JOURNAL OF RAMAN SPECTROSCOPY
J. Raman Spectrosc. 2007; **38**: 39–43
Published online 22 September 2006 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/jrs.1571

JRS

Thermal micro-Raman spectroscopic study of polymorphic transformation of famotidine under different compression pressures

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Received 7 April 2006; Accepted 17 June 2006

The objective of this study was to investigate the effect of pressure and/or temperature on the polymorphic transformation of famotidine from form B to form A by using a thermal confocal Raman microspectroscopy. A compact with a wide transparent zone in the center and an opaque zone surrounding it was prepared by compressing a conical mass of famotidine form B. Two unique Raman peaks at 2897 and 2920 cm^{-1} for famotidine forms B and A, respectively, were used as markers. The result indicates that the opaque zone in each compact was composed of famotidine from B, and it did not undergo any polymorphic transformation by preparing with higher compression pressure and/or by heating. The Raman peak intensity ratio of the 2920 cm^{-1} and 2897 cm^{-1} bands markedly increased starting from 120 °C for the transparent zone prepared by compressing with 19.61×10^4 kPa pressure, but increased from 100 °C with 49.03×10^4 kPa pressure, indicating the occurrence of thermally induced polymorphic transformation of famotidine from form B to form A. However, the transparent zone prepared by 9.81×10^4 kPa compression pressure retained the same Raman spectrum as that of the famotidine form B, revealing that the thermally induced polymorphic transformation of famotidine was dependent on the pressure applied. There was no polymorphic transformation of famotidine in the transparent zone when it was prepared by a higher compression pressure at a lower temperature or by a lower pressure at a higher temperature. The combined effect of compression and temperature was found to accelerate the polymorphic transformation from form B to form A in the transparent zone of famotidine.

KEYWORDS: famotidine; polymorphic transformation; compression pressure; temperature-dependent Raman spectra; thermal micro-Raman spectroscopy

INTRODUCTION

Compression is one of the important manufacturing processes in the preparation of tablets; it may not only affect the pharmaceutical properties of the tablets but also alter the crystalline form of the drug.[1,2] Tablet compression and the pressure applied have been reported to cause polymorphic transformation of many drugs such as acetaminophen, piroxicam, carbamazepine, phenylbutazone and chlorpropamide, to alter the physico-chemical properties of these drugs and influence the dissolution rate and bioavailability of their final drug products.[3–8] Thus, an abbreviated new drug application (ANDA) guidance for solid polymorphism in the pharmaceutical industry has been drafted by the FDA, in which the effect of drug polymorphism on the bioequivalence between the generic drug product and the innovator brand has been regulated.[9]

Famotidine is a third-generation histamine H_2-receptor antagonist with high potent inhibition for gastric and acid secretions in humans. Famotidine possessing two polymorphic forms, A and B, and was confirmed by the FDA as a generic drug.[3,10] Several investigations have focused on the characterization and crystal structure of famotidine polymorphs,[11–13] but only a few studies have reported the polymorphic forms of famotidine by the pressure effect.[14,15] However, Német *et al.*[15] have found that pressure alone did not cause the transformation of famotidine, but its transition could be triggered by temperature. This suggests that temperature also plays an important role in affecting the stability and phase transition in drugs.[16,17]

In our previous study,[18] we had reported that the grinding process not only decreased the crystallinity but

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JRS

also reduced the particle size of famotidine form B, resulting in easy induction of the polymorphic transformation of famotidine from form B to form A in the ground sample of famotidine. In addition, the mechanism of this polymorphic transformation of famotidine was found to be a zero-order kinetic model via grinding. Recently, a compact with a wide transparent zone near the center and an opaque zone surrounding it has been unexpectedly prepared by compressing a conical mass of famotidine form B (Scheme 1). It was interesting for us to explore how different crystal forms are in the transparent and the opaque zones within the compact. Raman spectroscopy has many advantages over other spectroscopic techniques, because it does not require preparation of the sample and is non-invasive and non-destructive.[19–21] It has already been applied in the identification of the polymorphs of pharmaceutical compounds,[22–24] but there is only a limited report by combining it with a thermal analyzer to determine the temperature-dependent Raman spectral change to characterize the thermally induced transformations of drug polymorphs.[25] Thus in this study, both the compression-induced and thermally induced polymorphic transformations of famotidine form B in the transparent and opaque zones of the compact were determined by thermal confocal Raman microspectroscopy.

EXPERIMENTAL

Materials

Famotidine was of pharmaceutical grade and purchased from China Chem. Synthesis Ind. Co., Ltd. (Shu-Lin, Taipei, Taiwan, ROC). The organic solvents were of analytical reagent grade (Nacalai Tesque, Kyoto, Japan).

Preparation of famotidine polymorphs

According to Hassan *et al.*'s report[12] and our previous study,[18] the polymorphic forms A and B of famotidine were prepared as follows:

(1) Form A: A certain amount of raw material of famotidine was suspended and dissolved in boiling acetonitrile and filtrated while hot. The filtrate was stored in a refrigerator for crystallization. The crystals were collected and dried under vacuum and stored in a silica gel desiccator at room temperature.
(2) Form B: Similar to the preparation method of form A, but acetonitrile was replaced by methanol. Here, the material of famotidine was proved to be form B.

Identification of famotidine polymorphs

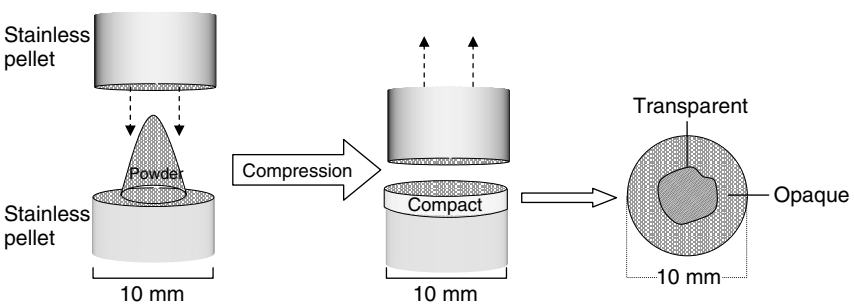
(1) Differential scanning calorimetry
Each polymorph of famotidine prepared was directly examined using a differential scanning calorimeter (DSC; DSC-910, TA Instruments Inc., New Castle, DE, USA) at a heating rate of 10 °C/min with an open pan system in a stream of N_2 gas from 30 to 200 °C.
(2) Confocal Raman microspectroscopy
A powder of each famotidine polymorph was placed on a glass slide and then the spectra recorded by a confocal micro-Raman spectrometer (Ventuno, Jasco Co., Tokyo, Japan) equipped with a 30 mW green (532 nm) solid-state laser as an excitation source.[26,27]

Preparation of compacts by compressing a conical mass of famotidine form B

Forty milligrams of famotidine form B powder was placed at the center of a stainless pellet and formed into a conical shape with a micro spatula. Then it was transferred to a KBr pellet die (diameter 10 mm) and directly compressed with an IR spectrophotometric hydraulic press (Riken Seiki Co., Tokyo, Japan) under different pressures (9.81×10^4, 19.61×10^4 or 49.03×10^4 kPa) for 5 min. The pressure was then removed quickly, resulting in a compact with a wide transparent zone near the center but an opaque zone surrounding it. (Scheme 1). In order to determine the polymorphic change of famotidine in each zone, several compacts were prepared.

Thermal Raman microspectroscopic study

Each compact was directly placed onto a temperature controlled microscope cell (THMS 600, Linkam Scientific Instruments Ltd, Surrey, UK). This hot–cold cell was then set in a confocal micro-Raman spectrometer. The laser beam was directly focused on each transparent or opaque zone by an Olympus long- working-length objective. The cell temperature was controlled by a temperature controller (TMS 94, Linkam Scientific Instruments Ltd, Surrey, UK).



Scheme 1. Schematic diagram for the preparation of the compacts with transparent and opaque zones.

DOI: 10.1002/jrs

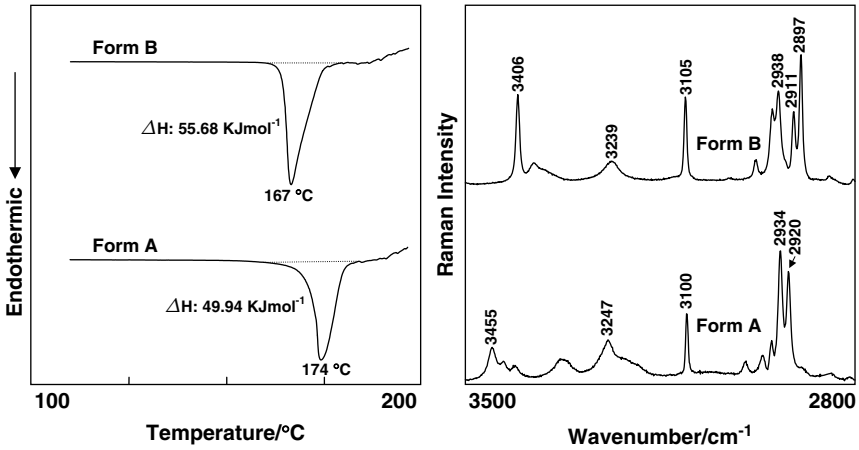


Figure 1. The DSC thermograms and Raman spectra of polymorphic forms (A) and (B) of famotidine.

The heating rate of the controller assembly was maintained at 10 °C/min under ambient conditions. At each prescribed temperature, the sample was isothermally maintained for 5 min before recording its Raman spectra.

RESULTS AND DISCUSSION

Identification of famotidine polymorphs

Figure 1 shows the DSC thermograms and Raman spectra of forms A and B of famotidine. Two endothermic peaks at 174 °C with an enthalpy of 49.94 KJ mol^{-1} for form A and at 167 °C with an enthalpy of 55.68 KJ mol^{-1} for form B of famotidine, respectively, were observed in the DSC thermograms. Both the data were consistent with the earlier reports,[10–14] suggesting that the preparation method for famotidine form A or B was proper. The raw material of famotidine used in this study proved to be of form B. The characteristic Raman bands for famotidine form B were 3406 and 3239 (NH stretching), 3105 (CH stretching of the heterocyclic ring), 2938 and 2911 (CH asymmetric stretching) and 2897 (CH symmetric stretching) cm^{-1}, while the Raman peaks for famotidine form A were 3455 and 3247 (NH stretching), 3100 (CH stretching of heterocyclic ring), 2934 and 2920 (CH asymmetric stretching) cm^{-1}.[28] Since the unique Raman bands at 3455 and 2920 cm^{-1} for form A and at 3406 and 2897 cm^{-1} for form B did not interfere with each other, they seem to actas markers to easily differentiate the two forms from the Raman spectra.

Thermally and compression-induced polymorphic transformation of famotidine

It is well known that the polymorphic conversion of a drug compound can be easily induced by stress, heat and solvent.[16,17] Mechanical compression is one of the important ways of applying stress and it is able to induce the polymorphic transformation of drugs.[1,2,4–8] In the present study, however, the mechanical compression did not influence the polymorphic transformation of famotidine since the Raman spectra of original famotidine form B powder and the compact before heat treatment were the same. Figure 2 shows the temperature-dependent Raman

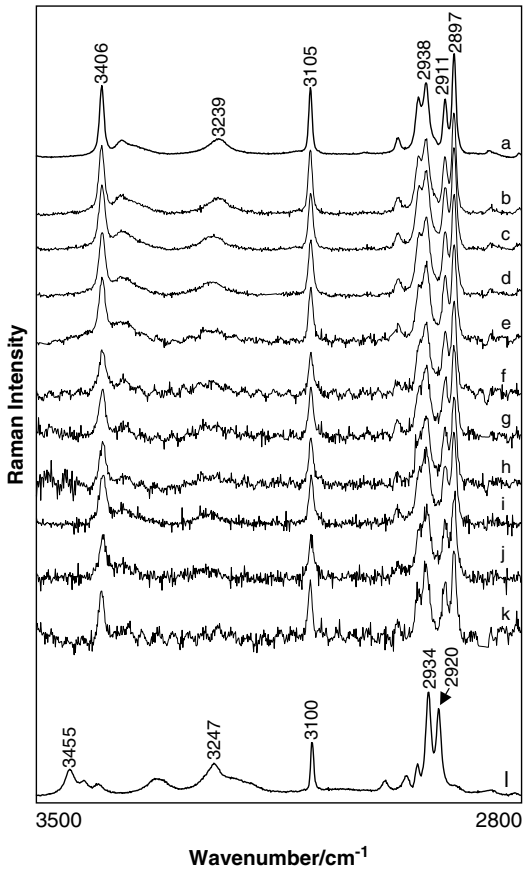


Figure 2. The temperature-dependent Raman spectral changes of the opaque zone in the compact prepared by compressing with 49.03×10^4 kPa pressure. Key: Different prescribed temperatures (°C): (b), 30; (c), 90; (d), 100; (e), 110; (f), 120; (g), 130; (h), 140; (i), 150; (j), 155; (a), form B; l, form A; (k), (j) sample cooled to 30 °C.

DOI: 10.1002/jrs

JRS

spectral changes of the opaque zone in the compact prepared by compressing with 49.03×10^4 kPa pressure. It is evident that Raman spectra from the opaque zone even by heating to 155 °C were the same as the spectrum of original famotidine form B. Although we do not show it here, the opaque zone in the other compacts prepared by compressing with 9.81×10^4 or 19.61×10^4 kPa pressure also revealed the same data as that of the compact prepared by compressing with 49.03×10^4 kPa pressure. This strongly indicates that the opaque zone consisted only of famotidine form B and was independent of the thermal and compression effect. There was no evidence for the thermally induced polymorphic transformation of famotidine form B even under the higher compression pressure of 49.03×10^4 kPa. This clearly demonstrates that a higher pressure alone does not induce the polymorphic transformation of famotidine from form B to form A, which was consistent with the result of Német *et al*.[15]

On the other hand, a temperature-dependent Raman spectral change in the Raman spectra was clearly found for the transparent zone in the compact prepared by using a compression pressure $>19.61 \times 10^4$ kPa, as shown in Fig. 3. Apparently, the Raman spectra of the transparent zone in the compact prepared by compressing with 9.81×10^4 kPa pressure (Fig. 3(A)) still exhibited the same Raman spectrum as that of famotidine form B and were independent of heating temperature. Once the compression pressure was larger than 19.61×10^4 kPa and the temperature was higher than 100 °C, however, the Raman spectral bands underwent a dramatic change. Obviously, the Raman peak at 2920 cm^{-1} assigned to the famotidine form A gradually appeared for the transparent zones in the compact prepared by compressing with both 19.61×10^4 or 49.03×10^4 kPa pressure with the increase of temperature (Fig. 3(B) and (C)). By increasing the temperature, the Raman peak intensity at 2920 cm^{-1} further increased accompanied by the reduction of the Raman peak at 2897 cm^{-1}. The Raman spectrum of the sample heated to 155 °C after cooling to 30 °C showed a Raman spectrum similar to that of famotidine form A (Fig. 3(B) or (C-(k)). This strongly suggests that combined mechanical compression and temperature could accelerate the polymorphic transformation of famotidine from form B to form A in the transparent zone.

Figure 4 reveals the thermally induced polymorphic transformation from form B to form A for the transparent zones in the compact prepared by different pressures. Two unique Raman peaks at 2897 and 2920 cm^{-1} assigned to the symmetric and asymmetric CH stretching vibrations for famotidine forms B and A were used as fingerprint markers to differentiate polymorphic forms A and B. It clearly shows that the Raman peak intensity ratio of the 2920 cm^{-1} and 2897 cm^{-1} peaks almost maintained a constant value for the transparent zone prepared by compressing with 9.81×10^4 kPa pressure, indicating there

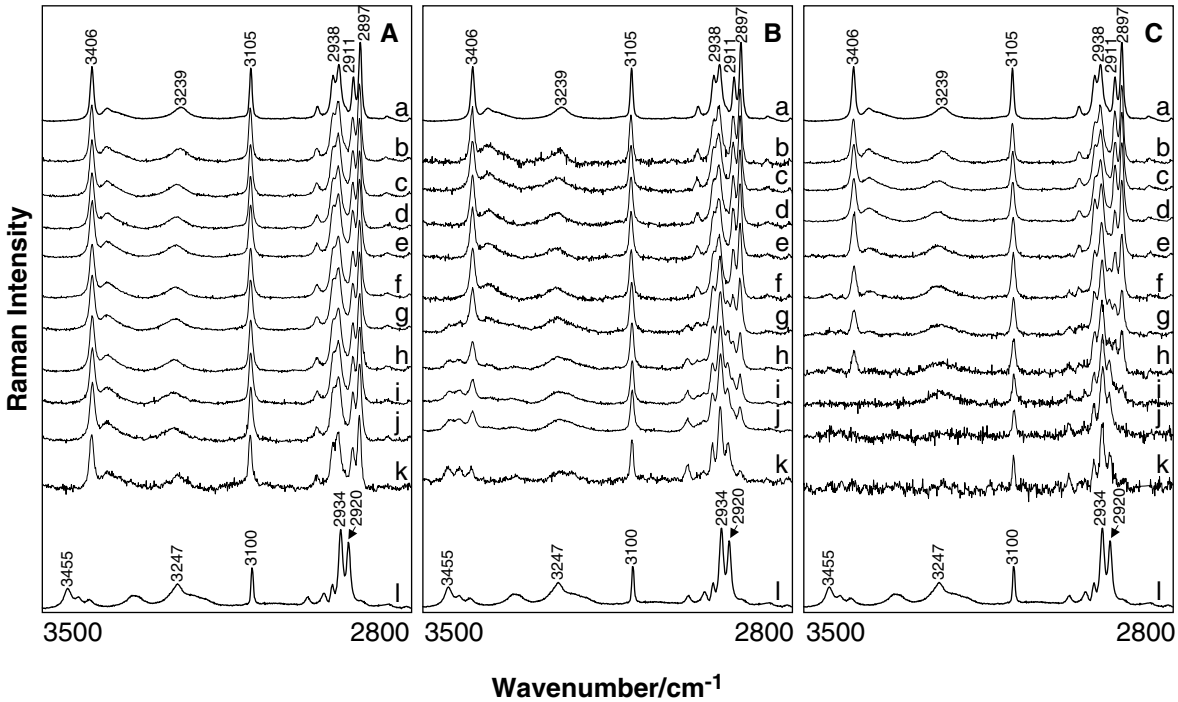


Figure 3. The temperature-dependent Raman spectral changes of the transparent zones in the compact prepared by using different compression pressures. Key: Different compression pressures (kPa): (A), 9.81×10^4; (B), 19.61×10^4; (C), 49.03×10^4. Different prescribed temperatures (°C): (b), 30; (c), 90; (d), 100; (e), 110; (f), 120; (g), 130; (h), 140; (i), 150; (j), 155; (a), form B; l, form A; (k), (j) sample cooled to 30 °C.

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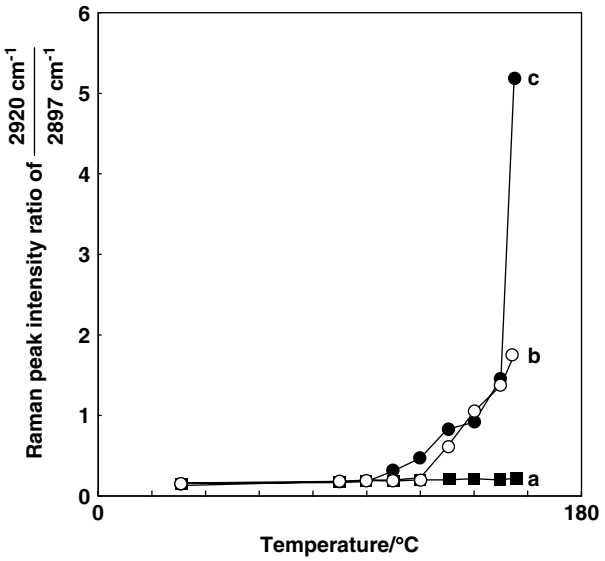

Figure 4. The thermally induced polymorphic transformation from form B to form A of famotidine in the transparent zones of the compact prepared by different compression pressures. Key: Different compression pressures (kPa): (a), 9.81×10^4; (b), 19.61×10^4; (c), 49.03×10^4.

was no polymorphic transformation. However, the Raman peak intensity ratio of the 2920 cm^{-1} and 2897 cm^{-1} peaks gradually increased its value starting from 120 °C or 100 °C for the transparent zone prepared by compressing with 19.61×10^4 or 49.03×10^4 kPa pressure, respectively. But the profile sharply and linearly grew from 150 °C for the transparent zone prepared by compressing with 49.03×10^4 kPa pressure, suggesting that the temperature of 150 °C was the critical point to accelerate the polymorphic conversion of famotidine from form B to form A. There was less influence of temperature from 30 to 100 °C, although the transparent zone was prepared by a higher compression pressure of 49.03×10^4 kPa. This demonstrates that the polymorphic transformation of famotidine from form B to form A was not influenced by higher pressures alone. The present study also indicates that the higher pressure seems to induce the polymorphic transformation of famotidine from form B to form A earlier than with a lower pressure.

CONCLUSIONS

A compact with a wide transparent zone near the center and an opaque zone surrounding it was prepared by compressing a conical powder mass of famotidine form B. The opaque zone in the compact consisted only of the famotidine from B and maintained this polymorph irrespective of whether applying a higher mechanical compression and/or heat treatment. However, the combined effect of mechanical compression and temperature could accelerate the polymorphic transformation of famotidine from form B to form A in the transparent zone. In addition, this thermally induced polymorphic transformation of famotidine from form B to form A was also dependent on the pressure applied.

Acknowledgements

This work was supported by the National Science Council, Taipei, Taiwan, Republic of China (NSC-95-2320-B-075-002-MY2).

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