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EXPERT REVIEW

An Overview of Famotidine Polymorphs: Solid-State Characteristics, Thermodynamics, Polymorphic Transformation and Quality Control

Shan-Yang Lin

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ABSTRACT Crystal polymorphism of pharmaceuticals has well-known profound effects on the physical, chemical, and pharmaceutical properties of drugs, which can result in changes in the solubility, stability, dissolution, bioavailability, and efficacy of drugs. In this review article, famotidine (FAM), which has a well-known trade name of Pepcid®, was selected as a model drug. Although FAM has three polymorphs (forms A, B and C), forms A and B have been commonly discussed. The active pharmaceutical ingredient (API) in the commercial version of FAM is the metastable form B. FAM has been a concern of FDA because of the physical properties, solubilities, bioavailabilities, or bioequivalencies of the different polymorphic forms. In addition, a patent infringement suit of FAM polymorph had been made sound legal arguments in the pharmaceutical market. We review the solid-state characteristics, thermodynamics, polymorphic transformation, and quality control of FAM in drug products. In particular, pharmaceutical processes, such as grinding, compression, and heating temperature have a significant effect on the polymorphic transformation of FAM. Moreover, environmental humidity and residual water content should be well controlled to prevent polymorphic transformation of FAM during pharmaceutical processing. Several thermal and spectroscopic analytical techniques used for qualitative and quantitative determinations of polymorphic transformation of FAM after different treatments or quality control of FAM in the commercial tablets before and after the expiration dates have been discussed.

KEY WORDS characteristics · famotidine · polymorphic transformation · quality control · thermodynamics

S.-Y. Lin (✉)
Laboratory of Pharmaceutics and Biopharmaceutics
Department of Biotechnology and Pharmaceutical Technology
Yuanpei University, No. 306, Yuanpei Street, Hsin Chu 30015
Taiwan, Republic of China
e-mail: sylin@mail.ypu.edu.tw

INTRODUCTION

Polymorphism comes from the Greek words *poly*, which means "many", and *morph*, which means "form" (1,2). It is defined as the ability of a solid material to exist in two or more crystalline phases with different arrangements or conformations in the crystal lattice. Drug polymorphs are different solid state crystalline forms of the same drug substance (3,4). More than 50% of active pharmaceutical ingredients (APIs) have been estimated to have more than one polymorphic form (5,6). Different API polymorphs have different physical and chemical properties, which can cause changes in the solubility, stability, dissolution, bioavailability, and final efficacy of drugs (7,8). To retain the stable polymorphs in marketed drug products, early discovery of API polymorphs is necessary for determining the most desirable physical form for development. Therefore, it is important to perform a polymorphic screening for each API and select the most stable polymorph. The most stable polymorph should be used in the marketed formulation to prevent polymorphic transformation during manufacturing, delivery, or storage. In general, the polymorph selected during the drug development process should be thermodynamically stable and remain stable during the manufacturing process (9).

In recent years, polymorphic transformation has been observed for several drugs during storage, which has caused problems with bioavailability (8,10). Particularly, if an API is in class II of the biopharmaceutics classification system (BCS), then studies on API polymorphs are essential (11). Accordingly, the US FDA has increasingly asked Investigational New Drug Applicants to submit drug polymorph information or Abbreviated New Drug Applicants to perform a drug polymorphism study for confirming drug equivalence of the polymorphs (11). A stringent regulatory requirement has been imposed on the identification and specification of polymorphs for particular APIs as part of the quality assurance process. In addition, the International Conference on Harmonization

Q6A guideline provides additional guidance on when and how polymorphic forms should be monitored and controlled for a new drug substance or drug product (12). More recently, generic manufacturers have been able to use Paragraph IV of the US FDA guidance to challenge original drug product patents. One of the claims for using Paragraph IV is that a generic drug product has a different API polymorph from that of the original API. The US FDA requires that a proposed generic drug product meets the standards for identity, exhibits sufficient stability, and is bioequivalent to the original drug product (13). In general, regulatory agencies worldwide require that a company demonstrates that it has made a reasonable effort to identify their API polymorphs in the formulation by the time of filing and has investigated the possibility of polymorphic interconversion. Moreover, manufacturers need to demonstrate that a drug polymorph is stable and can be reliably produced (14). Generally speaking, it should keep a more stable polymorph in a final drug product for entering the market.

SOLID-STATE CHARACTERIZATION, PREPARATION, AND IDENTIFICATION OF DRUG POLYMORPHS

Crystal polymorphism is often characterized as the ability of a drug substance to crystallize into two or more different crystal structures. Each polymorph has the same chemical structure but differs in the arrangement of molecules in the unit cell, which leads to different physical and chemical properties (1–3). Drug polymorphs include crystalline and amorphous forms as well as solvate and hydrate forms (4,5). Although polymorphs exhibit the same chemical entity, they behave differently in the solid state. The possible differences in physicochemical and pharmaceutical properties of various drug polymorphs are presented in Table I. These characteristics include different packing properties (density), thermodynamic properties (solubility, free energy, melting point), spectroscopic properties, kinetic properties (chemical reactivity, dissolution rate, stability), mechanical properties (hardness, tensile strength), and pharmaceutical properties (flowability, compatibility, tabletability) (1,2). These properties can have a direct effect on the ability to prepare, process, and/or manufacture the drug substance and drug product as well as on the stability, dissolution, and bioavailability of the drug product. Thus, polymorphism can markedly affect the quality, safety, and efficacy of the drug product in which differences in drug solubility are particularly important (7,15). Thus, development of methods to control polymorphic formation or preparation is an important issue in chemical and pharmaceutical industries.

Table I Physico-chemical and Pharmaceutical Properties of Various Drug Polymorphs

- Molar volume and density
- Refractive index/optical properties
- Morphology
- Crystal habit
- Melting point
- Enthalpy
- Spectral vibrational transitions
- Hygroscopy
- Intrinsic solubility
- Dissolution rate
- Stability
- Compatibility
- Handling, flowability, and blending
- Tabletability
- Hardness
- Bioavailability

In the process of drug development, polymorphism screening is designed to find a stable nonsolvated form with good properties. The purpose of this polymorphism screening is to find as many forms as possible to provide broad intellectual property rights protection. Recently, drug polymorphism has become an important aspect of the pharmaceutical industry because it can allow pharmaceutical companies to avoid patent issues with other pharmaceutical companies (16,17). Continuous monitoring is needed throughout drug development to ensure continued control of drug polymorphs. Polymorphism can cause differences in drug properties because of the differences in crystalline structures. It is well known that crystallization of APIs from different solvents may commonly produce different crystals, amorphous state or solvates depending upon the given processing conditions, as shown in Table II (18,19). Alterations of temperature, humidity, and mechanical effects in the preparation process of drug polymorphs may also cause polymorphic changes. Moreover, drug polymorphic changes can also be induced by several common stages of API processing, such as drying, grinding, granulation, and compression (20–29).

In general, parameters related to the manufacturing processes for obtaining drug polymorphs can be revealed by investigating the effects of (a) solvents, (b) concentration, (c) cooling rate, (d) time, (e) temperature, and (f) seeding (30,31). The quality and drug properties of a final API product are primarily determined by its shape, size, and polymorphic form. In addition, process analytical technology (PAT) involving scientifically based process design and optimization, appropriate sensor technologies, statistical and information tools

Table II Methods for Preparation of Drug Polymorphs

Crystallization from solution
Cooling crystallization
Seeded crystallization
Evaporative crystallization
Anti-solvent crystallization
Reactive crystallization
Ultrasound crystallization
Capillary crystallization
Crystallization in the presence of additives
Supercritical fluid technology (rapid expansion of a supercritical solution/ supercritical antisolvent solution)
Crystallization from melts
Slow cooling
Quench cooling
Mechanochemical methods
Grinding effect
Co-grinding effect
Thermal methods
Thermal-induced phase transformations
Melting-recrystallization process
Slurrying methods
Solvent-mediated transformation
Desolvation methods
Drying effect
Vacuuming effect

Modified from P.W. Cains, Classical methods of preparation of polymorphs and alternative solid forms, in "Polymorphism in Pharmaceutical Solids", 2nd Ed., H. G. Brittain (Editor), Informa Healthcare, New York, 2009

Table III Analytical Techniques Commonly Used for Characterizing Drug Polymorphs

Crystallography
Single-crystal X-ray diffractometry
Powder x-ray diffractometry
Spectroscopy
Infrared spectroscopy
Raman spectroscopy
Near infrared (NIR) spectroscopy
Solid-state nuclear magnetic resonance (NMR) spectroscopy
Terahertz spectroscopy
UV diffuse reflectance spectroscopy
Microscopy
Polarized light microscopy (PLM)
Hot-stage microscopy (HSM)
Scanning electron microscopy (SEM)
Atomic force microscopy (AFM)
Scanning probe microscopy (SPM)
Thermal techniques
Differential Thermal Analysis (DTA)
Differential Scanning Calorimetry (DSC)
Thermogravimetric Analysis (ATG)
Isothermal microcalorimetry (IMC)
Simultaneous combined techniques
DSC-FTIR microspectroscopy
Thermal (DSC)-Raman microspectroscopy
DSC-X-ray diffractometry
DSC-NIR spectroscopy

(chemometrics), and feedback process control strategies working together to produce quality products has been applied to the crystallization processes of API. Process controls for polymorph control have been applied to locate process end points, such as the correct polymorphic form or the correct particle size (32,33).

Except for the application of real-time PAT for analysis of drug polymorphs, numerous physicochemical measurements and techniques may be used to characterize all possible polymorphic forms of an API. Table III presents the analytical techniques commonly used for characterizing drug polymorphs. These analytical techniques including crystallography, spectroscopy, microscopy, thermal analysis, and simultaneous combined methods, are available for identification of different polymorphic forms (1,2,9,18–20,34). It is important to note that polymorphic changes can occur at almost any stage during processing of an API or formulation depending on the solid-state system. The above analytical techniques are helpful for determining the crystal forms in the system; some can be used for qualitative or quantitative testing. From a regulatory or an intellectual property viewpoint, it is important to identify and confirm the crystal form of an API presented in its marketed drug product (7,35).

SOLID-STATE CHARACTERISTICS AND POLYMORPHS OF FAMOTIDINE

Famotidine (FAM), 3-{[2-(diaminomethyleneamino)-1, 3-thiazol-4-yl]-methylthio} -N2-sulfamoylpropionamide (Fig. 1), is a histamine H_2-receptor antagonist that acts as a highly potent inhibitor of gastric acid secretion in humans (36). It is widely prescribed for gastric ulcers, duodenal ulcers, Zollinger–Ellison syndrome, and gastroesophageal reflux disease (37). Recently, a combination of ibuprofen and FAM has been approved in the USA for the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis and to decrease the risk of developing upper GI ulcers (38). Moreover, FAM also has been shown to be effective in reducing pain and decreasing calcification in patients with calcifying tendinitis (39) and

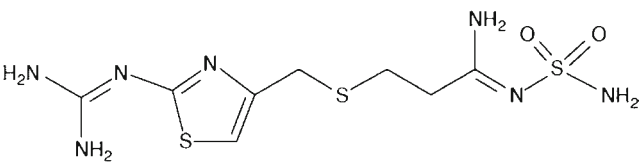

Fig. 1 Chemical structure of famotidine.

for treatment of Parkinson's and Alzheimer's diseases (40,41). FAM also has been used in combination with an H_1-antagonist to treat and prevent urticaria caused by an acute allergic reaction (42). These indications show the wide applicability of FAM. However, FAM was classified as a BCS class IV substance and has been reported to have low and variable bioavailability because of its poor aqueous solubility and low permeability (43,44). Therefore, the possibility of FAM polymorphic forms is an important consideration in the development of solid dosage forms (11,45).

FAM has been reported to have three polymorphs, A, B, and C, which depend on the cooling rate and solvent of crystallization (46,47). The form A is thermodynamically stable form A but form B is kinetically favored (46–49). Commonly, metastable polymorphs often exhibit better solubility than the stable polymorphic form (50). Thus, polymorph B of FAM is a commercial form and is metastable and active compared with polymorphs A and C. Polymorphs A and B show many differences in physical properties, particularly in arching capability, electrostatic charging, deformation, and rolling angle. The side chain in the stable polymorph A is in free rotation, whereas in the metastable polymorph B, one of the sulfamoyl oxygens interacts with a guanidine amine group (51,52). According to the data of Overgaard and Hibbs, crystals of polymorph A and polymorph B belong to the monoclinic crystal system (53). The unit-cell dimensions of polymorph A are $a=11.912$ Å, $b=7.188$ Å, $c=16.624$ Å, and $\beta=100.045°$, whereas those of polymorph B are $a=16.980$ Å, $b=5.285$ Å, $c=17.639$ Å, and $\beta=116.416°$. The conformational structure and crystal packing of the FAM polymorphs A and B are shown in Fig. 2 (45,53).

THERMODYNAMICS OF FAMOTIDINE

The thermodynamic relationships between polymorphic pairs can be classified into two basic types, enantiotropes and monotropes, depending on their stability with respect to the range of temperatures and pressures used (1,2,7). The former is defined as a polymorph that can be reversibly changed from one form to another by varying temperature or pressure, but the latter is defined as a polymorph that undergoes irreversible transition to another polymorph (34). For monotropic polymorphs, the high melting form will be the stable one at atmospheric conditions. For enantiotropic polymorphs, the low melting form will be the stable one at room temperature. Here, because FAM polymorph A (melting point: 174°C) is the thermodynamically favored form (stable form) and polymorph B (melting point: 167°C) is the kinetically favored form (metastable form), thus FAM is said to possess monotropic behavior (47,51). Figure 3 shows the DSC thermograms and FT-IR spectra of polymorphs A and B of FAM (49). The metastable polymorph B may undergo heat-induced or solvent-induced transformation to produce the thermodynamically stable polymorph A (49,54,55). This is consistent with the fact that the stable polymorph has the lowest energy state, highest melting point, and least aqueous solubility. In contrast, the metastable form has a higher energy state, lower melting point, and more rapid aqueous dissolution than those of the stable form.

For polymorphs, a plot of concentration *versus* temperature must yield the lowest solubility for the stable form (56). Lu *et al.* found that the solubilities of both FAM polymorphs increased with temperature, as shown in Fig. 4 (46,57). The van't Hoff plots [$(ln\ solubility) = -(\Delta H/RT) + (\Delta S/R)$] of the equilibrium solubility of both polymorphs clearly indicate that the dissolution enthalpies (ΔH: 57.5 (A) and 56.6 (B) kJ/mol) and dissolution entropies (ΔS: 189.6 (A) and 190.2 (B) J/k.mol) of both polymorphs in water are almost equal. There are no differences in the dissolution enthalpy and dissolution entropy of the two polymorphs. It has been reported that if the solubility curves of two polymorphs cross each other at a lower temperature, then they may be considered to be an enantiotropic polymorphic pair, whereas the system is considered to be monotropic if the solubility curves do not cross each other. The results of Fig. 4 show that there is no intersection of the two curves, which confirms the monotropic nature of the polymorphs for FAM (46,57).

PROCESSING-INDUCED SOLID-STATE POLYMORPHIC TRANSFORMATION OF FAMOTIDINE

It is well known that solid-state polymorphic transformation of an API can occur in various pharmaceutical manufacturing processes (granulation, drying, grinding, micronization, granulation, and compaction) (20–29,58,59). Exposure to environmental conditions, such as humidity and temperature, can also induce polymorphic conversion (11). Any transformed API or altered dosage form can exhibit an altered solubility, dissolution rate, and stability, which can lead to an undesirable bioavailability profile. Such phase transformations caused by scale-up of processing operations can affect the properties (dissolution, bioavailability, and stability) of the final products. Therefore, a better understanding of the mechanism, effects, and kinetics of transformation are essential for the quality control of final drug products (1–9,20,45). The polymorphic forms of an API are directly related to the control and optimization of process parameters in the development process.

Several manufacturing processes and associated unit operations used to prepare oral solid dosage forms are well established, and mechanical stress appears to induce solid phase transitions more often than others. Mechanical stress, by disruption of the crystalline drug structure, may increase

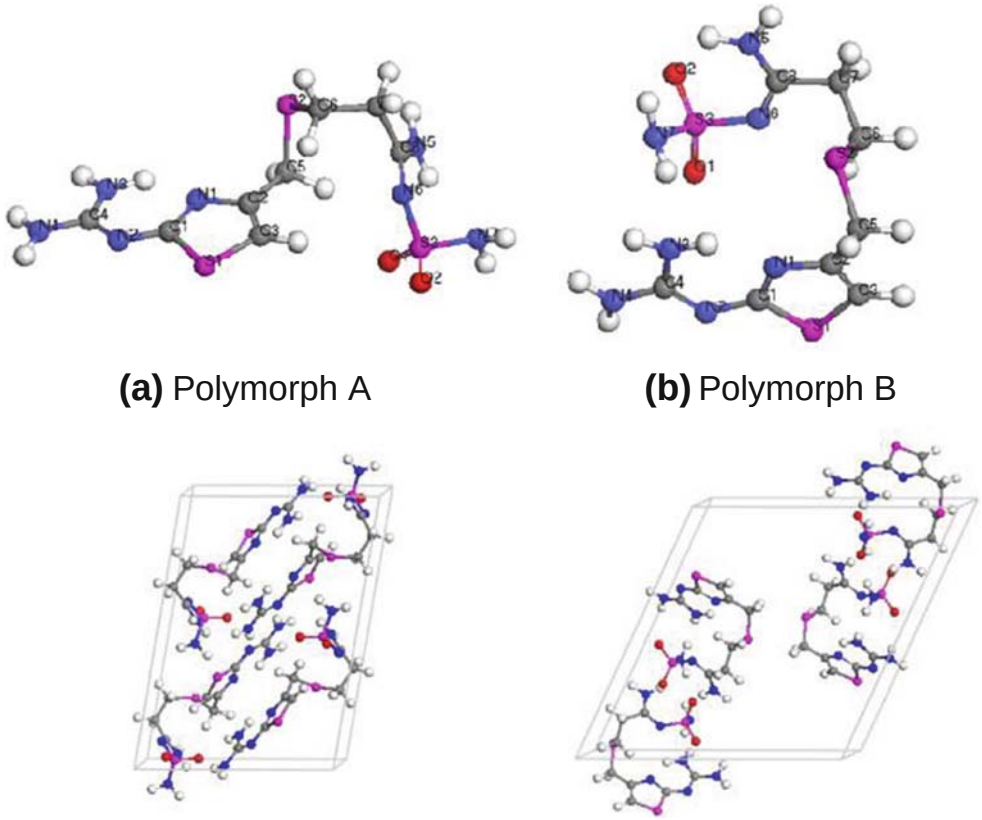

Fig. 2 The configurations of famotidine polymorphs of A and B and its crystal packings (modified from ref. (46) and (57)).

the surface area and produce solid deformation and even melting. The most common mechanical stresses used in pharmaceutical manufacturing processes are grinding and compression. During these processes, the crystal form of API can undergo mechanochemical changes, including polymorphic transformations (22–25,60–62). Table IV also presents the polymorphic characteristics and polymorphic transformations of FAM under different treatments through various analytical determinations. The influence of manufacturing processes and thermal effects on the physicochemical properties and polymorphic transformation of FAM in mixtures, and formulation detection of polymorphs presented are discussed below.

Grinding Effect

Grinding or milling are ancient techniques that are used extensively in manufacturing processes in the pharmaceutical industry. Lin *et al.* used two unique FT-IR spectral peaks at

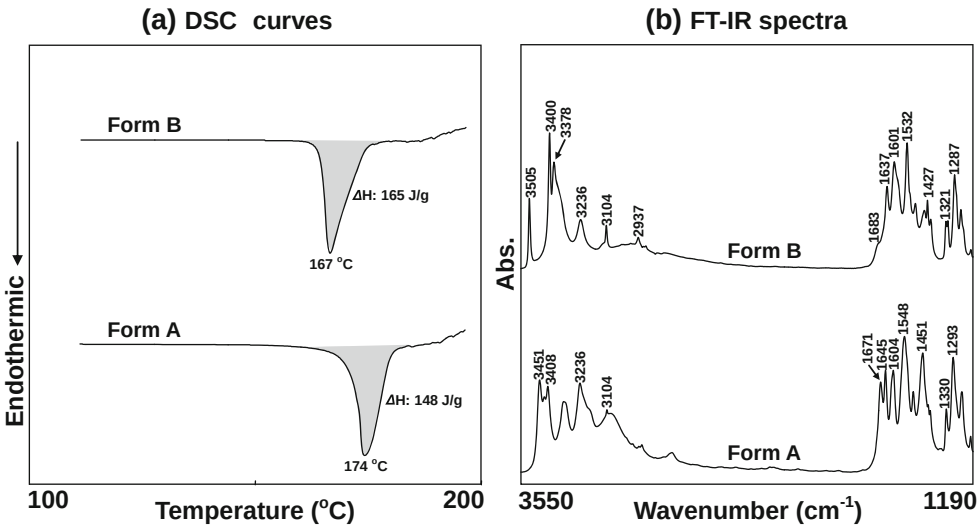

Fig. 3 DSC curves and FT-IR spectra of polymorphs A and B of famotidine (modified from ref. (49)).

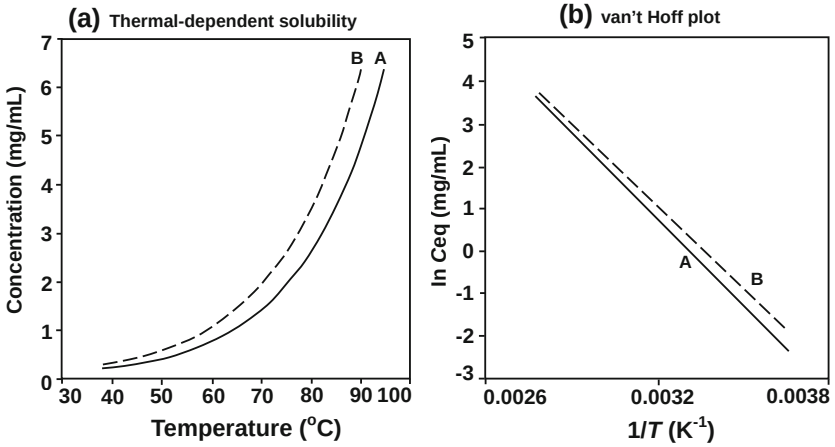

Fig. 4 Water solubility profiles of polymorphs A and B of famotidine (modified from ref. (46) and (57)).

3,451 (asymmetric NH_2 stretching for the sulfamoyl part) and 3,505 cm^{-1} (asymmetric NH_2 stretching for the guanidine part) as fingerprint markers to investigate the grinding effect of polymorphic transformation of FAM (49). They ground a certain amount of FAM (form B) for different times in a ceramic mortar under room temperature condition and found that a unique IR absorption band at 3,505 cm^{-1} for FAM form B gradually decreased in intensity but the intensity of another band at 3,451 cm^{-1} for FAM form A slowly increased with grinding time (Fig. 5). Moreover, a linear relationship between the band intensity ratio of 3,451/3,505 cm^{-1} and grinding time was also observed, which indicated that the grinding process indeed induced the polymorphic transformation of FAM from form B to form A. This linear plot suggests that the kinetics of polymorphic transformation from form B to form A in the grinding process was zero-order. Cheng *et al.* also used confocal Raman microspectroscopy to obtain similar results for both Raman bands at 2,920 (form A, CH asymmetric stretching) and 2,897 (form B, CH symmetric stretching) cm^{-1} as indicators (Fig. 5) (54). This result also shows that the content of FAM form A increased with grinding time, which indicated the successive promotion of polymorphic conversion of FAM from form B to form A.

The grinding-induced changes in DSC thermograms determined at three heating rates (1, 3, or 10°C/min) and enthalpies of fusion of different FAM ground mixtures examined at 10°C/min are also illustrated in Fig. 6 (49). It was found that the single endothermic peaks for the intact form B of FAM were observed near 160°C, 164°C, or 167°C for heating rates of 1°C, 3°C, or 10°C/min, respectively. The slower the heating rate used, the lower the endothermic peak temperature obtained. Once FAM form B had been ground, each endothermic peak temperature was shifted to a higher temperature and was closer to the endothermic peak temperature of FAM form A. These results again demonstrate the polymorphic transition of FAM from form B to form A during the grinding process. The relationship between the enthalpies of the FAM ground samples determined at 10°C/min and the grinding times are also shown in Fig. 6. The enthalpies of fusion for different FAM ground mixtures were reduced linearly with the increase in the grinding time. The declining enthalpy changes may be explained by the gradual formation of FAM form A during the grinding process. The enthalpy of fusion of the sample ground for 20 and 30 min were smaller than that of FAM form A, however, the reduction in the particle size, the alteration in the crystallinity, and/or the formation of some amorphous state of the FAM powder accompanied by the increase in the grinding time might be attributed to this phenomenon (60,61,74,75).

Pressure and Thermal Effects

Compression is also one of the main manufacturing processes used in the preparation of tablets. During the compressing process, the pressure applied may cause solid phase changes in either API or excipients *via* a solid-state mechanism. The compression pressure may alter the crystal form of the drug leading to a polymorphic transformation and also affect the tablet properties (3,76,77). Thus, more attention should be given to pressure-induced polymorphic transitions of solid dosage forms to ensure high product quality and that they meet regulatory requirements. Roux *et al.* had observed that pressure produced different modifications in the behavior of FAM form B samples in DSC analysis (67). When the pressure was applied from 2.0×10^5 to 10.0×10^5 kPa, two endothermic peaks were observed: the former endothermic peak at 165°C belonged to FAM form B, and the second one with a peak temperature near 174°C may be attributed to form A of FAM. These results indicate that the polymorphic transformation of FAM could be produced by pressure changes. In addition, Német *et al.* found that DSC measurement alone tended to deceptively amplify a tendency of the pure modification B to convert into the more stable form A under pressurization, whereas FT-IR and Raman spectroscopic methods or X-ray powder diffractometry exhibited no essential change in the crystal structure of the metastable form B of FAM (68).

Table IV Studies on Polymorphic Characteristics and Polymorphic Transformation of Famotidine *via* Various Analytical Determinations

API	Description/results of the study	Polymorphic forms	Analytical methods	References
I. Basic calculations				
Famotidine	Electron density distribution	A, B	Single-crystal x-ray diffraction	(53)
Famotidine	Geometric parameter calculations	A, B	FTIR, PXRD	(52)
Famotidine	Crystal and electronic structure calculations	A, B	X-ray crystallography	(63)
II. Identification				
Famotidine	Spectroscopic and physico-chemical studies	A, B	FTIR, PXRD, DSC, micromeritics	(51)
Famotidine	Characterization of three polymorphic forms	A, B, C	DSC, IR, PXRD, HSM	(47)
Famotidine	Polymorphism and crystallization	A, B	PXRD, FTIR, DSC, TGA, HSM, Raman, SEM	(57)
Famotidine	Characterization and selective crystallization	A, B	PXRD, FTIR, DSC, TGA, HSM, Raman, SEM	(46)
Famotidine	Quantitative analysis in binary mixture	A, B	PXRD Raman	(48)
Famotidine	Rietveld refinement of quantitative analysis in binary mixture	A, B	PXRD	(64)
Famotidine	Preparation and evaluation	Famotidine PVP polymorph Famotidine methanol polymorph	DSC, FTIR, SEM, PXRD	(65)
III. Processing-induced polymorphic transformation				
Famotidine	Grinding effect	A, B	DSC, FTIR, DSC-FTIR	(49)
Famotidine	Milling effect	A, B	Raman microspectroscopic mapping	(54)
Famotidine	Heating effect Compression effect	A, B*, B	Raman, DSC	(66)
Famotidine	Effect of pressure	A, B	DSC	(67)
Famotidine	Pressurization effect	A, B	DSC, FTIR, Raman, PXRD	(68)
Famotidine	Effect of compression pressure	A, B	Thermal-Raman, DSC	(69)
Famotidine	Effect of environmental humidity and water added	A, B	DSC, TGA, FTIR	(55)
IV. Formulation detection				
Famotidine	Qualitative and quantitative study in drug formulations	I (A), II (B)	Near infrared FT-Raman	(70)
Famotidine	Quality control on pharmaceutical products	A, B	Terahertz time-domain spectroscopy	(71)
Famotidine	Identification and multicomponent quantitative analysis	A, B	Terahertz spectroscopy (Terahertz spectroscopic imaging)	(72)
Famotidine	Electrospun formulations	Mixtures of A and B.	PXRD, DSC, SEM, Particle size analyzer	(73)

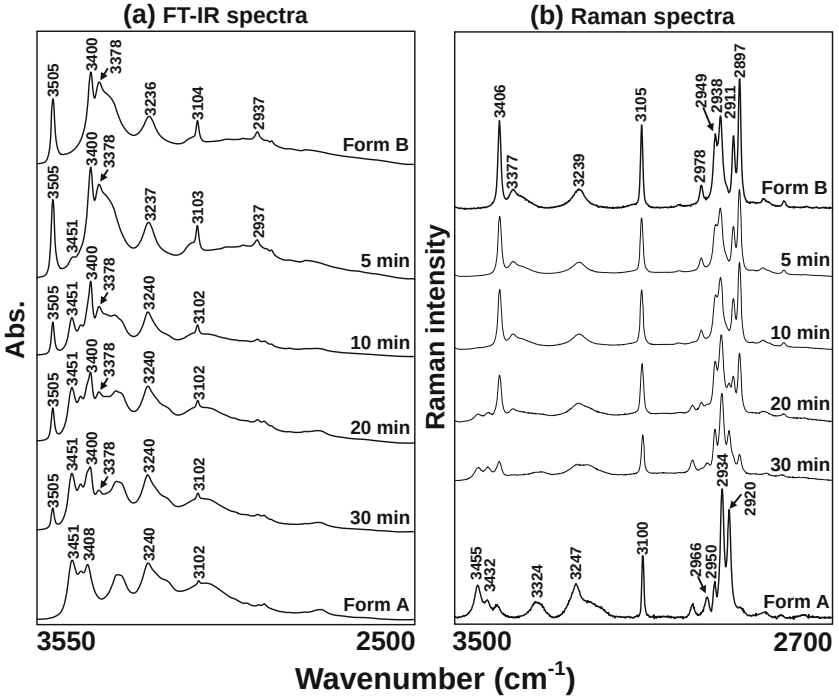

Fig. 5 Grinding process-induced polymorphic transformation of famotidine from form B to form A (modified from ref. (49) and (54)).

Lin *et al.* had also combined Raman and DSC analytical methods to investigate the compressed FAM compact (66), in which two types of FAM compacts (compact I or II) were prepared by compressing a conical shape or a flattened shape of powder bed of FAM form B. The compact I was constructed by a transparent zone in the center surrounding an opaque zone. The compact II was formed by a whole opaque zone after compressing a flat-shape mass of FAM form B. The Raman spectral results clearly indicate that all the compacts whether in any zone before DSC determination were only of FAM form B (Fig. 7). Under DSC determination, however, FAM form B in the transparent zone sample obtained from compact I was gradually transformed to FAM form A with the increase of compression pressure. It is interesting to note that a transitional phase of FAM form B (form B*) in the transparent zone of compact I was clearly detected after applying compression $>1.47\times10^4$ kPa, and then transformed to FAM form A under DSC continuous heating condition. However, this transitional phase and polymorphic transformation of FAM in the compact I could not be identified by using other spectroscopic methods. This transitional phase of FAM form B* in the transparent zone formed by applying the higher

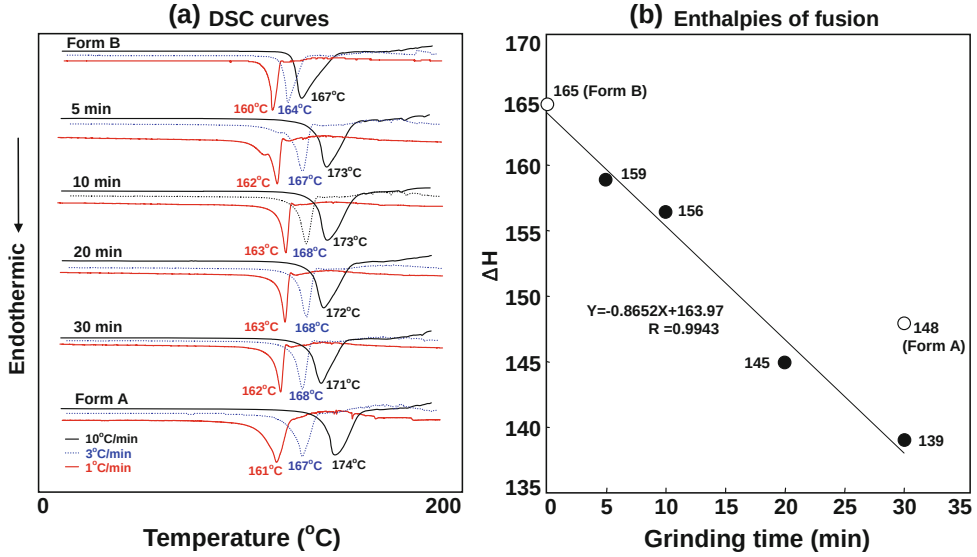

Fig. 6 The changes in DSC curves and enthalpies of fusion of famotidine with the increase of grinding time (modified from ref. (49))

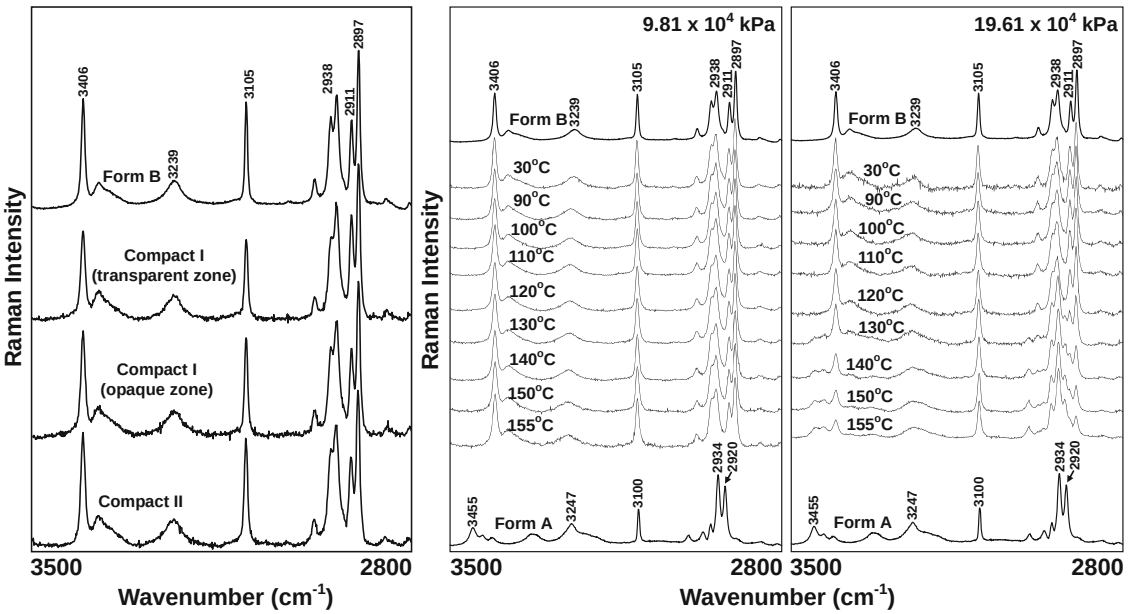

Fig. 7 Raman spectra of famotidine samples after different treatments and temperature-dependent Raman spectral changes of the transparent zones in the compact I after applying two compression pressures (modified from ref. (66) and (69)).

compression pressure might be proposed to be another metastable form of FAM form B, due to easy transformation to FAM form A after thermal treatment. Without DSC determination, all the Raman spectra in each zone of both FAM compacts exhibited a similar Raman spectrum of the intact FAM form B (Fig. 7). This was consistent with the results of Roux *et al.* and Német *et al.* (68,69), in which even the higher compression pressure also failed to cause the polymorphic conversion of FAM.

Thus, Lin *et al.* had used thermal-Raman microspectroscopy to investigate the polymorphic transformations of FAM form B in the transparent zone of compact I after applying different compression pressures (Fig. 7) (69). Under a pressure of 9.81×10^4 kPa applied, all the Raman spectra still exhibited the Raman spectrum of FAM form B and independent of heating temperature. Once the compression pressure was over 19.61×10^4 kPa and the temperature was higher than 100°C; however, the Raman bands underwent a dramatic change. The Raman peak intensity at 2,920 cm^{-1} assigned to the FAM form A gradually appeared for the transparent zones in compact I with an increase in temperature. By increasing the temperature, the Raman peak intensity at 2,920 cm^{-1} further increased accompanied by reduction of the Raman peak intensity at 2,897 cm^{-1}. This strongly shows that combined mechanical compression and temperature could accelerate the polymorphic transformation of FAM from form B to form A in the transparent zone. On the other hand, the opaque zone consisted only of FAM form B and independent of the thermal and compression effect. Here, the Raman spectrum of FAM form B* did not find.

Humidity and Water Effects

Cheng and Lin studied the effect of environmental humidity and additional water added on the polymorphic change of FAM in the process of grinding (55). Their results indicated that higher environmental humidity may actually accelerate the induction of the polymorphic transformation of FAM from form B to form A in the process of grinding. Moreover, the greater the amount of water externally added, the easier the polymorphic transformation of FAM from form B to form A obtained. Their study suggests that the environmental humidity of operation conditions and the residual water content in FAM sample should be well controlled to prevent the polymorphic transformation of FAM polymorphs in pharmaceutical grinding processes.

QUALITY CONTROL FOR FAMOTIDINE FORMULATIONS

Since FAM is an available API produced on an industrial scale and as such may be exposed to significant mechanical influences during the manufacturing procedure, extreme care is needed during formulation. Regulatory agency guidelines now also advise the monitoring of crystal forms in drug products and emphasize the need for applicable analytical methods. Apart from APIs, commercial solid drug products always contain one or more excipients, which may make identification of

individual crystal forms of a drug more difficult. FT-Raman spectroscopy has been suggested to be one of the fastest, most reliable and most suitable direct analytical techniques for identification of crystal forms in drug products and can be easily exploited routinely for monitoring phase changes in drug products and quality control assays (70). Auer *et al.* used FT-Raman spectroscopy to detect the Raman characteristic bands (e.g., at 1239.8, 1009.3, 971.4, and 740.1 cm^{-1}) of FAM by preventing the interferences of the vibration bands of the excipients present in the tablets, and the metastable form B was found in three commercial drug products.

Recently, terahertz spectroscopy has been extensively applied for detection of polymorphic forms of FAM in tablets (72,78,79). Terahertz waves penetrate many types of materials and can be used to confirm molecular uniformity as well as to identify crystal polymorphs. Terahertz time-domain spectroscopy (THz-TDS) is the most popular type of terahertz spectroscopy. A THz-TDS investigation is also being used in quality control in the pharmaceutical industry. A THz chemical imaging (TCI) system was developed by combining THz-TDS with a translational sample stage to nondestructively obtain two-dimensional distributions of molecular networks (80). Because TCI technology using the terahertz absorption spectrum can reveal the molecular network in addition to the molecular distribution, it can provide a new method for both drug identification and pathological examination. Figure 8 shows the terahertz absorption spectra of FAM tablets containing crystalline forms A and B of FAM with polyethylene binder as well as transmittance TCI images (79). Forms A and B of FAM were easily identified in the terahertz spectrum because there were differences in the absorption characteristic peaks of form A (1.2 THz) and form B (1.6 THz). In the test tablets, regions of the FAM form A tablet on the left and regions of the FAM form B tablet on the right could be clearly identified. On the other hand, in the commercial drug tablet images, there is almost no form A, whereas FAM form B is widely distributed as API. These results strongly suggest the potential use of TCI as a pharmaceutical nondestructive evaluation technique in the pharmaceutical industry.

Kawase *et al.* applied THz-TDS to clearly detect the differences in the THz spectra of FAM in the commercial tablets before and after the expiration dates (81). Because THz-TDS is very sensitive to the change of polymorphs and to the intermolecular interaction of molecules, the THz spectra could detect the difference between new and old FAM in tablets. In addition, because THz-TDS can perform nondestructive measurements of medicines, THz-TDS is a preferable method and a promising tool for quality control of medicine tablets.

CONCLUSIONS

FAM (trade name of Pepcid®) is a famous third generation H_2-receptor blocker for the treatment of gastrointestinal ulcers and other new indications (36–42). Although FAM has three polymorphs, forms A, B and C, the API of FAM commercialized in the market is the metastable form B. The existence of these FAM polymorphs has been a concern of the US FDA due to the differences in the physical properties,

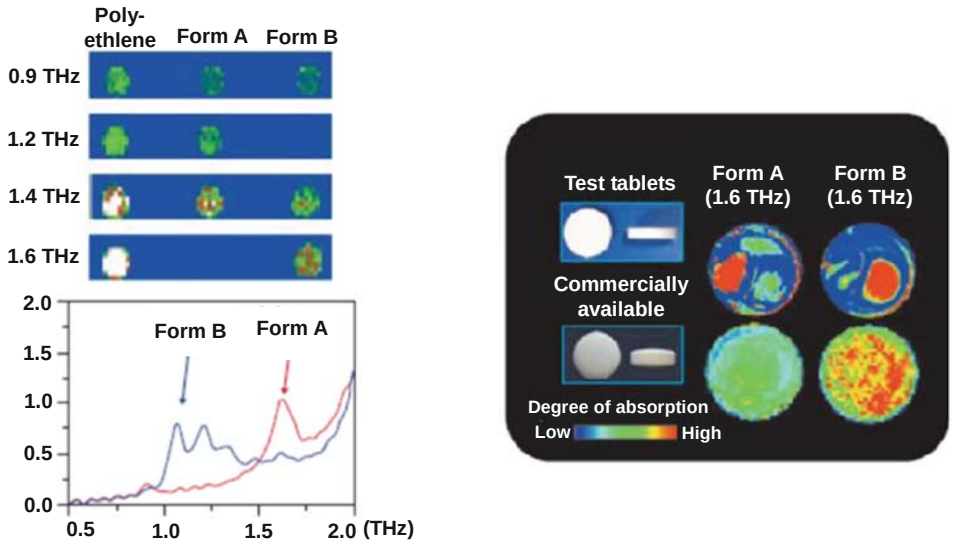

Fig. 8 TCI mapping of test and commercial famotidine tablets (modified from ref. (79)).

(a) Terahertz absorption spectra and transmittance images of a famotidine tablet with different polymorph A or B.

(b) Terahertz absorption images of test and commercial famotidine tablets.

solubilities, bioavailabilities, or bioequivalences of the polymorphic forms (8,11,46–51). Since several pharmaceutical processes, such as grinding, compression and heating temperature, have a significant influence on the polymorphic transformation of FAM, therefore, each unit operation in the pharmaceutical manufacturing processes must be carefully performed to ensure the more stable form of FAM existed in the final drug product. Moreover, environmental humidity and residual water content should be well controlled to prevent further polymorphic transformation of FAM during pharmaceutical processing. In addition, a patent infringement suit involving FAM polymorphs presented a particularly sound legal argument (82–84), which demonstrates the importance of solid-state polymorphism in the pharmaceutical industry. Recently, the potential use of a new instrument as a pharmaceutical nondestructive evaluation tool in the pharmaceutical industry has also paved the way for quality control of drug polymorphs in the pharmaceutical dosage forms.

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