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Research Article

# Design, Development and Evaluation of Enteric Coated Tablets of Famotidine

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## ABSTRACT

The aim of the present study was to formulate and evaluate of enteric coated Famotidine sodium sesquihydrate tablets by using manotol, dicalcium phosphate, microcrystalline cellulose, crossrmelose sodium, magnesium starate and talc. FT-IR study was carried out to check any possible interactions between the drug and the excipients manotol, dicalcium phosphate, microcrystalline cellulose, crosscarmelose sodium, Famotidine sodium sesquihydrate were prepared by direct compression method using different concentration of, Avicel PH (MCC) as filler, mannitol and dicalcium phosphate as diluents, croscarmellose sodium as disintegrating agents, magnesium stearate and talc was used as a glidant and lubricant respectively. The granules were evaluated for the precompression parameters like angle of repose, bulk density, tapped density and compressibility index. The flow characteristics of the granules were assessed by determining their angle of repose and Carr's Index. The values of compressibility index and angle of repose signify good flowability of the granules for all the batches. This shows that the granules had smooth flow properties ensuring homogenous filling of the die cavity during the compression (punching) of tablets.

**Keyword:** Famotidine, Preformulation, In vitro, Stability Studies

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## INTRODUCTION

For a variety of factors, oral administration accounts for more than 50% of pharmaceutical goods. This route of administration is said to be the most popular since it provides benefits such simplicity, adaptability, patient compliance, and precise dose. One of the significant formulation issues with such an oral medication is unpleasant taste. Gastric acid secretion is a complex, continuous process in which multiple central and peripheral factors contribute to a common endpoint: the secretion of H+ by parietal cells. Neuronal (acetylcholine, ACh), paracrine (histamine), and endocrine (gastrin) factors all regulate acid secretion. Their specific receptors (M3, H2, and CCK2 receptors, respectively) are on the basolateral membrane of parietal cells in the body and fundus of the stomach. The H2 receptor is a GPCR that activates the Gs-adenylylcyclase-cyclic AMP-PKA pathway. ACh and gastrin signal through GPCRs that couple to the Gq-PLC-IP3-Ca2+ pathway in parietal cells. In parietal cells, the cyclic AMP and the Ca2+-dependent pathways activate H+,K+-ATPase (the proton pump), which exchanges

hydrogen and potassium ions across the parietal cell membrane. This pump generates the largest known ion gradient in vertebrates, with an intracellular pH of about 7.3 and an intracanalicular pH of about 0.8. The most important structures for CNS stimulation of gastric acid secretion are the dorsal motor nucleus of the vagal nerve, the hypothalamus, and the solitary tract nucleus. Efferent fibers originating in the dorsal motor nuclei descend to the stomach *via* the vagus nerve and synapse with ganglion cells of the enteric nervous system. ACh release from postganglionic vagal fibers directly stimulates gastric acid

secretion through muscarinic M3 receptors on the basolateral membrane of parietal cells. The CNS predominantly modulates the activity of the enteric nervous system *via* ACh, stimulating gastric acid secretion in response to the sight, smell, taste, or anticipation of food (the "cephalic" phase of acid secretion). ACh also indirectly affects parietal cells by increasing the release of histamine from the enterochromaffin-like (ECL) cells in the fundus of the stomach and of gastrin from G cells in the gastric antrum. ECL cells, the source of gastric histamine secretion, usually are in close proximity to parietal cells. Histamine acts as a paracrine mediator, diffusing from its site of release to nearby parietal cells, where it activates H2 receptors. The critical role of histamine in gastric acid secretion is dramatically demonstrated by the efficacy of H2-receptor antagonists in decreasing gastric acid secretion. Gastrin, which is produced by antral G cells, is the most potent inducer of acid secretion. Multiple pathways stimulate gastrin release, including CNS activation, local distention, and chemical components of the gastric contents. Gastrin stimulates acid secretion indirectly by inducing the release of histamine by ECL cells; a direct effect on parietal cells also plays a lesser role. Somatostatin (SST), which is produced by antral D cells, inhibits gastric acid secretion. Acidification of the gastric luminal pH to <3 stimulates SST release, which in turn suppresses gastrin release in a negative feedback loop. SST-producing cells are decreased in patients with H. pylori infection, and the consequent reduction of SST's inhibitory effect may contribute to excess gastrin production. Enteric coated dosage forms, such as coated tablets, sugar-coated tablets, soft and hard gelatin capsules, granulates or pellets, have their firm place in the medical arsenal. The preparations most commonly provided with enteric coatings contain pancreatin and other proteolytic enzymes, diclofenac, cardiac glycosides, electrolyte preparations with sodium, potassium and magnesium salts as well as calcium, iron and manganese preparations. Bisacodyl preparations, preparations containing valproic acid as well as formulations with plant extract or terpenes are also common. Famotidine is a substituted benzimidazole derivative that targets gastric acid proton pumps,the final common pathway for gastric acid secretion. The drug covalently binding to the proton pumps, causing prolonged inhibition of gastric acidsecretion. But the drug causes irritation to gastric mucosa which may lead to nausea and vomiting. The stability of Famotidine is rapidly degrades in acid medium of the stomach, but has acceptable stability in alkaline conditions. Therefore, Famotidine should be delivered into the intestine. Hence, formulation of Famotidine as an enteric coated tablet may solve the stability problem of drug in the stomach and release the drug in the intestine.

## MATERIAL AND METHODS

### Enteric coating of Famotidine sodium compressed tablets by dipping method

The compressed tablets were coated with enteric coating polymer (Eudragit L100 or cellulose acetate phthalate) solution by dipping method. Desired tablet coating continued the dipping and weight gain was achieved.

The coated tablets were studied for its weight variation, thickness, uniformity of drug content and *in vitro* dissolution study[38,42].

### Physicochemical evaluation of coating films

The same polymer solution was used to prepare the polymeric films and was subjected for film thickness, film solubility. The polymeric films were prepared by casting the acetone with PEG the polymer solution was poured on the glass plate. The film was dried for 24 h at room temperature under a special cover with reduced solvent evaporation to obtained smooth homogenous films. The dried films were cut in to $1cm^2$ area the prepared polymeric film was studied for film thickness, and film solubility. The thickness of dried films was determined by thickness Digital micrometer. The film solubility was studied with pH 1.2 and pH 6.8. The $1\times1$ $cm^2$ coating film was selected, weighed and transferred in a beaker containing 20 mL of specified pH medium, which was mixed in a magnetic stirrer for 1 h at 37 ± 1°C and finally film solubility was examined.

### *In vitro* drug release studies

USP dissolution apparatus type II (Electrolab TDT-08L,Mumbai,India) was employed to study the *in vitro* drug release from various formulations prepared. The dissolution medium used was 900 mL of acidic buffer of pH 1.2 for 2 h and phosphate buffer of pH 6.8 for 1 hrs. The tablet was kept in to the basket. The temperature was maintained at 37 ± 0.5°C and the stirring rate was 100 rpm. Samples were withdrawn at regular time intervals and the same volume was replaced with fresh dissolution medium. The samples were measured by UV spectrophotometer at 283 nm (pH 1.2) and at 288 nm (pH 6.8) against a blank. The release studies were conducted in triplicate and the mean values were plotted versus time[28].

### Stability studies

Stability studies were performed as per the ICH guidelines. Selected formulations of Famotidine sodium tablet were sealed in aluminum foil cover and stored at (40 ± 2 °C / 75 ± 5 % R.H) for a period of 3 months. Samples from each formulation which are kept for examination were withdrawn at definite time intervals. The withdrawn samples were evaluated for physical appearance, hardness, drug content [29].

## RESULTS

Present study was done on enteric coating tablets with different formulation. Famotidine sodium sesquihydrate were prepared by direct compression method using different concentration of, microcrystalline cellulose, mannitol, dicalcium phosphate, croscarmellose sodium, magnesium stearate and talc, CAP and Eudragit L100 were used as enteric coating polymer, which prevent drug form gastric pH and release in intestinal pH.

### Preformulation studies

### Preparation of standard graphs

Standard graph for the drug Famotidine sodium was done separately in pH 1.2 acidic buffer and pH 6.8 phosphate buffer.

**Table** show the concentrations of Famotidine sodium in pH 1.2 acidic and pH 6.8 phosphate buffers and the respective absorbance. The Figure 4 and 5 show the calibration curves of Famotidine sodium in pH 1.2 acidic buffer and pH 6.8 phosphate buffer respectively.

## FTIR spectral study

FT-IR spectroscopy study was carried out separately to find out the compatibility between the drug Famotidine and Microcrystalline cellulose, mannitol, dicalcium phosphate, croscarmellose sodium. The FT-IR was performed for drug, polymer and the physical mixture of drug-polymer. The spectral obtained from FT-IR spectroscopy studies.

The peaks obtained in the spectra of drug and polymers mixtures correlates with each other. This indicates that the drug was compatible with the formulation components. IR studies indicated no interaction between drug and polymers.

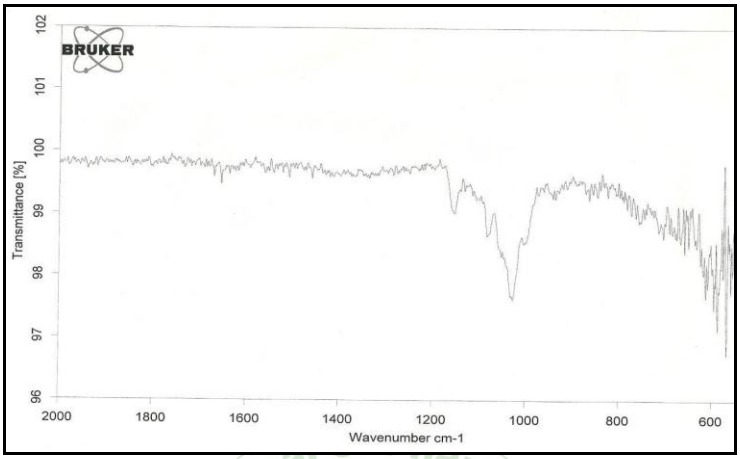


**Figure 1:** FTIR Spectrum of Famotidine sodium

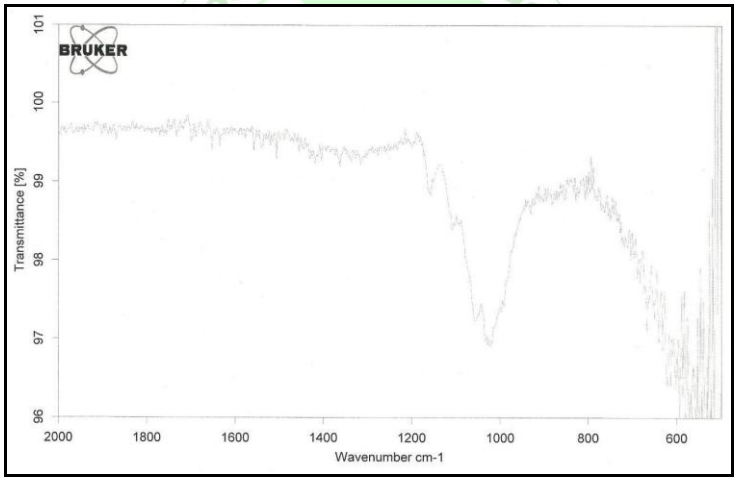


**Figure 2:** FTIR Spectrum of physical mixture of Famotidine sodium with mannitol

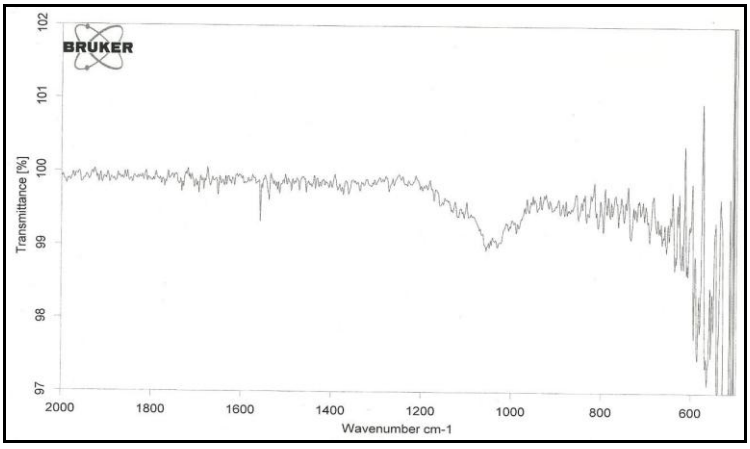


**Figure 3:** FTIR Spectrum of physical mixture of Famotidine sodium with dicalcium phosphate

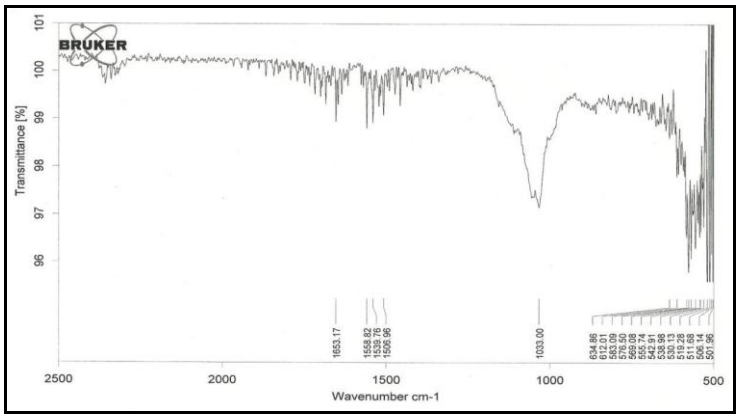


**Figure 4:** FTIR Spectrum of physical mixture of Famotidine sodium with Dicalcium phosphate and mannitol

**Table 1:** Standard band frequency of Famotidine Sodium

| Wave number in $cm^{-1}$ | Characteristic |
|---|---|
| 1900 | C=H |
| 1650 - 1580 | N-H bending |
| 1600 - 1400 | Aromatic C=C stretching |
| 1400 - 1000 | C-N bending |
| 1373 | C-F |
| 1049 | S=O |

The spectra obtained from the physical mixture show that all the principle peaks are at or around the requisite wave number of pure drug. Thus it may be inferred that there was no chemical interaction between drug and polymer and the purity and integrity of drug was maintained in the physical mixtures

## Evaluations

### Precompression parameters

The prepared Famotidine powder blend for tabletting was prepared by direct compression method. The prepared Famotidine powder blend were evaluated angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index as given on **Table.** The bulk densities of the granules were found to be in the range of 0.306 ± 0.03 to 0.384. ± 0.04 gm/mL, while the tapped densities were ranged between 0.313 ± 0.04 to 0.429 ± 0.05 gm/mL. The flow characteristics of the granules were assessed by determining their angle of repose and Carr's Index. The values of compressibility (5.74 ± 0.13 to 10.48 ± 0.20%) signify good flowability. The angle of repose of all formulation was less than 30 º (25.79 ± 0.24 to 29.52 ± 0.14) also indicate the good flowability of the prepared granules.

### Formulation studies

### Preparation of Famotidine sodium tablets

The Famotidine sodium sesquihydrate tablets were prepared by direct compression method A total of nine formulations (F1-F9) by using a rotary tablet compression machine (8 mm diameter, Riddhi 10 stn mini tablet press RDB4-10, Rimek, Ahmedabad, India). Compositions of the Famotidine sodium sesquihydrate tablets are shown in **Table.**

**Table 2:** Pre compression parameters of Famotidine sodium

| Formulation Code | Parameter | | | | |
|---|---|---|---|---|---|
| | Bulk density (gm/mL) | Tapped density (gm/mL)* | Carr's Index (%)* | Hausner's ratio* | Angle of repose (Θ)* |
| **F1** | 0.357±0.03 | 0.384±0.05 | 7.03±0.09 | 1.075±0.04 | 28.31±0.26 |
| **F2** | 0.312±0.04 | 0.335±0.02 | 6.86±0.15 | 1.073±0.05 | 27.20±0.14 |
| **F3** | 0.306±0.03 | 0.326±0.03 | 6.13±0.12 | 1.065±0.02 | 29.13±0.34 |
| **F4** | 0.312±0.03 | 0.334±0.06 | 6.58±0.14 | 1.070±0.06 | 26.13±0.26 |
| **F5** | 0.306±0.03 | 0.334±0.05 | 8.38±0.17 | 1.091±0.08 | 26.78±0.18 |
| **F6** | 0.384±0.04 | 0.429±0.05 | 10.48±0.20 | 1.117±0.07 | 25.79±0.24 |
| **F7** | 0.358±0.05 | 0.385±0.04 | 7.01±0.13 | 1.075±0.03 | 29.52±0.14 |
| **F8** | 0.286±0.05 | 0.313±0.04 | 8.62±0.07 | 1.094±0.03 | 26.95 ±0.15 |
| **F9** | 0.348±0.08 | 0.328±0.05 | 5.74±0.13 | 1.06±0.08 | 26.13±0.26 |

*****Mean ± SD n=3

### *In vitro* drug release studies of enteric coated tablets

The *in vitro* release of Famotidine sodium from the prepared tablets was studied in ph 1.2 for 2 h and in phosphate buffer pH 6.8 for 1 h. *In vitro* dissolution studies were performed using USP Type II rotating paddle dissolution apparatus (Electrolab TDT-08L, India) by using 1.2 N HCl and phosphate buffer (pH 6.8) as a dissolution medium. Formulation which shows most satisfactory result is C2F9, where drug release started after 2 hrs, and released maximum 99.72 by 3 hrs. Remaining were respectively,

released started maximum, CIF3-90 min and 96.42 in 3 hrs, C2F3-2 hrs and 94.59 in 195 min, E1F3- 90 min and 98.15 in 165 min, E2F3-105 min and 97.54 in 3 hrs, C1F9-90 min and 99.79 in 165 min, EIF9-90 min and 97.97 in 165 min, E2F9-2 hrs and 97.39 in 3 hrs. The cumulative percentage releases of Famotidine

sodium from the tablets were shown in **Table 12-19 and Figure 11-12.**

**Table 3:** *In vitro* drug release of Famotidine sodium (C1F3)

| Time (min) | Absorbance | Conc. (µg/mL) | Conc. in 900 mL (mg /mL) | Loss | Cumulative loss | Cumulative drug released | Cumulative percentage drug released * |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 45 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 60 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 75 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 90 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 105 | 0.024 | 0.6469 | 5.822 | 0 | 0 | 5.822 | 14.62±0.52 |
| 120 | 0.06 | 1.6172 | 14.555 | 0.0064 | 0.0064 | 14.561 | 36.58±0.40 |
| 135 | 0.091 | 2.3884 | 21.496 | 0.0161 | 0.0226 | 21.518 | 54.05±0.90 |
| 150 | 0.121 | 3.1758 | 28.582 | 0.0238 | 0.0465 | 28.629 | 71.91±0.39 |
| 165 | 0.142 | 3.7270 | 33.543 | 0.0317 | 0.0782 | 33.621 | 84.46±0.17 |
| 180 | 0.162 | 4.2519 | 38.267 | 0.0372 | 0.1155 | 38.383 | 96.42±0.40 |

*Mean±SD,*n*=3

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