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# Differential Scanning Calorimetry with Curve-Fitting Program Used to Quantitatively Analyze the Polymorphic Transformation of Famotidine in the Compressed Compact

**Wen-Ting Cheng**
*Department of Medical Research & Education, Taipei Veterans General Hospital, Taipei, and Department of Applied Chemistry, National ChiaYi University, ChiaYi, Taiwan, Taiwan, Republic of China*

**Shan-Yang Lin**
*Department of Medical Research & Education, Taipei Veterans General Hospital, Taipei, Republic of China*

**Shun-Li Wang**
*Department of Applied Chemistry, National ChiaYi University, ChiaYi, Taiwan, Taiwan, Republic of China*

**Differential scanning calorimetry (DSC) combined with a curve-fitting program was utilized to quantitatively determine the polymorphic composition of famotidine in the compacts prepared by different compression treatments. Two types of famotidine compacts (compact I or II) were prepared by compressing a conical shape or a flattened shape of powder bed of famotidine form B. The compact I was constructed by a transparent region in the center with an opaque region surrounded outside, but the compact II was formed by a whole opaque region only. A drilled disc sample was prepared and then directly determined by DSC analysis. The Raman spectral results clearly indicate that all the compacts whether in any region before DSC determination were only of famotidine form B and independent of compression pressure applied. Under DSC determination, however, the curve-fitted relative compositions of form B in the drilled disc I sample were gradually reduced to 23–24% with the increase of compression pressure, whereas the curve-fitted relative composition of form A was slowly increased up to 76–77%. A transitional phase of famotidine form B (form B*) in the transparent region of the compact I after applying >150 kg/cm$^2$ of compression pressure was easily detected, and then transformed to famotidine form A under DSC heating process. But this transitional phase and polymorphic transformation of famotidine could not be detected by other spectroscopic methods. This suggests that the DSC heating system was a preferred method not only to quantitatively analyze the polymorphic transformation of famotidine but also to find a newly transitional phase of famotidine in the compressed compact.**

**Keywords** famotidine; compression pressure; compact; drilled disc; DSC; Raman; polymorphic transformation; curve-fitting

Address correspondence to Shan-Yang Lin, Department of Medical Research and Education, Taipei Veterans General Hospital, Taipei, Taiwan, Republic of China. E-mail: sylin@vghtpe.gov.tw

## INTRODUCTION

Of all pharmaceutical preparations, tablet is one of the most commonly used oral solid dosage forms to deliver the drug for therapy. The compaction is an important process in pharmaceutical tableting, because it can markedly influence the dissolution rate, stability, and the bioavailability of the drug formulation (Morris, Griesser, Eckhardt, & Stowell, 2001; Sanchez-Castillo, Anwar, & Heyes, 2003; Singhal & Curatolo, 2004). In the compaction process of a tablet, the pressure applied to the tablet die is not homogeneous and causes the uneven and heterogeneous pressure distributed in compacted tablets (Byrn, Pfeiffer, Ganey, Hoiberg, & Poochikian, 1995; Koivisto, Heinanen, Tanninen, & Lehto, 2006). This phenomenon not only seems to affect the physicochemical properties of drug in the outer and inner layers of the tablet, but also has a significant influence on drug dissolution from dosage forms. The compression pressure may alter the crystal form of drug leading to a polymorphic transformation and a change of the tablet properties (Byrn, Pfeiffer, Ganey, Hoiberg, & Poochikian, 1995; Koivisto, Heinanen, Tanninen, & Lehto, 2006; Vippagunta, Brittain, & Grant, 2001). The transformational extent of caffeine was found to be dependent on the pressure zone of the tablet after compression (Brittain, 2002). Thus the compression-induced polymorphic transformation of solid dosage form should be paid more attention to ensure product quality and meet regulatory requirements.

Famotidine (Figure 1) belongs to one of the third-generation of the histamine blocker families to prevent the release of acid into the stomach. It is always used to treat stomach and duodenal ulcers, reflux of stomach acid into the esophagus, and Zollinger–Ellison syndrome (Ray, Secrest, Ch'ien, & Corey, 2002). Famotidine has two polymorphs, A and B, in which form A is more stable than form B (Ferenczy, Párkányi, Ángyán, Kálmán,

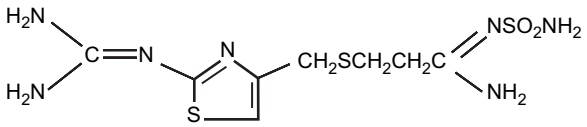


FIGURE 1. Chemical structure of famotidine.

& Hegedüs, 2000; Hassan, Salem, Sueliman, & Najib, 1997; Hegedus et al., 1989). However, the active pharmaceutical ingredient (API) of famotidine commercialized in the market belongs to form B. Because the metastable phase of drug after compression may be transformed to a stable one (Byrn, Pfeiffer, Ganey, Hoiberg, & Poochikian, 1995; Koivisto, Heinanen, Tanninen, & Lehto, 2006; Vippagunta, Brittain, & Grant, 2001), the compaction in the pharmaceutical processing seems to alter the crystal form of this metastable famotidine and influence the physicochemical and pharmaceutical properties of solid dosage form. There are a few studies that were focused on the characterization and crystal structure of famotidine polymorphs (Ferenczy, Párkányi, Ángyán, Kálmán, & Hegedüs, 2000; Hassan, Salem, Sueliman, & Najib, 1997; Hegedüs et al., 1989); only few investigations have reported the pressure effect on the polymorphic forms of famotidine (Német, Hegedűs, Szántay, Sztatisz, & Pokol, 2005; Roux, Dávalos, & Jiménez, 2002). However, the quantitative changes in polymorphic transformation of famotidine after compression are unclear.

Our previous study has indicated that the grinding process could easily induce the polymorphic transformation of famotidine from metastable form B to stable form A (Lin, Cheng, & Wang, 2006). In order to explore the effect of compression pressure on polymorphic conversion of famotidine, different compaction methods had been attempted. In our preliminary study, a compact with a transparent region in the center but an opaque region surrounded outside was unexpectedly prepared by compressing a conical shape of famotidine form B powder. Whereas a whole opaque compact was given by compressing a flattened shape of famotidine form B powder, as shown in Scheme 1. Based on these preliminary data, we became interested in investigating the polymorphic forms of famotidine in the transparent and opaque samples. The polymorphic transformation and its relative compositions of famotidine forms A and B in the transparent and opaque samples after different compression treatments were quantitatively determined by using a differential scanning calorimetry (DSC) combined with a curve-fitting program.

## MATERIALS

Famotidine was of pharmaceutical grade and purchased from China Chemical Synthesis Industrial Co., Ltd. (moisture content <0.01%, Lot No. 90113902, Shu-Lin, Taipei, Taiwan, ROC). The organic solvents were of analytical reagent grade (Nacalai Tesque, Kyoto, Japan).

## METHODS

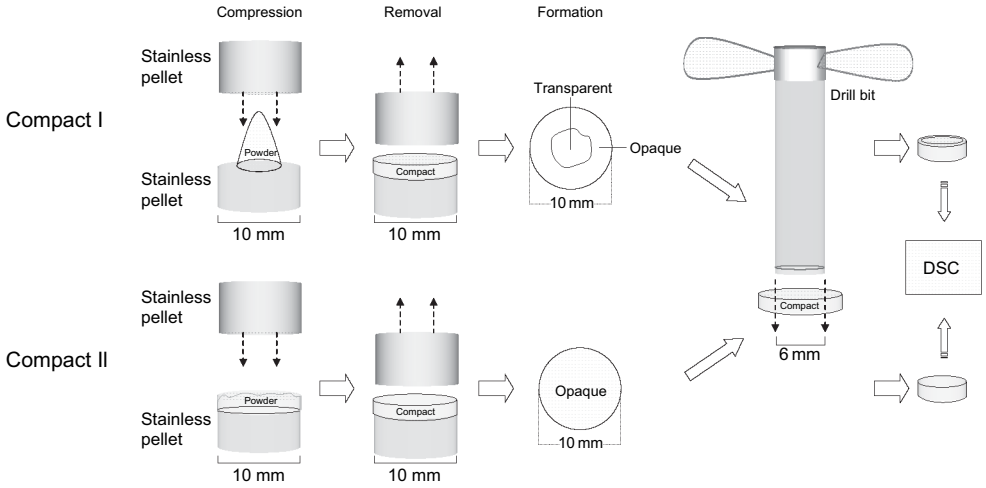
### Preparation and Identification of Famotidine Polymorphs

According to Hassan's report and our previous study (Hassan, Salem, Sueliman, & Najib, 1997; Lin, Cheng, & Wang, 2006), polymorphic forms A and B of famotidine were recrystallized from acetonitrile and methanol, respectively. Here, the raw material of famotidine used was proved to be a form B.

### Preparation of Famotidine Form B Compact

*Compact I Prepared by Compressing a Conical Shape of Famotidine Form B Powder*

A certain amount (40 mg) of famotidine form B powder was previously filled into an Eppendorf tube (0.5 mL) with tapping




SCHEME 1. Schematic diagram for preparation of compacts I and II, as well as their drilled disc samples.

and then upend on the center of KBr pellet die (diameter 10 mm) to form a conical shape and directly compressed with an IR spectrophotometric hydraulic press. The conical shape of famotidine powder bed was 9 mm in height and 5.2 mm in diameter. The angle of repose was about 72°. Two variables were determined: (a) under a constant compression pressure of 400 kg/cm$^2$ for different compression times (0.25–5.0 min); (b) under different compression pressures from 100 to 500 kg/cm$^2$ for 5 min, respectively. After quickly removing the compression pressure, a compact with a transparent region in the center but an opaque region surrounded outside was observed. In order to directly determine the polymorphic conversion in the compact, a drilled disc sample was prepared by using a drill bit (diameter 6 mm) through the center of each compact. Different proportions of transparent and opaque regions were included in the drilled disc I samples. The higher the compression pressure applied, the more the proportion of transparent region obtained.

*Compact II Prepared by Compressing a Flat Shape of Famotidine Form B Powder*

The same amount of famotidine form B powder was directly flattened on the KBr pellet die (diameter 10 mm) and directly compressed with an IR spectrophotometric hydraulic press. The rest of procedures were the same as the preparation method of compact I sample. However, an opaque compact in whole area was obtained.

### Studies of Each Region in the Compact by Raman Microspectroscopy and Differential Scanning Calorimetry

The Raman spectra of both transparent and opaque regions in the drilled disc I samples or the opaque regions in the drilled disc II samples were, respectively, determined by using a dispersive micro-Raman spectrophotometer (Ventuno, Jasco Co., Tokyo, Japan) equipped with a 30-mW green (532-nm) solid-state laser as standard. The pixel resolution was 1.3 cm$^{-1}$ (Chen, Cheng, Li, Yang, & Lin, 2005; Lin, Chen, Cheng, Ho, C. T. & Wang, 2007).

In addition, each drilled disc sample was also directly placed into a DSC sample pan (diameter 6.5 mm) without breaking and examined by means of 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. The DSC cell was calibrated with indium (Hu, Wang, Chen, & Lin, 2002; Lin, Cheng, & Wang, 2006).

All samples for different determinations were analyzed in triplicate.

### Data Analysis of DSC Thermograms

The relative compositions of polymorphic forms A and B of famotidine in each drilled disc sample were estimated quantitatively from DSC thermograms by a GRAMS curve-fitting program with a Gaussian–Lorenzian function (Hu, Wang, Chen, & Lin, 2002). The best curve-fitting was performed by iterative fits toward a minimum standard error. The relative proportion of a component was computed to be the fractional area of the corresponding peak divided by the sum of areas of all the peaks.

## RESULTS AND DISCUSSION

### Identification of Famotidine Polymorphs

Famotidine with two polymorphs A and B has been reported to be a monotropic behavior, in which form A belonged to the thermodynamically stable modification but form B was the metastable modification (Ferenczy, Párkányi, Ángyán, Kálmán, & Hegedüs, 2000; Hassan, Salem, Sueliman, & Najib, 1997; Hegedus et al., 1989). Figure 2 shows the DSC thermograms and Raman spectra of famotidine forms B and A. Two endothermic peaks, at 167°C with an enthalpy of 165 J/g for famotidine form B and at 174°C with an enthalpy of 148 J/g for famotidine form A, were observed. Both data were consistent with the other reports (Ferenczy, Párkányi, Ángyán, Kálmán, & Hegedüs, 2000; Hassan, Salem, Sueliman, & Najib, 1997; Hegedus et al., 1989). The commercial famotidine used in this

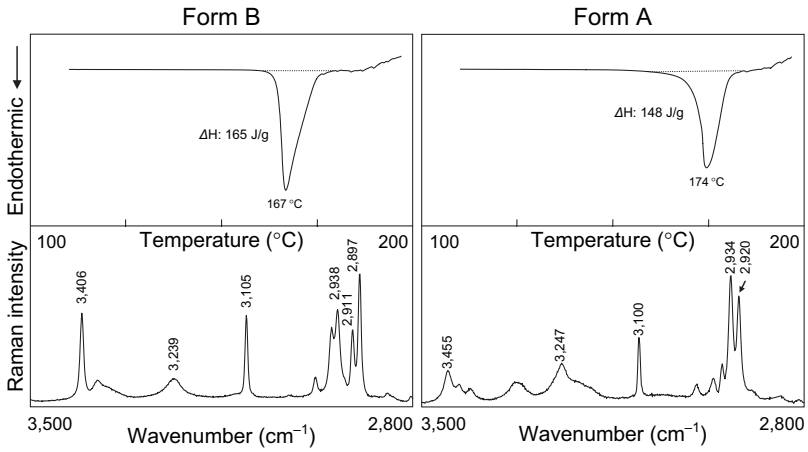



FIGURE 2. DSC thermograms and Raman spectra of polymorphic forms B and A of famotidine.

study was proved to be a form B. The characteristic Raman bands for famotidine form B were 3,406 and 3,239 (NH stretching), 3,105 (CH stretching of the heterocyclic ring), 2,938 and 2,911 (CH asymmetric stretching), and 2,897 (CH symmetric stretching) $cm^{-1}$, whereas the Raman peaks for famotidine form A were 3,455 and 3,247 (NH stretching), 3,100 (CH stretching of heterocyclic ring), and 2,934 and 2,920 (CH asymmetric stretching) $cm^{-1}$. Because the unique Raman bands at 3,455 and 2,920 $cm^{-1}$ for form A as well as at 3,406 and 2,897 $cm^{-1}$ for form B did not interfere with each other, they are used to differentiate these two forms from the Raman spectra.

## Effect of Compression Time on the Polymorphic Transformation of Famotidine in the Compact Under Thermal Treatment

It is well known the compression pressure is one of the important stresses and can cause the polymorphic transformation of drug (Chawla & Bansal, 2004; Okumura, Ishida, Takayama, & Otsuka, 2006). In this study, a transparent region appeared in the center of compact I was obtained by compressing a conical mass of famotidine form B powder. This might be because the conical shape of powder bed of famotidine form B was suffered higher compression pressure in the center than that of the flat-shape and formed a tight compact. The crystalline form B of famotidine in the central part after compression might convert to glass state and resulted in the formation of transparent region in the tight compact (Brittain, 2002; Koivisto, Heinanen, Tanninen, & Lehto, 2006; Sanchez-Castillo, Anwar, & Heyes, 2003; Shekar & Rajan, 2001;Vippagunta, Brittain, & Grant, 2001). The Raman spectra of intact famotidine form B powder, both transparent and opaque regions in the drilled disc I samples, as well as the whole drilled disc II samples are given in Figure 3. Obviously, all the Raman spectra for each region were the same as that of the Raman spectrum of intact famotidine form B. This suggests that even the higher compression pressure also failed to cause the polymorphic conversion of famotidine, which was also consistent with the result of Német, Hegedüs, Szántay, Sztatisz, & Pokol (2005).

The DSC thermograms of the drilled disc I samples prepared by using 400 $kg/cm^2$ pressure at different compression times are displayed in Figure 4, in which only two endothermic peaks at 166 and 173°C were observed. Although the data are shown here, the DSC curves of the drilled disc II samples still revealed the same result as the DSC curve of famotidine form B at 167°C, suggesting that there was no polymorphic transformation occurred in the compact II. Because the drilled disc I samples whether in the transparent or opaque region before thermal treatment still exhibited a Raman spectrum similar to that of the Raman spectrum of famotidine form B (shown in Figure 3), these two endothermic peaks in Figure 4 might be attributed to the famotidine form B being present and the famotidine form A newly formed during the DSC determination. Here, we propose that the opaque region in the drilled disc I sample was only of famotidine form B but a transition state of famotidine form B (defined as B*) might be formed in the transparent

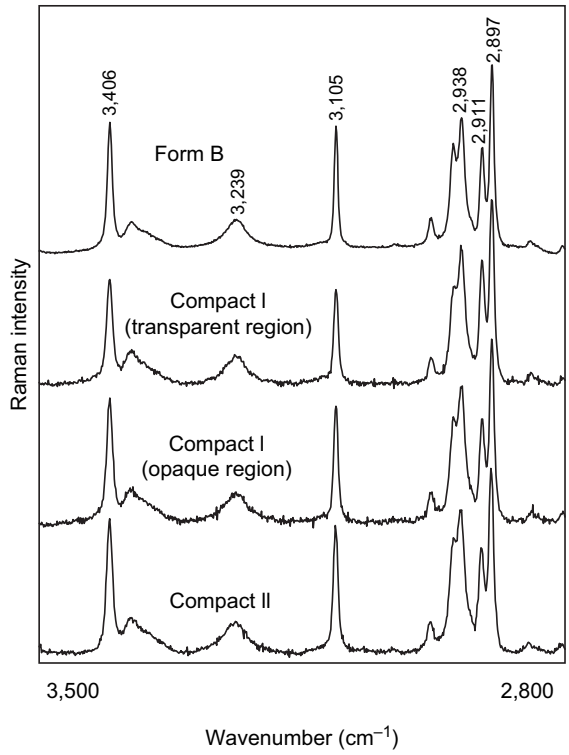



FIGURE 3. Raman spectra of the intact famotidine form B powder, both transparent and opaque regions in the drilled disc I sample, as well as the drilled disc II sample.

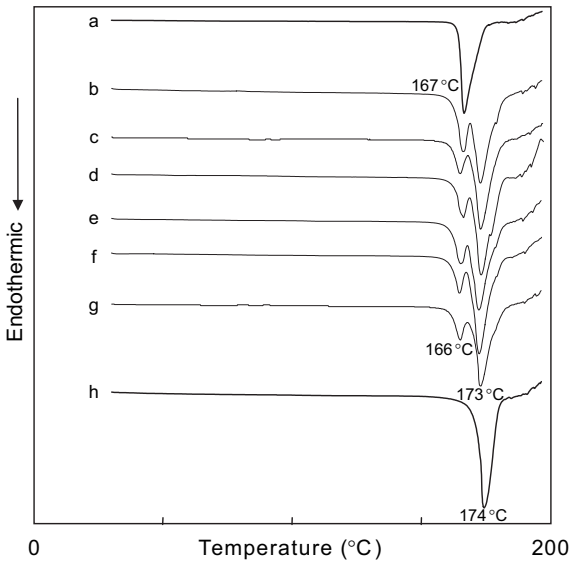



FIGURE 4. DSC thermograms of the drilled disc I samples prepared by using 400 $kg/cm^2$ pressure at different compression times. Compression times (min): b, 0.25; c, 0.5; d, 0.75; e, 1.0; f, 3.0; g, 5.0; a, intact famotidine form B; h, intact famotidine form A.

region of the drilled disc I sample. During DSC determination, the intact famotidine form B present in the sample still showed an endothermic peak at 167°C as shown in Figure 2 but the famotidine form B* was transformed to 173°C of form A. All the DSC curves in Figure 4 exhibited a similar pattern except for the shorter compression time, implying that the compression time was less effective in the DSC curve under the higher compression pressure.

Figure 5 shows the curve-fitted profiles of the famotidine forms A and B from DSC curve in Figure 4. It is evident that only two endothermic peaks were contributed to the DSC curve after curve-fitting. The best curve-fitted results for the famotidine forms A and B with respect to the compression times are shown in Figure 6A. Obviously, about 70–80% of form A transformed and 20–30% of form B present were obtained after different compression times. The relative polymorphic compositions of famotidine forms A and B were almost constant beyond compression time for 1 min, suggesting that they were independent of the compression time when the compression pressure was maintained at 400 kg/cm$^2$. From these results, we presume that before DSC determination, about 20–30% of form B and 70–80% of form B* of famotidine were, respectively, contained in the opaque and transparent regions of the drilled disc I samples prepared by using 400 kg/cm$^2$ pressure at different compression times.

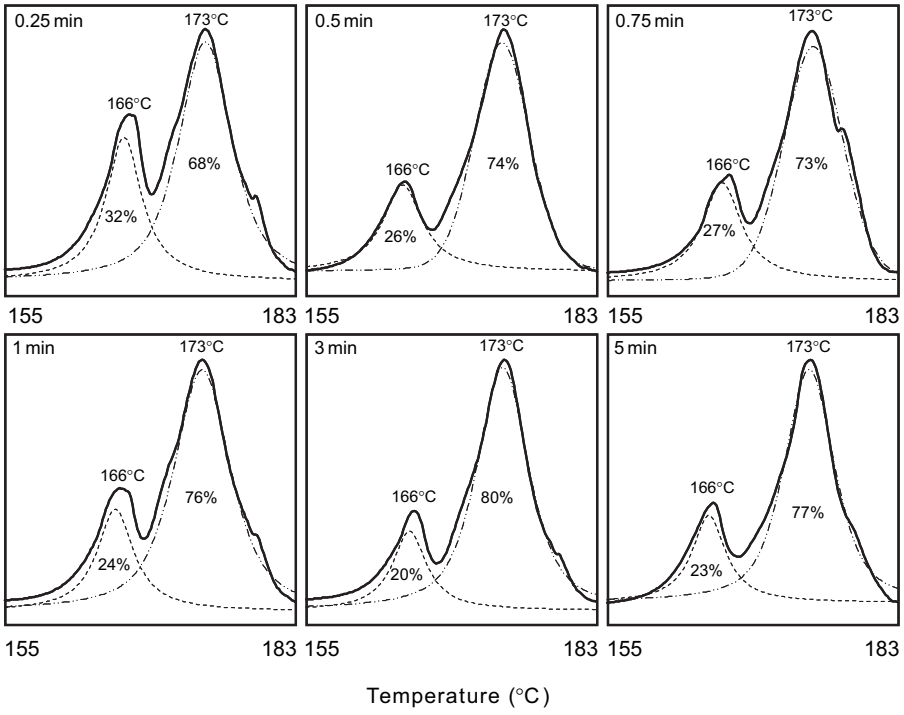



FIGURE 5. The curve-fitted profiles of famotidine forms A and B in the drilled disc I samples (from DSC curves of Figure 3).

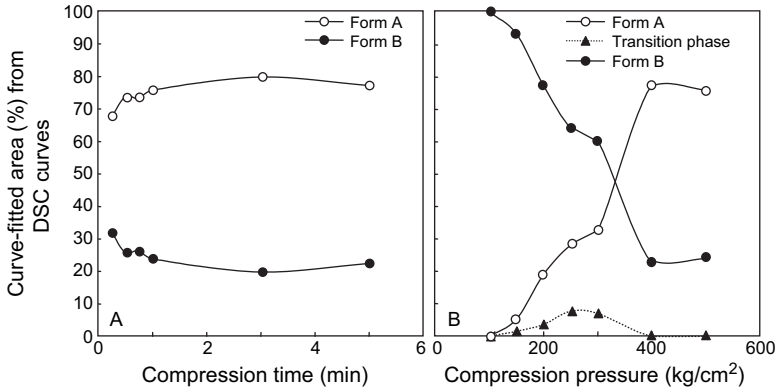



FIGURE 6. Relationships between the best curve-fitted results for the drilled disc I samples and the compression times (A) as well as compression pressure (B).

### Effect of Compression Pressure on the Polymorphic Transformation of Famotidine in the Compact Under Thermal Treatment

Figure 7 indicates the effect of compression pressure on the changes in DSC curves of the drilled disc I and II samples. Here, the compression pressure was changed from 100 to 500 kg/cm$^2$, but the compression time was maintained at 5 min. As shown in Figure 7, the peak intensity at 173°C in DSC curves gradually appeared and sharpened with the compression pressure applied, whereas the peak intensity at 167°C slowly reduced and shortened. From the results of Figures 4, 5, and 7, we deduce that the more the compression pressure applied, the lesser the famotidine form B remained and the higher the form B* obtained. This strongly illustrates that under thermal treatment, the higher compression pressures might easily induce polymorphic transformation of famotidine in the drilled disc I samples, but the lower compression pressure was less effective. However, there was no polymorphic transformation for the drilled disc II samples. It should be noted that the opaque region in the outer surrounding region of compact I also exhibited an endothermic peak at 166°C, as the result of the compact II.

The curve-fitted profiles of famotidine forms A and B from the DSC curves of Figure 7 are displayed in Figure 8. Obviously, the drilled disc I sample obtained from the lower compression pressure (100 kg/cm$^2$) exhibited an endothermic peak at 166°C of famotidine form B alone, indicating that the lower compression pressure did not induce the polymorphic transformation even by a thermal treatment. With the increase of compression pressure from 150 to 300 kg/cm$^2$, on the contrary, two additional peaks at 171 and 173 (174)°C were observed. The former peak might belong to famotidine form B*, but the latter peak should be due to the formation of famotidine form A transformed from form B*. When the compression pressure was beyond 400 kg/cm$^2$, only two endothermic peaks at 166°C for form B and at 173°C for form A were observed. Moreover, the curve-fitted data for the endothermic peak at 173°C were enlarged with the compression pressure applied.

The relationship between the best curve-fitted results for the drilled disc I samples and the compression pressures is given in Figures 6B. The relative composition of famotidine form B was reduced from 100% to 23–24% with the increase of compression pressure, whereas the relative composition of famotidine form A formed was increased from 0 to 76–77%. It is interesting to note that the DSC curve and the relative composition of famotidine form B* were only detected under the middle compression pressure but this transitional phase of form B* could not be detected by Raman measurement. Although this transitional phase of famotidine was also proposed in the result of Német, Hegedűs, Szántay, Sztatisz, & Pokol. (2005), its quantitative compositions about 10–16% were first determined by this study.

Until now although the transitional phase of famotidine form B* could not be determined by any spectroscopic methods, from the above DSC results, we deduce that famotidine form B in the transparent region of compact after compression presents two transition states, defined as forms $B_1$* and $B_2$*. Form $B_1$* may be a transition state located at the less transparent region of compact, whereas form $B_2$* may be another transition state appeared at the high transparent region in the compact. Under DSC determination, the form $B_1$* showed an endothermic peak at 171°C in DSC thermogram, but form $B_2$* might be quickly transited to form A without showing an endothermic peak in the DSC curve, as proposed in Scheme 2. Both component peaks were quantitatively obtained from DSC thermogram after application of curve-fitting program. These two transition states proposed may be related to the extent of

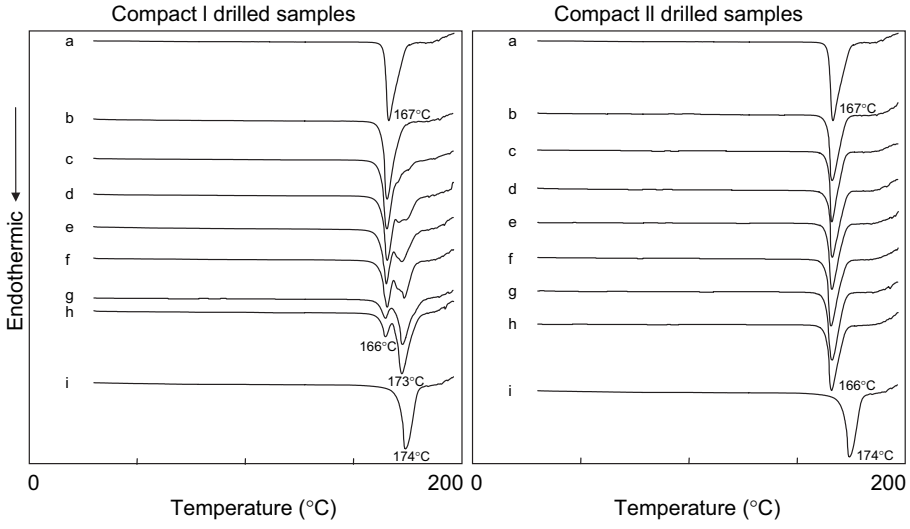



FIGURE 7. Effect of compression pressure on the changes in DSC thermograms of the drilled disc I and II samples. Compression pressures (kg/cm$^2$) for 5 min: b, 100; c, 150; d, 200; e, 250; f, 300; g, 400; h, 500; a, intact famotidine form B; i, intact famotidine form A.

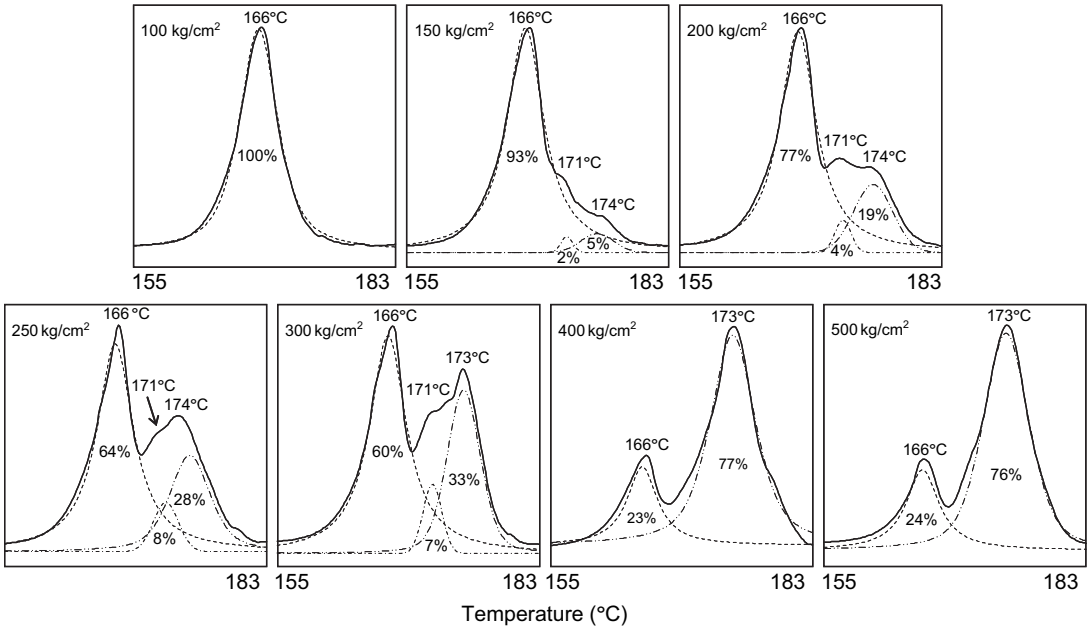
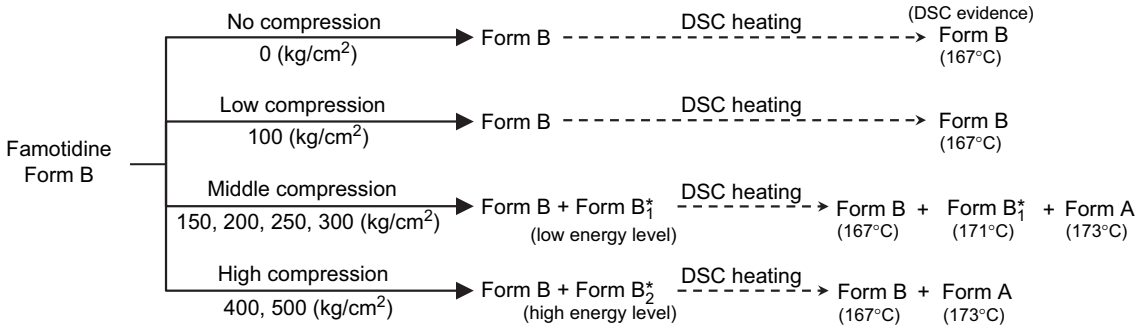



FIGURE 8. The curve-fitted profiles of famotidine forms A and B in the drilled disc I samples (from DSC curves of Figure 6).




SCHEME 2. The proposed polymorphic changes of famotidine compacts after different compression pressures and DSC heating treatment.

compression pressure applied. Moreover, under thermal treatment the relative compositions of famotidine forms A and B prepared by the higher compression pressure (>400 kg/cm$^2$) were almost maintained at a constant level. How to prove the existence of famotidine form B* in the compressed compact will be further studied by other analytical methods.

## CONCLUSIONS

In this study, a transparent region appeared in the center of compact was obtained by compressing a conical mass of famotidine form B powder with higher compression pressure. Only the higher compression pressure did not induce the polymorphic transformation of famotidine from form B to form A, but this transformation might occur during thermal treatment. A transitional phase of form B (form B*) in the transparent region of the compact might be formed by applying the higher compression pressure. This famotidine form B* might be transformed to form A by further DSC determination, due to the polymorphic transformation. Thus, the DSC heating system was a preferred method compared with other analytical methods to induce this polymorphic transformation. In addition, a curve-fitting program was easily used to quantitatively determine the relative composition of polymorphic forms of famotidine in the compacts from the DSC curves.

## ACKNOWLEDGMENTS

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