Original Article

Formulation and Development of Famotidine Solid Dispersion Tablets for their Solubility Enhancement

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ABSTRACT

Background: Famotidine is BCS class II drug having a low aqueous solubility and low oral bioavailability. It needs to develop into its novel form for solubility and dissolution rate enhancement. **Materials and Methods:** The aim of the current work was to formulate famotidine (FAM)-poloxamer 188 solid dispersions (SDs) by kneading method for solubility enhancement. The problems of low solubility were eliminated by preparing the SDs using the poloxamer 188 as hydrophilic carrier. **Results and Conclusion:** The prepared tablets of SDs were characterized by employing solubility, FTIR, disintegration test, friability, wetting time and *in-vitro* drug release. The optimum values of solubility and *in-vitro* drug release of prepared novel formulation were maximum than conventional dosage form. The famotidine (FAM)-poloxamer 188 solid dispersions were successfully prepared and seem to be promising for enhanced dissolution rate (solubility) and oral bioavailability.

Key words: Solid dispersions (SDs), Kneading method, Famotidine, Solubility, Dissolution rate, Bioavailability.

INTRODUCTION

Solubility is a major physicochemical factor which affecting absorption/onset of action of drug and its therapeutic potency. If drug having poorly aqueous solubility they may face problem in dosage form design as well as effective therapeutic action. The low dissolution rate and aqueous solubility of drug candidate affects the oral bioavailability of drug. The enhancement of the solubility and dissolution rate of drugs is one of the major factors which affect in development of dosage form. Several methods have been employed to eliminate the problem of poor solubility.[1]

Problems of solubility and dissolution rate of poorly soluble drugs involved various methods are available such as liquisolid, in which drug molecules is adsorbed over or loaded into inert carrier's molecules.[2] Various surfactants of different charges also helpful in improve wettability and solubility of various hydrophobic drug formulations.[3] Another approach i.e. drug micronization is unsuitable method because product after micronization has been agglomerated. The solid dispersion is also one of the methods to formulate solid dispersions because of its more effective, simplicity of preparation, not require expensive instruments and ease of optimization.[4] In solid dispersion techniques, whereby the active moiety were dispersed in a inert carrier molecules or polymer, usually with a view to enhancing solubility, dissolution rate and oral bioavailability.[5] Famotidine is a thiazole ring containing compound which act tightly on H_2 receptors and reduced acid secretion. Famotidine is categories in biopharmaceutical BCS II drug having a low solubility and high permeability and it protect mucosal acid secretions for 10-12 hrs then metabolized and elimination by renal route.[6,7] Famotidine also decrease both basal, food-stimulated acid secretion by 90% as well as promotes healing of duodenal ulcer.[8]

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This drug is BCS class II drug having low solubility. Therefore, it needs to formulate into its novel form for solubility enhancement.[9] In this study, novel SDs was prepared using poloxamer 188 as hydrophilic carrier. The dissolution rates of drug from SDs formulation were investigated in phosphate buffer pH-7.4. The aim this work was to design, prepare and evaluate solid dispersions (SDs) tablet of famotidine (FAM) and poloxamer 188 using kneading method for solubility enhancement of famotidine.

MATERIALS AND METHODS

Materials

The active API famotidine (FAM) was obtained as a gift sample from Milan Pharmaceuticals Ltd., Navi Mumbai. Poloxamer 188 was purchased from Alembic pharmaceutical Pvt. Ltd. Badodara. Lactose, Polyvinyl Pyrollidone, Magnesium stearate and Sodium Starch glycolate were purchased from Loba Chemie Pvt Ltd, Mumbai, India respectively. All other chemicals and reagents were of analytical grade and used as provided.

Methods

Preparation of the Solid dispersion (SDs)

The Kneading method (KM) was used for the preparation of solid dispersion. Six different batches containing different drugs: carriers (F1-F6) ratio was used for preparation solid dispersion. Famotidine and poloxamer 188 were weighed according to weighed ratios given in Table 1. The famotidine and poloxamer 188 were triturated using a small volume of isopropyl alcohol to give a thick paste, which was kneaded for 30 min and then dried at 40°C in an oven. The dried powder was then pulverized, then passed through mesh no. 30, stored for 48 hrs in a vacuum desiccator packaging in an airtight container.[10]

Saturation solubility studies

The 5 mg pure famotidine and 5 mg equivalent weight of famotidine containing SDs prepared by kneading method were added separately in conical flask containing 20 ml of distilled. All mixtures were sonicated for 10 min at room temperature and after sonication, shaken for 24 hr at 37 ± 2°C (using orbital shaking incubator, Remi, India). After shaking 5 ml sample aliquots were collected and filtered through Whatman filter paper. The filtrate was analyzed by UV/Visible Spectrophotometer (U-2900, Hitachi, Japan) at 248 nm.[11]

Preparation of Tablets of Solid Dispersions

Tablets of solid dispersion containing 20 mg equivalent weight of famotidine were prepared by direct compression. The blend of all excipients subjected to compressed on a 10-station rotary tablet punching machine. The composition of tablet is given in Table 2.

Physical Evaluation of Granules[12]

Angle of Repose

The above test was performed for each powder blend by glass funnel method. Weighed the powder sample accurately and passed through the funnel so as to form a heap. The height of funnel was so adjusted that the tip of funnel just touched the apex of the heap. The diameter of the powder cone was measured and the angle of repose was calculated using the following equation.

$$\text{Tan } \theta = h/r$$

Where, h = height of cone

r = radius of powder cone

Bulk Density

About 25 gm of granules pour through a glass funnel into a 100 ml graduated cylinder. The volume of granules occupied the measuring cylinder without compaction was measured and noted (V_o). Bulk density was calculated as below-

$$\text{Bulk density (g/ml)} = M/Vo$$

Where, M = mass of powder

V_o = apparent unstirred volume

Tapped Density

The tapped density was determined as 25 gm solid dispersion granules was poured through a glass funnel into a 100 ml graduated cylinder. The cylinder containing granules was tapped until a constant volume obtained. Volume of granules was occupied after tapping was recorded and tapped density was calculated.

$$\text{Tapped density (g/ml)} = M/V_f$$

Where,

M = weight of sample powder

V_f = tapped volume

Compressibility

The compressibility index was performed by comparing the bulk density and tapped density. A useful empirical guide is given by Carr's Index.

$$\text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

It provides an indication of the degree of densification that could result from vibration of feed hopper. It is another parameter to analyzed flow ability of granules.

Significant value is suggesting as lower the hausner ratio better is the flowability.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Physical characterization of Tablets

Drug content of tablets formulation

For drug content analysis, Triturate about 30 mg equivalent weights of tablet and added to 100 ml phosphate buffer (pH 7.4) in a stoppered conical flasks and mixture were shaken for 30 min. After shaking 5 ml aliquots were withdrawn and filtered using whatman filter paper no 40. The filtrate was analyzed in UV spectrophotometrically at 265 nm.

$$\text{Drug content (\%)} = \frac{\text{Weight of drug determined (mg)}}{\text{Weight of drug added (mg)}} \times 100$$

Weight variation

Twenty tablets were selected at a random from each formulation and average weight was determined. Then individual tablets were weighed using digital electronic balance and the individual weight was compared with the average weight. The mean ± SD (standard deviation) values were calculated.[13]

Hardness or tablet crushing strength (fc)

Hardness means force in kg/cm^2 or newton needed to break a tablet. Tablets for hardness testing was done using monsanto tablet hardness tester. Randomly five tablets were selected from each batch and subjected to hardness testing by using monsanto hardness tester. The mean values and standard deviation for all the respective batches were calculated.

Friability (F)

Friability testing of the prepared tablets was conducted using Roche friabilator. The pre-weighted tablets placed in plastic transparent chamber at 25 rpm and rotated for 100 revolutions. Then tablets were de-dusted by using a muslin cloth and weighed again. The friability (F) is obtained by the using formula.

F = (Winitial - Wfinal / Winitial) x 100

In-vitro disintegration time

The *in-vitro* disintegration time for all batches was determined using disintegration test apparatus. For testing, each tablets were added in the each tubes of the apparatus and disc was placed on each tube where require. The time needs in seconds for complete disintegration of the tablets was measured.

Wetting time

Tablet was placed in a petri plate (internal diameter is 6.5 cm) having a piece of tissue paper double folded containing 6 ml of water. Then measured time required in seconds for complete wetting.[14,15]

Fourier transforms infra-red spectroscopy

Drug-polymer compatibility were detected by FTIR spectrophotometer (Shimadzu, FTIR-8400). FTIR study of the pure famotidine and prepared famotidine tablet was carried out by KBr pellet method. The mixture of sample and KBr were manual press into a disc in a KBr press. The spectrum was recorded from range of 4000 to 400 cm$_{-1}$.[16]

In-vitro drug release studies

Dissolution studies for famotidine SDs tablet and pure famotidine were carried out separately using the USP paddle method at 37°C in dissolution tester (Electrolab auto-sampler dissolution tester TDT-08L) at 50 rpm with 900mL of phosphate buffer pH-7.4 as dissolution media. The weight of SDs equivalent to 30 mg of famotidine and 30 mg pure famotidine were filled into the hard gelatin capsules separately and then exposed to the dissolution media separately for 2 hrs. The samples were collected at predetermined time (i.e.10, 20, 30, 45, 60, 90 and 120 min) and then filtered using a whatman filter paper. In order to maintain the sink condition 5 ml fresh medium was added after each 5 ml sample collection and filtrate was analyzed by UV spectrophotometer at 265 nm.[17,18]

RESULTS AND DISCUSSIONS

The saturation solubility of famotidine in distilled water and phosphate buffer pH 7.4 were 0.0066 mg/L and 0.0075 mg/L respectively. The prepared granules were subjected for characterizations and the results are given in the Table 3. The compressed tablets of SDs were analysed for physical properties and tabulated in Table 4. The drug content of tablets formulations were in range of 64.14 to 92.33 % for all experimental run. The hardness of prepared formulation were in range of 3.60 kg/cm^2 to 4.0 kg/cm^2 for all six batches and in case of hardness of marketed formulation was about 4.053.60 kg/cm^2. The uniformity of weight of all prepared formulation was in range of 188 mg to 205 mg. The % friability of all F1 to F6 formulations were in ranges of 0.53% to 0.77 % and the % friability of marketed formulation was about 0.7 %. The wetting time for all six formulations and marketed formulation were in range of 45-59 sec and 63 sec respectively. The disintegration

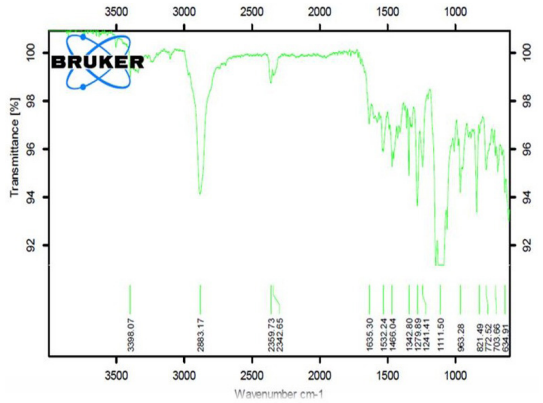

Figure 1(a): FTIR spectra of pure famotidine.

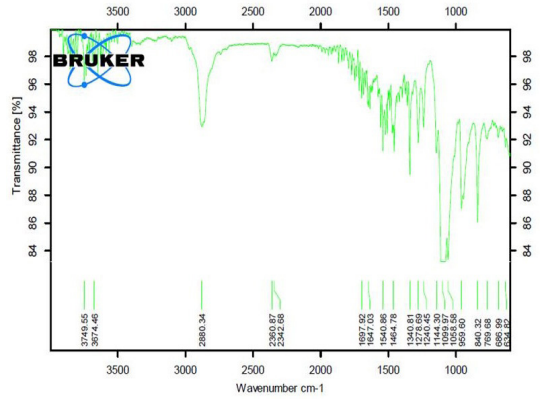

Figure 1(b): FTIR spectra of famotidine + Poloxamer 188.

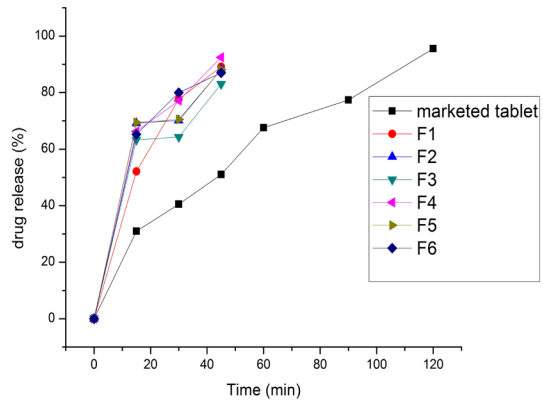

Figure 2: Dissolution profiles of all six prepared famotidine formulation and marketed famotidine tablet.

Table 1: Drug- polymer proportion		
Code	**Solid Dispersion**	**Drug: Polymer**
F1	Famotidine : Poloxamer 188	1:1
F2	Famotidine : Poloxamer 188	1:2
F3	Famotidine : Poloxamer 188	1:3
F4	Famotidine : Poloxamer 188	1:4
F5	Famotidine : Poloxamer 188	1:5
F6	Famotidine : Poloxamer 188	1:6

Table 2: Composition of tablets of solid dispersions	
Ingredients	**Formulation (mg)**
Solid dispersion is equivalent to 20 mg	120
Starch	10
Lactose	168.8
Talc	1
Magnesium stearate	0.2

Table 3: Pre-compressed parameter for granules	
Parameters	**Results**
Angle of Repose (θ)	26.71
Bulk Density (g/ml)	0.472
Tapped Density (g/ml)	0.566
% Compressibility	15.1
Hausner Ratio	1.184

time of all F1-F6 batches were in range of 3.25 min to 4.27 min. The FTIR spectra of pure famotidine Figure 1(a) shows major peaks in 3398 cm^{-1} (N-H), 2883 cm^{-1}, 2359 cm^{-1} (C-H),, 2342 cm^{-1} (C-H), 1636 cm^{-1}, 1535 cm^{-1} (N=O) and 1466 cm^{-1} (N=O). And FTIR spectra of prepared tablets formulation Figure 1(b) shows characteristic peaks in 3674 cm^{-1}(O-H), 2880 cm^{-1} (C-H), 2342 cm^{-1} (O=C=O), 1697 cm^{-1} (C=O) and 1647 cm^{-1} (C=C). From the FTIR studies, we conclude that there is no major interaction between drug and polymer. The *in vitro* release of marketed formulation was about 95.57 % in 120 min and all prepared formulation released the drug in range of 82.91 to 92.45% of drug in 45 min see Figure 2. It concludes that, dissolution profile of pre-

Table 4: Post Compression Evaluation of Marketed & Formulated Tablet							
Parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**Marketed Tablet**
Weight Uniformity (mg)	198	196	188	205	199	192	199.60
Drug content of tablets(%)	64.14	80.77	92.33	75.36	69.74	77.96	96.45
DT (min)	4.04	3.30	3.53	3.25	4.25	4.14	4.11
Friability (%)	0.61%	0.77%	0.53%	0.66%	0.75%	0.69%	0.7 %
Hardness (kg/cm^2)	3.8	3.6	3.7	3.8	4.0	3.7	4.05
Wetting time (sec)	59	55	45	59	54	48	63

pared formulation was increased with respect to marketed formulation.

CONCLUSION

In the present study, famotidine- poloxamer 188 Solid Dispersions (SDs) by kneading technique was successfully prepared. The results of solubility testing and *in vitro* dissolution studies conclude that, the prepared tablet of solid dispersion shows higher solubility that marketed formulation. Increased in solubility and dissolution rate of SDs occur due to the decreased in particle size, increased in surface area and increased wettability of drug because complex with hydrophilic carrier. SDs of famotidine developed by kneading method may represent a promising approach for solubility enhancement.

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CONFLICT OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

ABBREVIATIONS

BCS: Biopharmaceutics classification of drug; **FAM:** Famotidine; **SDs:** Solid dispersions; **KM:** Kneading method; **FTIR:** Fourier transform infrared spectroscopy; **KBr:** Potassium bromide.

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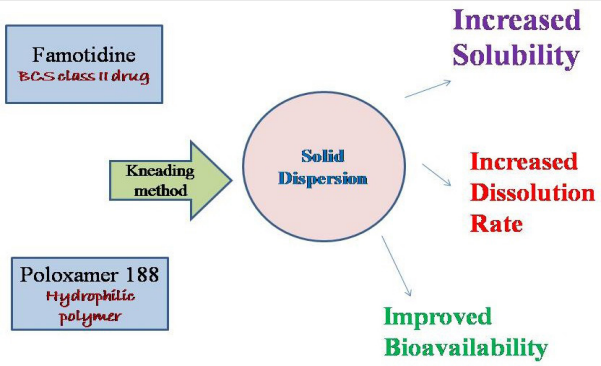
SUMMARY

Solubility plays a key role in effective therapeutic action of drugs. Lesser the solubility and dissolution rate of poorly aqueous-soluble drugs leads to lesser efficiency as well as oral bioavailability. For the enhancement of solubility of BCS class II drugs i.e. famotidine, we prepared solid dispersion of famotidine using a kneading method and poloxamer 188 as hydrophilic carrier. The prepared novel formulation were evaluated using different techniques like solubility analysis, FTIR, disintegration test, friability, wetting time and *in-vitro* drug release. The optimum values of solubility and *in-vitro* drug release of prepared novel formulation were found maximum than conventional dosage form. From the study, we conclude that, the prepared formulation is improved solubility, dissolution rate and oral bioavailability of famotidine.

PICTORIAL ABSTRACT



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