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Thermodynamic and kinetic characterization of polymorphic transformation of famotidine during grinding

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Abstract

Two polymorphs of famotidine were prepared by recrystallization from acetonitrile for form A and methanol for form B, respectively. The effect of grinding process on the polymorphic transformation of famotidine was investigated. Each famotidine sample ground for various grinding times in a ceramic mortar was determined by differential scanning calorimetry (DSC), conventional and thermal Fourier transform infrared (FT-IR) microspectroscopy. The results indicate that the raw material of famotidine was proved to be a form B. A unique IR absorption band at 3505 cm^{-1} for famotidine form B gradually decreased its intensity with the grinding time, while two newer IR absorption bands at 3451 and 1671 cm^{-1} for famotidine form A slowly appeared. The peak intensity ratio of 3451/3505 cm^{-1} was linearly ($r = 0.9901$) increased with the grinding time, suggesting that the grinding process could induce the polymorphic transformation of famotidine from form B to form A by a zero-order process. The DSC endothermic peaks also confirmed this polymorphic transformation from famotidine form B (167 °C, ΔH: 165 J/g) to famotidine form A (174 °C, ΔH: 148 J/g) in which the values of enthalpy were linearly reduced with the increase of grinding time ($r = 0.9943$). The phase transition temperature of the different ground famotidine samples could be easily and only evidenced by using thermal FT-IR microspectroscopy, rather than by DSC analysis. These phase transition temperatures of the famotidine form B ground for 5–20 min quickly reduced from 144 to 134 °C and maintained a constant at 134 °C even after 20–30 min grinding. The grinding process not only decreased the crystallinity of famotidine form B but 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 ground famotidine sample.

Keywords: Famotidine; Grinding; Polymorphic transformation; DSC; Thermal FT-IR

1. Introduction

More than half of the pharmaceutical drug compounds exhibit a solid-state polymorphism. Pharmaceutical solid polymorphism is defined as the ability of a drug compound to crystallize into more than one different crystalline forms, which the molecules have different packing arrangements and/or conformations within the crystal lattice (Byrn et al., 1995; Bugay, 2001; Chawla and Bansal, 2004). Different crystalline polymorphs can significantly influence the physicochemical properties, formulation development and manufacturing production of drug, resulting in the problems of compactibility, dissolution, bioavailability, bioactivity and shelf-life of drug substance (Newman and Byrn, 2003; Yu et al., 2003).

In common, the most stable polymorph is preferred in a marketed formulation to prevent the polymorphic transformation during processing or storage. This phase transformation has caused the bioavailability problem of drug. In 1998, Abbott Laboratories had temporarily withdrawn their HIV protease inhibitor drug (Norvir) from the market until they corrected its polymorphism, because of the phase transformation of an unwanted polymorph of the drug produced during storage (Morissette et al., 2003; Raw et al., 2004). Thus, FDA has recently paid more attention to regulate the effect of polymorphism on the bioequivalence between generic drug product and the innovator brand in the application of ANDA (Yu et al., 2003; Raw et al., 2004). A stringent regulatory requirement has been imposed on the identification and specification of

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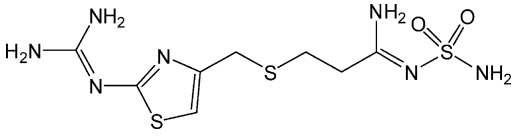
polymorphs for particular drug materials as part of the quality assurance process.

Famotidine is a representative third generation of a histamine H_2-receptor antagonist, which is commonly used to treat stomach and duodenal ulcers, reflux of stomach acid into the esophagus, and Zollinger–Ellison syndrome (Langtry et al., 1989). Famotidine has two polymorphic forms (A and B) that differed by the arrangement of intra/intermolecular hydrogen bonds, but another form C had also been found (Hegedus et al., 1989; Hassan et al., 1997; Ferenczy et al., 2000; Roux et al., 2002). FDA has convinced that famotidine was one of the generic drug products having different physical forms (Yu et al., 2003; Chawla and Bansal, 2004). Although the characteristics and crystal structure of two polymorphs of famotidine have been considerably investigated (Hegedus et al., 1989; Hassan et al., 1997; Ferenczy et al., 2000), the influence of pharmaceutical manufacturing process on the polymorphic transformation of famotidine was scanty reported.



It is well known that the grinding or milling is one of the manufacturing processes in pharmaceutical industry. Grinding process can modify the physical and chemical properties of drugs, such as introduction of a significant lattice strain within the crystalline drug, alteration of crystallinity of drug, reduction of particle size, and induction of polymorphic transformation of drug polymorphs (Yonemochi et al., 1999; Taddei et al., 2002; Rasenack and Muller, 2004). The purpose of this study was to investigate the thermodynamic and kinetic behavior of the polymorphic solid-state transformation processes of famotidine during grinding.

2. Materials and methods

2.1. Materials

Famotidine was kindly obtained from China Chem. Synthesis Ind. Co. Ltd. (Shu-Lin, Taipei, Taiwan, ROC). The organic solvents were of analytical reagent grade (Nacalai Tesque, Kyoto, Japan). The KBr crystals for the pellets were obtained from Jasco Parts Center (Jasco Co., Tokyo, Japan).

2.2. Preparation of two crystalline forms of famotidine

According to the report of Hassan et al. (1997), forms A and B of famotidine were recrystallized as follows:

(1) Form A: The powder of famotidine was suspended and dissolved in boiling acetonitrile, then filtrated while hot. The filtrate was stored in a refrigerator for crystallization. The crystals collected were dried under vacuum and stored in a silica gel desiccator.

(2) Form B: The same preparation method of form A, but acetonitrile was replaced by methanol. Here, the raw material of famotidine was proved to be a form B.

2.3. Preparation of ground samples

A certain amount of famotidine (form B) was respectively ground for different times (ranging from 5 to 30 min) in a ceramic mortar. No decomposition was detected by TLC in the course of grinding process.

2.4. Differential scanning calorimetric study

Each famotidine sample was directly examined using differential scanning calorimetry (DSC; DSC-910, TA Instruments Inc., New Castle, DE, USA) at a heating rate of 1, 3 or 10 °C/min with an open pan system in a stream of N_2 gas from 30 to 200 °C.

2.5. Conventional and thermal FT-IR microspectroscopic study

A trace powder of each famotidine sample was respectively smeared on one piece of KBr pellet and then directly compressed with an IR spectrophotometric hydraulic press (Riken Seiki Co., Tokyo, Japan) under 200 kg/cm^2 for 15 s, and quickly removed the pressure. The compressed KBr disc was respectively determined by Fourier transform infrared (FT-IR) microspectroscopy (Micro FT-IR 200, Jasco Co., Tokyo, Japan) with a mercury cadmium telluride (MCT) detector by transmission technique.

Another compressed KBr disc was placed onto a micro-hot stage (DSC microscopy cell, FP 84, Mettler, Greifensee, Switzerland). The DSC microscopy cell was placed in an FT-IR microscopic spectrometer (Micro FT-IR 200, Jasco Co., Tokyo, Japan). The system was operated in transmission mode. The temperature of the DSC microscopy cell was monitored with a central processor (FP 80HT, Mettler, Switzerland). The heating rate of the DSC assembly was maintained at 3 °C/min under ambient conditions. Each sample disc was equilibrated to the starting temperature (30 °C) and then heated from 30 to 160 °C. The thermal-responsive IR spectra were simultaneously recorded during heating (Lin and Chien, 2003).

2.6. Data analysis

All experiments were conducted at least in triplicate ($n = 3$) and results were expressed as mean ± standard deviation. Spectral manager software (Jasco Co., Tokyo, Japan) was used for data acquisition and handling. The representative spectrum or curve was the average of three determinations.

3. Results and discussion

3.1. FT-IR spectra and DSC thermograms of two famotidine polymorphs

It has been reported that the polymorphic forms A and B of famotidine exhibit a monotropic behavior, in which form A

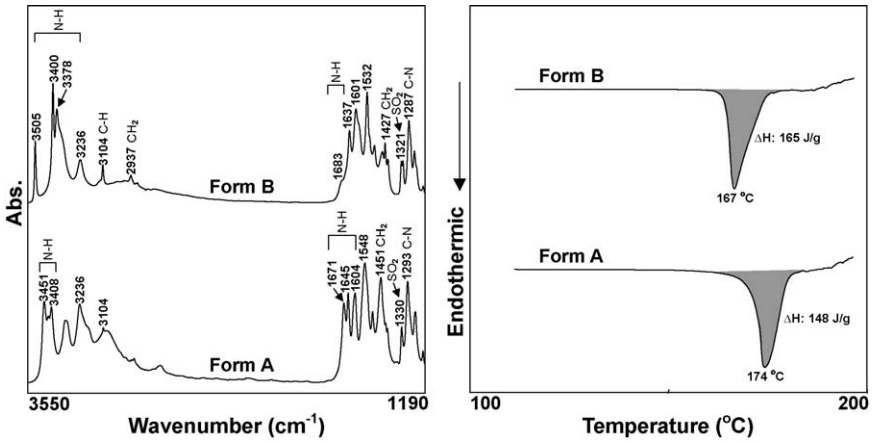


Fig. 1. The representative FT-IR spectra and DSC thermograms of polymorphic forms A and B of famotidine.

was more stable than form B (Ferenczy et al., 2000). Fig. 1 shows the representative FT-IR spectra and DSC thermograms of polymorphic forms A and B of famotidine. It is evident that several characteristic absorption bands and their assignments at 3451, 3408, 1671, 1645, 1548, 1451, 1330 and 1293 cm^{-1} were observed in the IR spectrum of form A, while at 3505, 3400, 3378, 1637, 1601, 1532, 1427, 1321 and 1287 cm^{-1} appeared in the IR spectrum of form B, respectively. On the other hand, two endothermic peaks at 174 °C with enthalpy of 148 J/g for form A and at 167 °C with enthalpy of 165 J/g for form B were respectively found in their DSC thermograms. Both data of this study were consistent with the reports of other studies (Hegedus et al., 1989; Hassan et al., 1997). The raw material of famotidine used in this study was proved to be a form B. In particular, the IR absorption bands at 3451 and 3505 cm^{-1} may be used as a fingerprint-marker to differentiate the polymorphs A and B of famotidine.

3.2. Grinding effect on the polymorphic transformation of famotidine polymorph

In preparing pharmaceutical solid dosage forms, grinding process is generally used for reducing the particle size of a solid drug to increase its dissolution rate, particularly for water-insoluble drug. Many papers have reported about the effect of grinding on the physical and chemical properties of drugs with or without additives (Mura et al., 2002; Mirmehrabi et al., 2004). In the present study, the famotidine form B was ground with time. The changes in FT-IR spectra and DSC thermograms of famotidine form B samples after grinding were determined. The

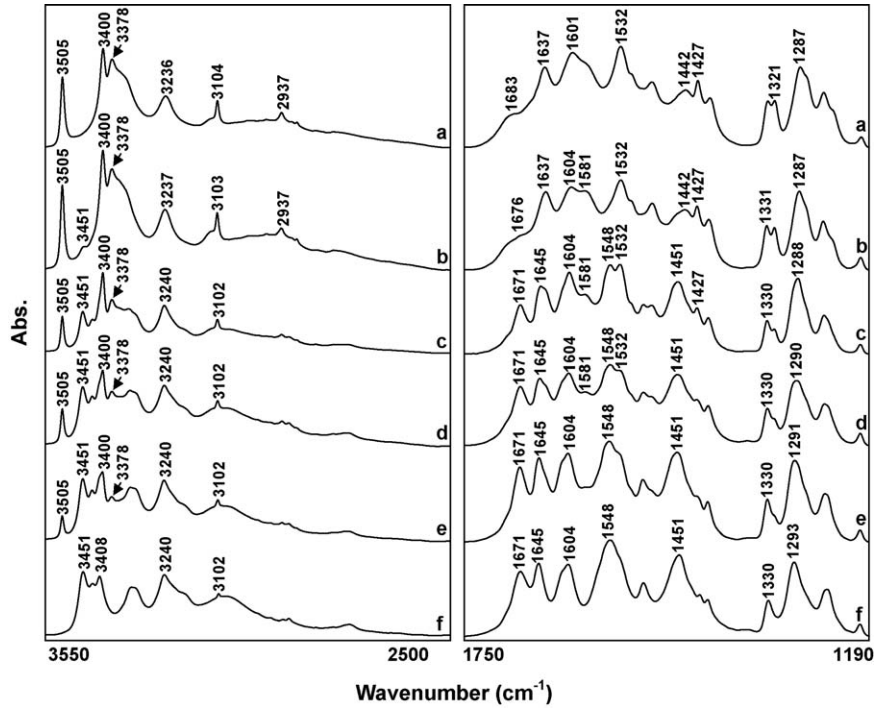


Fig. 2. Grinding time-dependent changes in the representative FT-IR spectra of famotidine form B samples. Key: intact famotidine form B before grinding (a), famotidine form B after grinding for 5 min (b), 10 min (c), 20 min (d) and 30 min (e), intact famotidine form A before grinding (f).

effect of grinding time on the representative FT-IR spectra of famotidine form B is displayed in Fig. 2. Obviously, a unique IR absorption band at 3505 cm^{-1} for famotidine form B gradually decreased its intensity with the grinding time, while two new IR absorption bands at 3451 and 1671 cm^{-1} for famotidine form A slowly appeared. Several absorption bands at 3400, 1637, 1601, 1532, 1427, 1321, and 1287 cm^{-1} were shifted to 3408, 1645, 1604, 1548, 1451, 1330 and 1293 cm^{-1} with different grinding times, respectively. The relationship between the peak intensity ratio of 3451/3505 cm^{-1} and grinding time is shown in Fig. 3. It is readily observed that the plot is linear (correlation coefficient, $r = 0.9901$) over the grinding time, as determined by using the least-squares method, suggesting that the grinding process correspondingly induces the polymorphic transformation of famotidine from form B to form A. This linear plot implies that the mechanism of polymorphic transformation from form B to form A for famotidine seems to be a zero-order kinetic model during grinding process.

The DSC thermograms of two polymorphs A and B recrystallized, as well as the different famotidine ground samples determined by three heating rates are indicated in Fig. 4. Clearly, each single endothermic peak for famotidine form B was respectively observed near 160, 164 or 167 °C for heating rate of 1, 3 or 10 °C/min (Fig. 4a). The value of 167°C was almost consistent with the 166.4 °C in DSC curve found for famotidine form B recrystallized from boiling methanol by using a heating rate of 10 °C/min (Hassan et al., 1997). This suggests that our sample used was an intact form B of famotidine. The slower the heating rate used the lower the endothermic temperature obtained. Once the famotidine form B was ground beyond 5 min, each above endothermic peak was increased from 160 to 162, 164 to 167 or 167 to 173 °C, respectively (Fig. 4b). Even grinding for 30 min, each corresponding endothermic peak was almost maintained within 162–163, 167–168 or 172–173 °C (Fig. 4e) which was near to the DSC curve for famotidine form A used in this study (Fig. 4f) and other reports (Hegedus et al., 1989; Hassan et al., 1997). This strongly demonstrates that the polymorphic transformation of famotidine was performed from form B to form A during grinding process. It is interesting to note that two endothermic shoulders at 158 and 162 °C were observed in the DSC curve of famotidine form B with heating rate of 1 or 3 °C/min after only grinding for 5 min. Both shoulders were transferred to 162 and 167 °C, which was near to the DSC curve of famotidine form A. These two shoulders might be proposed as a polymorphic phase transition temperature from form B to form A under the heating rate of 1 or 3 °C/min for the 5 min-ground mixture.

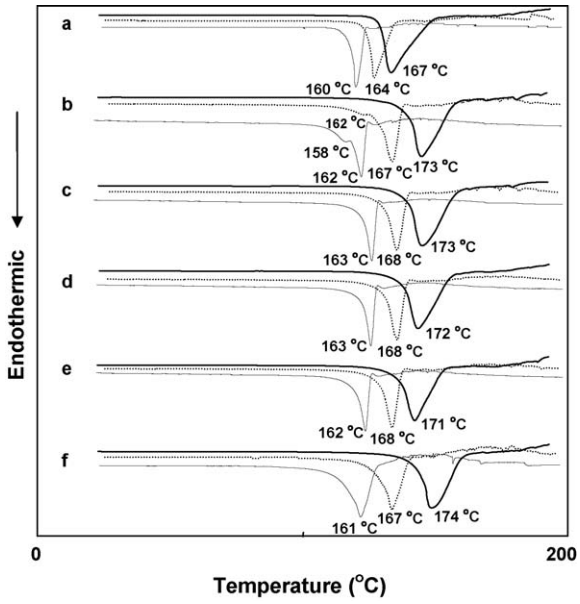


Fig. 4. The effect of heating rate on the DSC thermograms of two polymorphs A and B recrystallized, as well as the different famotidine ground samples. Key: intact famotidine form B before grinding (a), famotidine form B after grinding for 5 min (b), 10 min (c), 20 min (d) and 30 min (e), intact famotidine form A before grinding (f). Heating rate: thin solid line, 1 °C/min; dotted line, 3 °C/min; thick solid line, 10 °C/min.

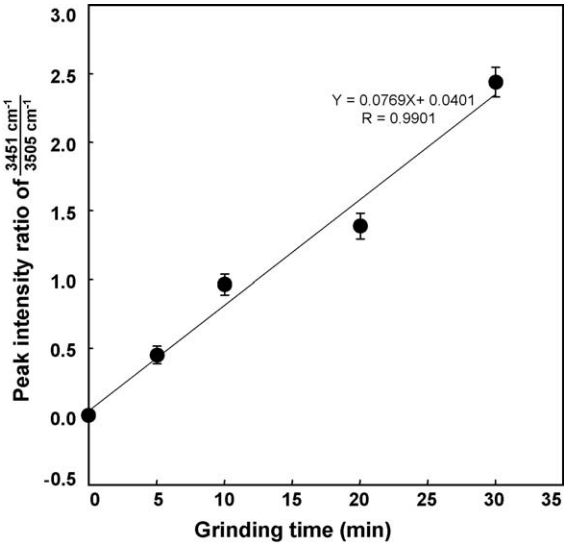


Fig. 3. The relationship between the peak intensity ratio of 3451/3505 cm^{-1} and grinding time.

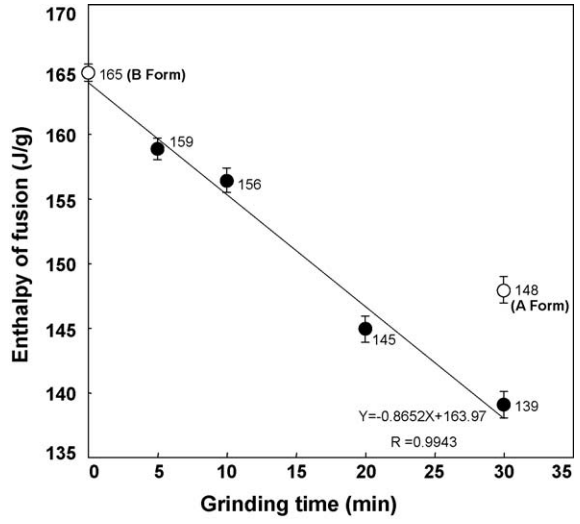


Fig. 5. The grinding time-dependent changes in DSC enthalpy of fusion for the ground famotidine mixture determined with 10 °C/min.

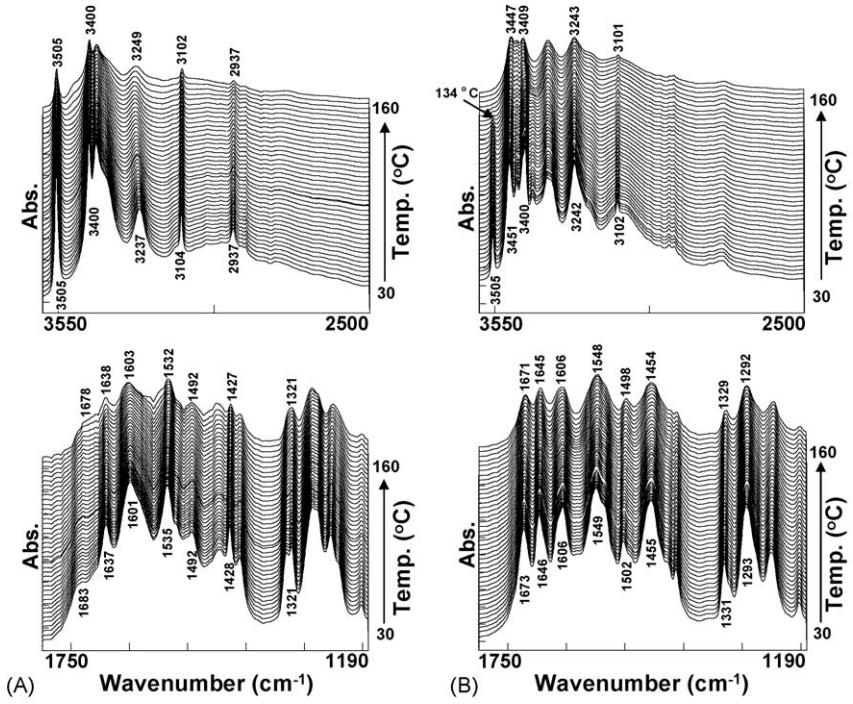


Fig. 6. Three-dimensional plots for the representative FT-IR spectra of famotidine form B (A) and its 30 min-ground sample (B) as a function of temperature.

Fig. 5 shows the grinding time-dependent changes in DSC enthalpy of fusion for the famotidine ground mixture determined with 10 °C/min. Obviously, the values of enthalpy of fusion for different ground mixtures of famotidine form B were linearly reduced with the increase of grinding time ($r = 0.9943$). The decreasing trend of the enthalpy might be explained by the gradual formation of famotidine form A with grinding time, in which the enthalpy of intact form A was about 148 J/g near to other studies (Roux et al., 2002). Moreover, the alteration of crystallinity and reduction of particle size for famotidine form B accompanying with the increase of grinding time might also cause the decrease of the heat of fusion (Yonemochi et al., 1999; Taddei et al., 2002; Rasenack and Muller, 2004).

3.3. Phase transition temperature of the different ground famotidine samples determined by thermal FT-IR microspectroscopy

Fig. 6 reveals the three-dimensional plots for the representative FT-IR spectra of famotidine form B and its 30 min-ground sample as a function of temperature. There was lack significant change in the three-dimensional plot of FT-IR spectra for the intact famotidine form B, indicating the absence of polymorphic transformation for form B without further treatment. However, it clearly evidences that the IR peak intensity at 3505 cm^{-1} for the 30 min-famotidine form B ground sample was markedly reduced from 134 °C with temperature. As indicated in Fig. 2, the 30 min-ground sample was consisted of a mixture of forms A and B

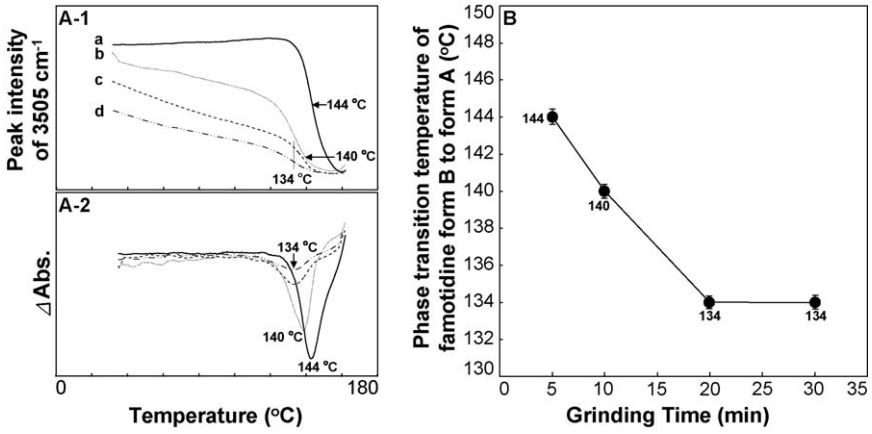


Fig. 7. The grinding time-dependent changes in the peak intensity of 3505 cm^{-1} (A-1) and its corresponding first derivative line (A-2), and phase transition temperature of famotidine form B to form A (B). Key: the grinding time for famotidine form B: 5 min (a), 10 min (b), 20 min (c), and 30 min (d).

of famotidine. The 160 °C-heated sample after cooling to room temperature exhibited the same FT-IR spectra as that of the form A of famotidine. Thus the disappearance of 3505 cm^{-1} peak assigned to the characteristic peak of form B might be due to the polymorphic transformation from form B to form A during grinding, 134 °C was assigned to the phase transition temperature. A novel and powerful Fourier transform infrared (FT-IR) microspectroscope equipped with a thermal analyzer has been extensively used to simultaneously determine the correlation between the thermal response and the structural change of polymers and polymorphism of drugs (Spragg, 2000; Wang et al., 2002). The phase transition temperature of the different ground famotidine samples in this study could be easily and only evidenced by using thermal FT-IR microspectroscopy, rather than by DSC analysis. The FT-IR spectroscopy fast providing quite informative spectra of structural changes of sample than DSC thermograms might be responsible for this result.

The phase transition temperature of each ground sample was obtained from the time-dependent changes in the peak intensity of 3505 cm^{-1} (Fig. 7A-1) and its corresponding first derivative line (Fig. 7A-2). The effect of grinding time on the phase transition temperature of famotidine form B to form A is shown in Fig. 7B. The result clearly demonstrates that the phase transition temperature of the famotidine form B ground for 5–20 min was quickly reduced from 144 to 134 °C, but the temperature was maintained constant at 134 °C even grinding for 20–30 min. The decrease of crystallinity and/or the reduction of the particle size of famotidine form B during grinding might be responsible for the marked reduction of the phase transition temperature of the ground famotidine sample. The results shown in Fig. 2 seem to confirm this reason.

4. Conclusions

The result of this study demonstrates the polymorphic transformation of famotidine from form B to form A might be occurred during grinding process. The mechanism of this polymorphic transformation of famotidine seems to be a zero-order kinetic model via grinding. The grinding process not only decreased the crystallinity but 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 famotidine sample.

Acknowledgement

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References

Bugay, D.E., 2001. Characterization of the solid-state: spectroscopic techniques. Adv. Drug Deliv. Rev. 48, 43–65.

Byrn, S., Pfeiffer, R., Ganey, M., Hoiberg, C., Poochikian, G., 1995. Pharmaceuticals solids, a strategic approach to regulatory considerations. Pharm. Res. 12, 945–954.

Chawla, G., Bansal, A.K., 2004. Challenges in polymorphism of pharmaceuticals. CRIPS 5, 9–12.

Ferenczy, G.G., Párkányi, L., Ángyán, J.G., Kálmán, A., Hegedüs, B., 2000. Crystal and electronic structure of two polymorphic modifications of famotidine. An experimental and theoretical study. J. Mol. Struct. (Theochem.) 503, 73–79.

Hassan, M.A., Salem, M.S., Sueliman, M.S., Najib, N.M., 1997. Characterization of famotidine polymorphic forms. Int. J. Pharm. 149, 227–232.

Hegedus, B., Bod, P., Harsanyi, K., Peter, I., Kalman, A., Parkany, L., 1989. Comparison of the polymorphic modifications of famotidine. J. Pharm. Biomed. Anal. 7, 563–569.

Langtry, H.D., Grant, S.M., Goa, K.L., 1989. Famotidine. An updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in peptic ulcer disease and other allied diseases. Drugs 38, 551–590.

Lin, S.Y., Chien, J.L., 2003. In vitro simulation of solid–solid dehydration, rehydration, and solidification of trehalose dihydrate using thermal and vibrational spectroscopic techniques. Pharm. Res. 20, 1926–1931.

Mirmehrabi, M., Rohani, S., Murthy, K.S., Radatus, B., 2004. Solubility, dissolution rate and phase transition studies of ranitidine hydrochloride tautomeric forms. Int. J. Pharm. 282, 73–85.

Morissette, S.L., Soukasene, S., Levinson, D., Cima, M.J., Almarsson, O., 2003. Elucidation of crystal form diversity of the HIV protease inhibitor ritonavir by high-throughput crystallization. Proc. Natl. Acad. Sci. U.S.A. 100, 2180–2184.

Mura, P., Cirri, M., Faucci, M.T., Gines-Dorado, J.M., Bettinetti, G.P., 2002. Investigation of the effects of grinding and co-grinding on physicochemical properties of glisentide. J. Pharm. Biomed. Anal. 30, 227–237.

Newman, A.W., Byrn, S.R., 2003. Solid-state analysis of the active pharmaceutical ingredient in drug products. Drug Discov. Today 8, 898–905.

Raw, A.S., Furness, M.S., Gill, D.S., Adams Jr., R.C., Holcombe, F.O., Yu, L.X., 2004. Regulatory considerations of pharmaceutical solid polymorphism in abbreviated new drug applications (ANDAs). Adv. Drug Deliv. Rev. 56, 397–414.

Rasenack, N., Muller, B.W., 2004. Micron-size drug particles: common and novel micronization techniques. Pharm. Dev. Technol. 9, 1–13.

Roux, M.V., Dávalos, J.Z., Jiménez, P., 2002. Effect of pressure on the polymorphic forms of famotidine. Thermochim. Acta 394, 19–24.

Spragg, R.A., 2000. Combining FTIR microspectroscopy. with differential scanning calorimetry. Analusis 28, 64–67.

Taddei, P., Torreggiani, A., Fini, G., 2002. Vibrational study of polymorphism of tetralin derivative for treatment of cardiovascular diseases. Biopolymers 67, 289–293.

Wang, S.L., Lin, S.Y., Wei, Y.S., 2002. Transformation of metastable forms of acetaminophen studied by thermal Fourier transform infrared (FT-IR) microspectroscopy. Chem. Pharm. Bull. (Tokyo) 50, 153–156.

Yonemochi, E., Kitahara, S., Maeda, S., Yamamura, S., Oguchi, T., Yamamoto, K., 1999. Physicochemical properties of amorphous clarithromycin obtained by grinding and spray drying. Eur. J. Pharm. Sci. 7, 331–338.

Yu, L.X., Furness, M.S., Raw, A., Outlaw, K.P., Nashed, N.E., Ramos, E., Miller, S.P., Adams, R.C., Fang, F., Patel Jr., R.M., Holcombe, F.O., Chiu, Y.Y., Hussain, A.S., 2003. Scientific considerations of pharmaceutical solid polymorphism in abbreviated new drug applications. Pharm. Res. 20, 531–536.