carried out to study the interaction between the drug and polymer used. N-Hstretching of primary amine, C-H stretching, C-S stretching, C-H deformation, N-H out of plainbending of pure famotidine and famotidine with polymer were almost

in the same region of wavenumber ranging from 608 cm-1 to 3402 cm-1. It showed that there wasno significant interactionbetween the drug and polymer and they are compatible with each other.

Dissolution Studies

The tablets were evaluated for invitrodissolution studies to determine the percentage of drug released fromfamotidine matrix tablet formulations with polymer, marketed tablet and famotidine tabletformulationwithout polymer (Control). The results were shown in the Table-4

- **Table-4**

Time(hrs)	F1%	F2%	F3%	F4%
1	27 – 29	25 - 27	21 - 25	92 - 95
2	30 – 35	29 - 35	23 - 30	--
3	33 – 40	32 - 38	29 - 33	--
4	40 – 47	36 - 43	35 - 37	--
5	50 – 54	40 - 50	40 - 43	--
6	60 – 65	55 - 59	48 - 51	--
7	67- 71	62 - 66	57 - 61	--
8	73 – 79	68 - 73	60 - 67	--
9	85 – 88	75 - 81	66 - 73	--
10	90 – 95	88 - 90	80 - 85	--

The percentage drug release of all formulations after 10 hours using HPMC K100M as polymerwas found to be 90% (F1), 88% (F2) and 84%(F3).It was found that the cumulativepercentage drug release of the formulation (F1) was more than (F2) and (F3) .The cumulativepercentage of drug release in the formulation (F3) showed controlled release than (F1) and (F2).Thepolymer concentration played a major role in drug release. At higher concentration of thepolymer, the drug release was prolonged than the lower concentration of the polymer. In-vitrorelease of famotidine from the tablet formulation without polymer (Control) was found to be 94% in 30minutes.Thegraphical representation data of the famotidine matrix tablet formulations with polymer is with polymer is shown in figure.

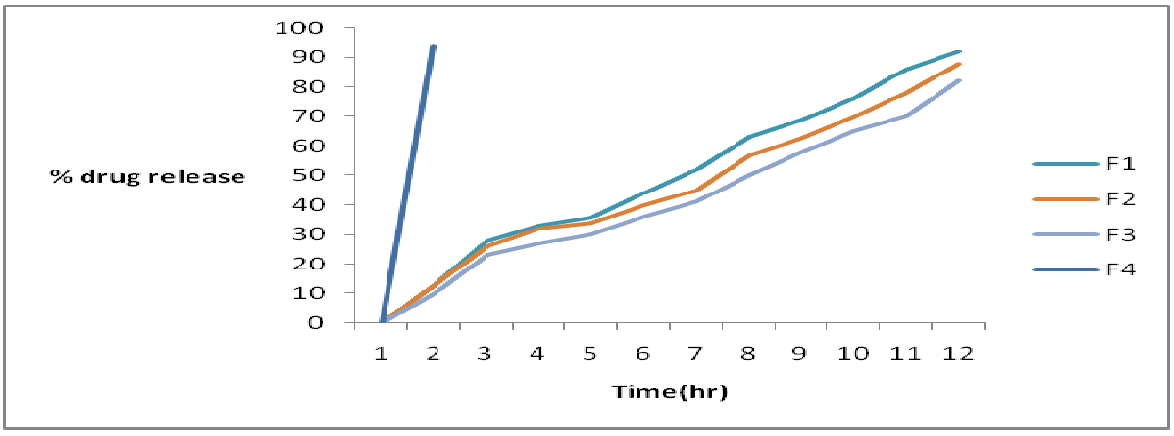

Figure-I: Percentage drug release of Famotidine matrix tablet formulations

Stability Studies

Famotidine matrix tablets from all the formulations were stored at 45°C, 75% RH upto45 days. Tablet evaluation tests were carried out at every 15 days intervals. All the formulationsare 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 in-vitrodrug release profiles. It showedthat all the formulations are chemically stable.

CONCLUSION

The results of experimental studies of famotidine matrix tablets proved that the granules offamotidine showed good flow properties, tablet evaluation tests are within the acceptable limits,IR spectral analysis proved that there was no drug- polymer interaction and stability studies revealedthat all the formulations were found to be stable after storing at 45°C, 75% RH for 45days. The drawbacks of the conventional dosage forms of famotidine can be minimized byFamotidine 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 granulationmethod, which will provide continuous release of drug at a predetermined rate and for apredetermined time.

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