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Assessment of the Compatibility of Famotidine with Selected Pharmaceutical Excipients

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Abstract

A drug–excipient compatibility study was performed to investigate the stability of Famotidine in combination with Polyvinylpyrrolidone (PVP K30), Polyethylene Glycol (PEG 6000), and Hydroxypropyl Methylcellulose (HPMC) under accelerated storage conditions. Physical mixtures of Famotidine and excipients were stored at 40°C/75% Relative Humidity (RH) and 50 ± 2°C for an appropriate duration (typically 30–90 days) and evaluated for possible physical and chemical interactions. The compatibility studies conducted under accelerated conditions of 40°C/75% RH and 50 ± 2°C demonstrated that Famotidine is compatible with PVP K30, PEG 6000, and HPMC. No significant physical changes, chemical degradation, or drug–excipient interactions were observed during storage. The characteristic thermal and spectroscopic properties of Famotidine were retained throughout the study period. Therefore, PVP K30, PEG 6000, and HPMC are considered suitable excipients for the formulation development of Famotidine, particularly in solid dispersions, tablets, and other solid dosage forms requiring enhanced solubility and stability.

Keywords: Famotidine, Drug-Excipient compatibility, FTIR, DSC

1. Introduction

Preformulation research is the necessary step that takes place between drug discovery and clinical development. In this vital phase of drug development, the physicochemical profile of the active pharmaceutical ingredient is determined and then used to plan the course of subsequent activities [1]. One important activity is to plan a schedule of crystallization conditions in order to maximize the likelihood of finding polymorphs or solvatomorphs, since different crystal forms will likely exhibit different solution characteristics that may be either harmful or helpful toward a particular formulation [2].

Another important activity is to select excipients that enable the drug substance to be administered with its intended efficacy. Preformulation can therefore be described as the step that deals with the acquisition of data on the drug compound and its excipients, which are then analyzed or processed into information and ultimately transformed into knowledge in the form of a recommended formulation [3].

Among various novel drug delivery approaches, buccal drug delivery has emerged as a promising alternative route for systemic and local drug administration [6]. The buccal mucosa, located inside the cheek cavity, offers a highly Excipients have traditionally been thought of as being inert; experience has shown that they can interact with a drug to affect its absorption and bioavailability. Indeed, some excipients are added to a formulation specifically to take advantage of the interaction when it affects the bioavailability of the drug [4].

Excipients have traditionally been classified according to the function they perform in a formulation, although many excipients perform multiple functions. Diluents allow the formulation of a practically sized tablet and can form a large proportion by weight of a formulated product. Disintegrants tend to swell when wetted and so are added in a formulation to facilitate the breakdown of the dosage form into granules and powder particles. The newer disintegrants, called super disintegrants, cause an extremely rapid breakup of a tablet owing to their ability to swell to many times their original size [5].

Binders provide cohesiveness to a powder mixture to ensure that a tablet formulation will be compressible and remain intact throughout its shelf-life yet will still disintegrate in vivo. Lubricants tend to be hydrophobic substances that act by coating particles to prevent adhesion of the tablet to the dies and punches of the tableting machine, to aid in ejection of the tablet from the die by reducing the interparticulate friction and improving flow of the powder

mixture[6]. Famotidine is a histamine H2-receptor antagonist widely used in the treatment of gastric and duodenal ulcers, gastroesophageal reflux disease (GERD), Zollinger–Ellison syndrome, and other acid-related gastrointestinal disorders. It acts by selectively inhibiting histamine H2 receptors located on gastric parietal cells, thereby reducing gastric acid secretion and promoting ulcer healing. Owing to its therapeutic importance, Famotidine is extensively formulated into various oral dosage forms [7].

Pharmaceutical excipients such as binders, diluents, disintegrants, lubricants, antioxidants, solvents, surfactants, and polymers are commonly used during the formulation development of Famotidine dosage forms [8].

Although these excipients are generally regarded as inert substances, they may interact with the active pharmaceutical ingredient during manufacturing or storage, thereby affecting the stability, efficacy, and safety of the formulation. Therefore, drug–excipient compatibility studies are considered an essential part of preformulation investigations [9].

A preliminary compatibility study of Famotidine with various pharmaceutical excipients, including antioxidants, binders, diluents, disintegrants, glidants, lubricants, pH modifiers, preservatives, solvents, surfactants, and sweetening agents, was carried out under laboratory conditions. Certain Famotidine–excipient mixtures exhibited changes in physical appearance, including discoloration, agglomeration, and alterations in spectroscopic characteristics upon storage. These changes suggested possible interactions between the drug and specific excipients [10].

Based on the preliminary observations, polyethylene glycol 6000 (PEG 6000), polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), and butylated hydroxyanisole (BHA) were selected for detailed compatibility studies. The drug–excipient blends were stored under various conditions, namely 25 ± 3°C, 50 ± 2°C, 2–8°C, and 40 ± 2°C/75 ± 5% relative humidity for a period of three months to evaluate their stability [11].

Differential Thermal Analysis (DTA) and Differential Scanning Calorimetry (DSC) were employed as screening techniques to detect changes in melting behavior, peak temperatures, and enthalpy values of the drug–excipient mixtures, which may indicate possible interactions. Furthermore, Fourier Transform Infrared Spectroscopy (FTIR) was used to investigate changes in the characteristic functional groups of Famotidine and to confirm the presence or absence of incompatibility [12].

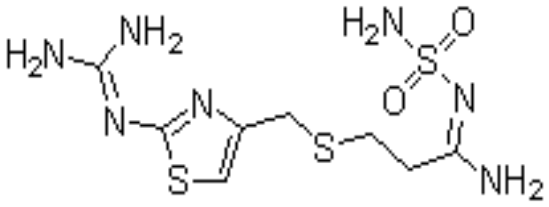


Fig. 1: Structure of Famotidine

2. Material and Methods

2.1 Material

Famotidine (F) was obtained as a gift sample from Torrent Research Labs (Ahmadabad). Polyethylene glycol 6000 (PEG) (Qualigens Fine Chemicals), Polyvinyl pyrrolidone (PVP) (Loba Chemie), Hydroxy propyl methyl cellulose (HPMC) (Samar chemicals), Acetonitrile, Methanol, Triethylamine (Qualigens Fine Chemicals) and all other chemicals used were of analytical grade.

2.2 Methods

The samples of Famotidine and its physical mixtures with different pharmaceutical excipients in a 1:1 ratio (20 mg each) were stored for a period of 3 months under accelerated conditions at 50 ± 2°C in a hot air oven (Hicon, New Delhi, India) and at 40 ± 2°C/75 ± 5% RH in a stability chamber (Thermolab Scientific Equipment, Thane, India).

The stored samples were periodically evaluated for any physical changes by visual inspection with respect to colour, appearance, texture, and solid characteristics. The changes were further confirmed using a Motic microscope (DMWB1-223 ASC, Canada). The pH of a 0.2% aqueous solution of Famotidine and its excipient blends was determined using a digital pH meter (Electronics, India).

Solutions containing 8 µg/mL of Famotidine and its blends with excipients were prepared and scanned using a UV–Visible spectrophotometer (JASCO, Tokyo, Japan) in the wavelength range of 200–400 nm. A calibration curve was constructed using freshly prepared Famotidine solutions, and quantitative analysis was performed at the λmax of Famotidine, approximately 265 nm. The fresh and stored samples were further analyzed using a Fourier Transform Infrared (FTIR) spectrophotometer (Shimadzu-8400S, Kyoto, Japan). Forty scans were recorded in transmission mode with a resolution of 4 cm^{-1} over the spectral range of 4000–400 cm^{-1} to identify possible changes in the characteristic functional groups and to detect any drug–excipient interactions.

Thermal analysis of pure Famotidine and its blends with selected excipients was carried out using Differential Thermal Analysis (DTA) (TA Instruments, USA) and Differential Scanning Calorimetry (DSC).

Approximately 5–10 mg of each sample was sealed in aluminium pans and scanned over a temperature range of 0–400°C at a heating rate of 10°C/min under a nitrogen atmosphere throughout the experiment. The thermal and spectroscopic data obtained from these studies were used to evaluate the compatibility of Famotidine with selected pharmaceutical excipients and to assess their influence on the stability of the drug under accelerated storage conditions.

3. Result and discussion

3.1 Physical changes

The physical changes were recorded visually by comparing the change in nature, color, solid characteristic of exposed F, MHCl and their blends F with equivalent number of excipients such as F-HPMC, F-PEG, F-PVP.

3.2 pH measurement

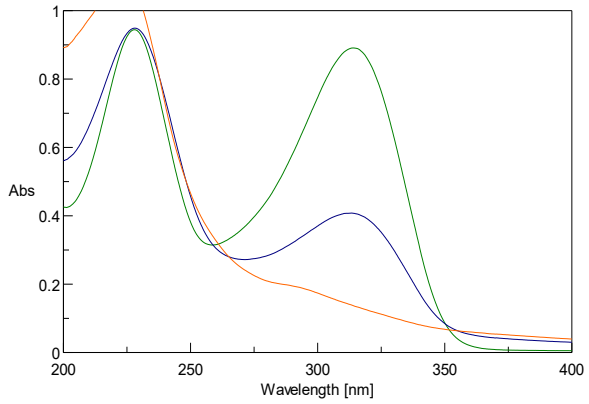
0.2% w/v solution of unexposed and exposed samples of F and their blends of F-BHT, F-HPMC, F-PEG, F-PVP, F-LAC, F-TAL (1:1) in water were prepared and the pH were determined using Digital pH meter (Naina Solariss, NIG-333

Table 1: Physical changes and pH determination of F and its blends with excipients stored at 50 ± 2 0C and 40 ± 2 0C/75 ± 5 % RH for 90 days

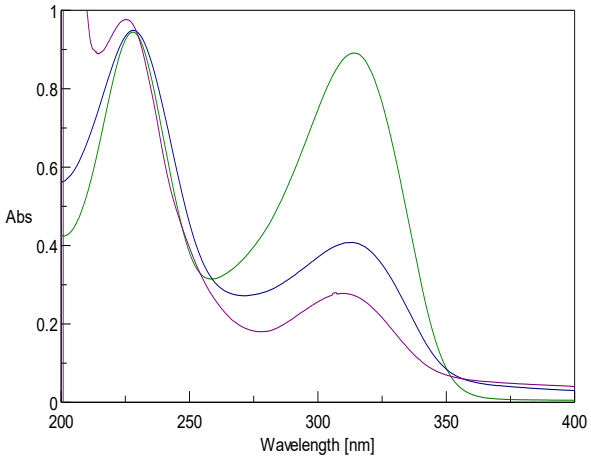
	Physical Changes		pH Analysis	
Drug: Excipient (1:1)	50 ± 2 ^{0}C	40 ± 2 ^{0}C/75 ± 5 % RH	50 ± 2 ^{0}C	40 ± 2 ^{0}C/ 75 ± 5 % RH
F-PVP	No change in colour	No change in colour	6.10	7.02
F-HPMC	Dark brown wet mass	Dark brown liquid	3.75	3.67
F-PEG	Dark brown liquid	Black brown liquid	4.35	4.25
MHCL-PEG	Dark brown wet mass	Dark brown wet mass	3.99	4.41
MHCL-PVP	Dark brown wet mass	Dark brown wet mass	3.73	3.43
MHCL-BHA	No change in colour	No change in colour	6.82	6.89
DRUG_F	Dark brown wet mass	Dark brown wet mass	6.4	7.00
DRUG_MHCL	Dark Yellow wet mass	Dark brown wet mass	6.98	7.12

UV spectrophotometry

The fresh and exposed samples of F alone and mixtures of F with equal amount of HPMC, PEG, PVP



(A)



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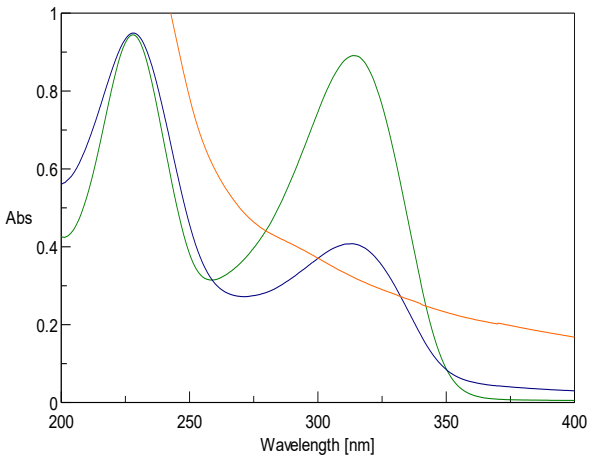
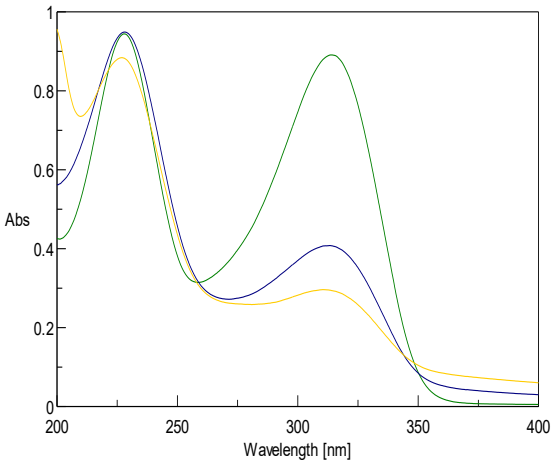
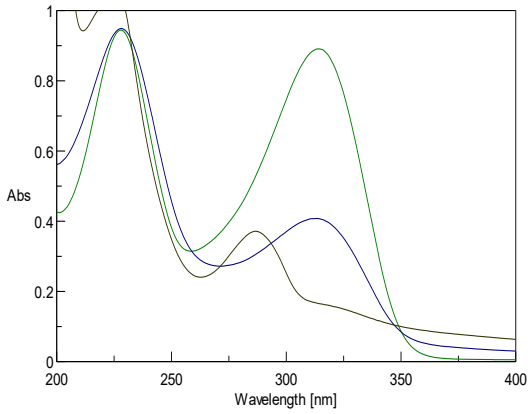


(C)

Figure 2: UV spectrum of Famotidine - its blends with A) HPMC, B) PEG, C) PVP stored at 50 ± 2 ^{0}C for 90 days.



(A)



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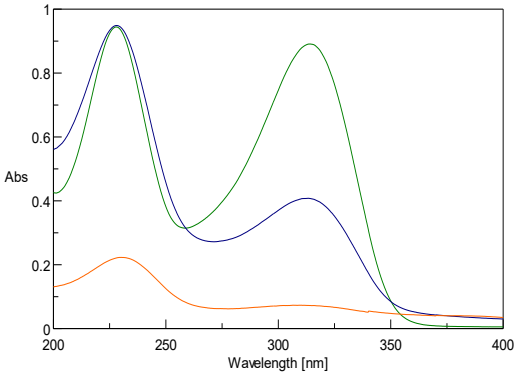

(C)

Figure 3: UV spectrum of Famotidine - its blends with A) HPMC, B) PEG, C) PVP stored at 50 ± 2 ^{0}C for 90 days.

3.3 High performance liquid chromatography

HPLC chromatograms were obtained of each suitably diluted solution of fresh and exposed F alone, mixture of famotidine with equal amount of HPMC, PEG, PVP (1:1), using JASCO HPLC system employing Crest Pak C18 T-5 column with MD-2010 Plus Multiwavelength detector. The fresh samples of F and its blend with excipient (1:1) were first analyzed and checked for the system suitability with the selected mobile phase at flow rate of 1 ml/min.

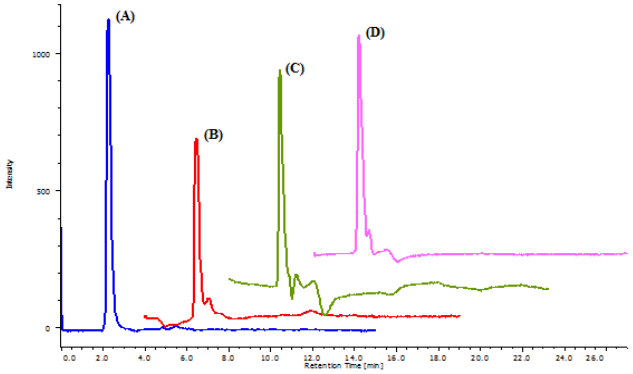

Figure 4: HPLC chromatograms of Famotidine and its blends with A) Famotidine alone, B) F-HPMC, C) F-PEG, D) F-PVP at 50 ± 2 ^{0}C.

3.4 Differential scanning calorimetric (DSC) analysis

Thermal analysis of fresh and exposed samples of F alone as well as their blends of F-HPMC, F-PEG, F-PVP (1:1) were conducted by Differential Scanning Colorimeter (Perkin Elemer-DSC-7). The samples of 6-15 mg were prepared in a covered 40 ml aluminium crucible with a hole in the lid to allow venting. The heating rate of 10 0C/min was employed. The sensors and the crucibles were kept under the flow of nitrogen during the experiment. The fresh and exposed samples were scanned in the temperature range of 50-600 0C.

Sample	Endothermic Peak Temperature (°C)	Peak Description	Observation
Famotidine (Pure Drug)	163.8	Sharp endothermic peak	Characteristic melting peak of Famotidine
PVP K30 (Pure Excipient)	85.4	Broad endothermic peak	Moisture loss/dehydration peak
PEG 6000 (Pure Excipient)	63.1	Sharp endothermic peak	Characteristic melting peak of PEG 6000
HPMC (Pure Excipient)	88.7	Broad endothermic peak	Moisture loss/dehydration peak
Famotidine + PVP K30 (1:1)	162.4	Drug melting peak retained with slight shift	No significant change in peak shape or intensity
Famotidine + PEG 6000 (1:1)	161.8	Drug melting peak retained with slight shift	Minor reduction in peak intensity due to dilution effect
Famotidine + HPMC (1:1)	163.0	Drug melting peak retained	No appearance of new peaks

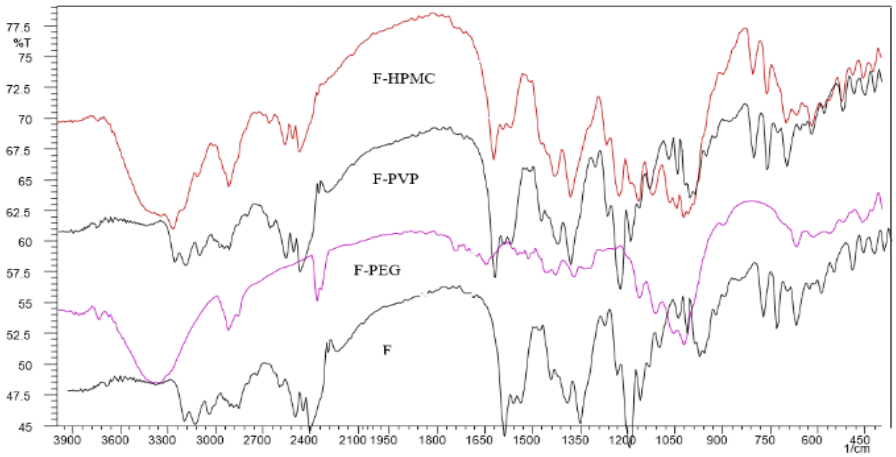

Figure 5: DSC Thermogram of Famotidine.

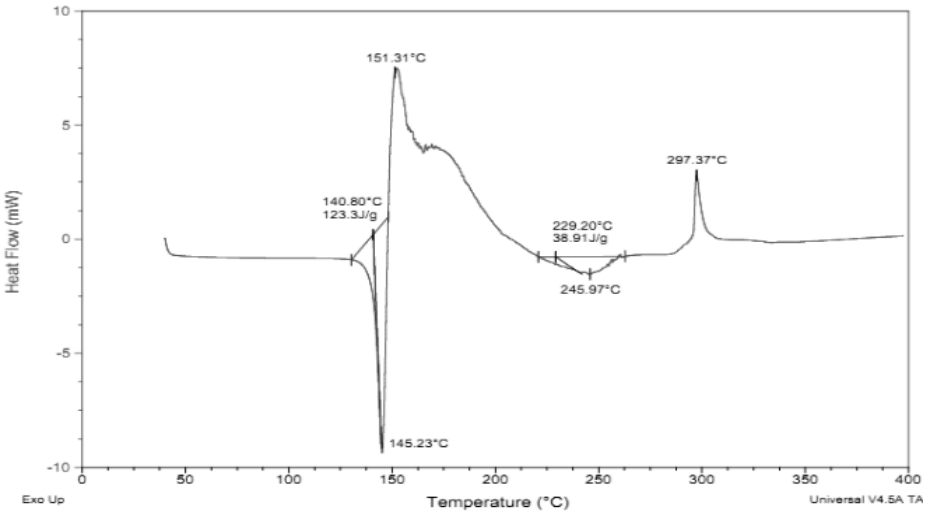

Figure 6: FTIR of F, F- PVP, F-PEG and F-HPMC

Other peaks observed at 3215.11 cm-1, 2947.03 cm-1, 2829.38 cm-1, 2673.15 cm-1, 2360.71 cm-1, 1353.94 cm-1, 1299.93 cm-1, 1240.14 cm-1, 1163.00 cm-1, 1010.63 cm-1, 939.27 cm-1, 804.26 cm-1, 757.97 cm-1 could not be assigned. Analysis of FTIR spectrum showed the entire characteristics peak as depicted in the above table when compared with the unexposed Famotidine. FTIR spectrum of unexposed F showed multiple bands around 3300 - 2400 cm-1 characteristics peaks of NH stretching and CH stretching.

These bands are broaden when exposed to 40 ± 2 0C/75 ± 5 % RH which may be associated with humidity condition. Comparison of FTIR spectrum of unexposed and exposed F showed slight changes in spectral pattern but retain peak at same wavenumber as in unexposed F which indicates some chemical changes in F following its storage at 40 ± 2 0C/75 ± 5 % RH for 90 days.

4. Conclusion

A drug–excipient compatibility study was performed to investigate the stability of Famotidine in combination with Polyvinylpyrrolidone (PVP K30), Polyethylene Glycol (PEG 6000), and Hydroxypropyl Methylcellulose (HPMC) under accelerated storage conditions. Physical mixtures of Famotidine and excipients were stored at 40°C/75% Relative Humidity (RH) and 50 ± 2°C for an appropriate duration (typically 30–90 days) and evaluated for possible physical and chemical interactions.

The compatibility studies conducted under accelerated conditions of 40°C/75% RH and 50 ± 2°C demonstrated that Famotidine is compatible with PVP K30, PEG 6000, and HPMC. No significant physical changes, chemical degradation, or drug–excipient interactions were observed during storage. The characteristic thermal and spectroscopic properties of Famotidine were retained throughout the study period.

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