ELSEVIER

International Journal of Pharmaceutics 140 (1996) 195–206

international journal of pharmaceutics

Polymorphic transitions of cimetidine during manufacture of solid dosage forms[1]

A. Bauer-Brandl*

Albert-Ludwigs-Universität Freiburg, Department of Pharmaceutical Technology, Hermann-Herder-Str. 9, D-79104 Freiburg, Germany

Received 1 December 1995; revised 24 April 1996; accepted 6 May 1996

Abstract

Four modifications of cimetidine (A, B, C, D) and a monohydrate (M1) were prepared in pure form according to published protocols. Modification D, however, could only be obtained after substantial alterations of the protocol. In many cases crystal phase mixtures of the water-free forms were yielded. Melting points of the modifications being very close to each other, neither differential scanning calorimetry (DSC) nor thermomicroscopy would hint at the existence of different modifications, but light microscopy, X-ray diffraction (XRD) and IR spectroscopy do. Stabilities of polymorphs under conditions of industrial production of solid dosage forms were assessed: during dry storage all the pure modifications, even the monohydrate, were found to be stable for more than a year. In aqueous suspension, modification A changed completely into B after a short time, whereas it transformed to D in 50% ethanol. Transformation in the dry state was observed upon milling. Both B and C transformed to A, whereas A transformed into D only upon nucleation. In all cases milling caused substantial amorphisation. Upon compression no transformation was found. Tabletability of the raw materials was investigated. The results indicate that form A, which is used in the marketed tablets, shows fairly good properties only surpassed by M1.

Keywords: Cimetidine; Polymorph; X-ray diffraction; Differential scanning calorimetry; Tablet; Grinding

1. Introduction

Even though many drug substances show distinct crystal polymorphism, neither the United States nor the European Pharmacopoeia consider this phenomenon widely (for a review see Borka et al., 1991). Drug polymorphism, however, may not only cause confusion in analytics but also

* Corresponding author. Tel.: +49 761 2036365; fax: +49 761 2036366; e-mail: brandl@sun2.ruf.uni-freiburg.de

[1] Dedicated to: Professor Dr. H. Rupprecht on the occasion of his 60th birthday.

PII S0378-5173(96)04587-5

affect the chemical stability of the drug substance itself as well as the physical stability of the dosage forms (for a review on pharmaceutical aspects see Haleblian and Mc Crone, 1969). Furthermore, the crystal structure is crucial for the dissolution behaviour and therapeutic effectiveness of drugs and dosage forms. As a rule the metastable, i.e. thermodynamically instable modifications show best solubilities, fastest dissolution rates and highest bioavailabilities. On the other hand it can be expected that the metastable modifications in particular give rise to stability problems by transforming to more stable modifications during processing and storage, as was found for example for caffeine (Chan and Doelker, 1985; Pirttimäki et al., 1993).

An analytical problem often arising with organic substances is that relatively large single crystals needed for the elucidation of the explicit crystal structure by X-ray diffraction (XRD) cannot be produced. Then it is difficult to distinguish real modifications from 'crystalline phases' (Verma and Krishna, 1966). A critical review about the meaningfulness of phenomenological description of crystal phases (e.g. observation of transformation in the hot stage microscope, comparison of DSC-curves and IR-spectra) is given by Burger (Burger, 1982).

In the present study cimetidine was chosen for the following reasons: transformation from one crystal modification into another during processing is of particular significance with high-dose drugs, because only a minor proportion of excipients can be added to improve properties of manufacture and performance (tabletability, dissolution rate, bioavailability). Cimetidine is therapeutically used in maximum doses of 800 mg per tablet having a drug content of 70–90% (calculated from Pharmazeutische Bestimmungsliste, 1994/95). With cimetidine in particular, the effectiveness as an inhibitor of histamine mediated gastric acid secretion (H_2-antagonist) is correlated with a high dissolution rate in the stomach: the drug acts as a competitive inhibitor of histamine at histamine receptors of the parietal cells. It is important to mention that cimetidine also has a systemic effect on the production of gastric acid. Blood levels of above 0.5 μg/ml are required for 90% inhibition of basal gastric secretion (Burland et al., 1975; Pounder et al., 1976).

The particular aim of the present study was to investigate polymorphic transitions of cimetidine during processes which are applied during the industrial manufacturing of dosage forms such as milling, wet granulation, drying at increased temperatures, tableting and storage. Four anhydrous 'modifications' (two of them with explicit X-ray structures published) were studied as well as one monohydrate (for a review see Hegedüs and Görög, 1985), but no salts nor complexes which are readily formed by cimetidine also (Greenaway et al., 1980; Burns et al., 1983; Shibata et al., 1983b; Kamiya et al., 1985). The nomenclature of Hegedüs (Hegedüs and Görög, 1985) is used throughout the paper.

2. Materials and methods

2.1. Preparation of the modifications

Cimetidine raw material came from Allphamed (Allphamed Pharma GmbH, D-Göttingen, Ident. Nr. 327900). Fractional crystallisation was carried out using distilled water and analytical grade solvents after the following instructions:

- Modification A: crystallisation from warm (60°C) methanol water mixture (80% v/v) (Prodic-Kojic et al., 1979) or preferably isopropanol (Bavin et al., 1976) at room temperature
- Modification B: hot 15% (w/w) aqueous solution (70°C) is cooled slowly (Hegedüs and Görög, 1985)
- Modification C: 5% (w/w) aqueous solution is cooled rapidly to 5°C (Hegedüs and Görög, 1985)
- Modification D: a saturated solution of cimetidine in methanol/water mixture (1:1, v/v) at 25°C of pH 6 (adjusted using acetic acid) is brought to pH 8.5 in an ice bath by adding concentrated ammonium. The mixture was left in the ice bath for 1 h prior to separating the crystals by filtration and washing using cold water (no reference).

- Monohydrate M1: hot 15% (w/w) aqueous solution is poured into threefold the amount of ice (Harsanyi et al., 1981)

2.2. Methods of analysis

- Microscopy was carried out using a Zeiss Axioskop interference contrast microscope (Carl Zeiss, Oberkochen, Germany)
- Thermomicroscopy (Reichert 'Thermovar' hot stage microscope, C. Reichert AG, Vienna, Austria), heating rate 2 K/min; for visualisation of evaporating solvents from the crystals in liquid paraffin
- DSC: PL-Thermal Sciences Ltd (Epsom, Surrey, U.K.); closed aluminium cups, sample weight 9–10 mg, starting temperature 25°C, heating rate 5 K/min
- Karl-Fischer-Titration: (Metrohm Multi-Dosimat E415, Herisau, Germany); Methrohm Automat E 547; reagents: Hydranal™ (Merck, Darmstadt, Germany)
- IR-Spectroscopy: Perkin-Elmer 841 (Perkin Elmer Corporation, Norwalk, CT, USA); scan limits: 4000–600 cm $^{-1}$: resolution 2.4 cm $^{-1}$, noise 0.5% of transmission; KBr-pellet of 12 mm diameter, weight 300 mg; 0.5 mg pure substance compressed to maximum 10^5 N. Evaluation was done by comparison with band tables given by Hegedüs and Görög (1985).
- X-ray powder diffraction: Stoe (Darmstadt, Germany), Cu K_α radiation, 40 kV, 35 mA, step: 0.02° of 2θ from 5 to 50°; fixing of powdered samples between adhesive tape
- Tableting: Korsch EK2 (Korsch Maschinenfabrik, Berlin, Germany), force and displacement instrumented, described in detail elsewhere (Röscheisen, 1994); tablet diameter 10 mm. Tableting was done under standard conditions: no addition of any excipients to the powders; punches and dies were lubricated with a suspension of magnesium stearate in acetone; hand-filling and compression to 5 kN maximum force and to the same tablet thickness for all materials
  Tablet properties: Schleuniger breaking strength tester (Dr. K. Schleuniger + Co, Solothurn, Switzerland)
- 'Pulverisette'-mortar-mill with agate mortar and pestle (Retsch GmbH, Haan, Germany)
- Sorption isotherms apparatus after Schepky (1982), modified after Trautmann (1990); thermostatisised at 25 ± 0.1°C using the following salt solutions: LiCl (12% r.h.), $MgCl_2$ (33% r.h.), K_2CO_3 (44% r.h.), NaBr (57% r.h.), NaCl (76% r.h.), $(NH_4)_2SO_4$ (80% r.h.), KCl (84% r.h.) and dried P_2O_5 (0% r.h.); sample size ca. 1 g of the dried substance (3 days above P_2O_5); gravimetrical determination of the amount of water until weight constancy (took ~3 weeks).

3. Results and discussion

3.1. Preparation and characterisation of the modifications

3.1.1. Modification A

Modification A can be prepared easily, because it is the only modification of cimetidine crystallising spontaneously from isopropanol at high supersaturation (Sudo et al., 1991a). Modification B can only be formed in isopropanol in the presence of seeding crystals (Sudo et al., 1991a), whereas the other modifications cannot be formed in isopropanol at all. The explicit X-ray structure of modification A has been resolved by (Hädicke et al., 1978). By comparing theoretical and measured peaks in the powder XRD pattern, identity and purity of the obtained crystals was found (peak tables not shown).

3.1.2. Modification B

Modification B could be gained using the protocol in the literature (Hegedüs and Görög, 1985), where it is called both a modification and amorphous at the same time. In our hands it contained quite an amount of amorphous material, which can be estimated from a 'hill' in the background baseline of the powder X-ray pattern at small Bragg angles. As the explicit structure of the crystal is not yet elucidated, and the substance is

not characteristic in the microscope, characterisation could only be carried out by IR spectroscopy in comparison with those of Hegedüs (Hegedüs and Görög, 1985) (data not shown).

Modification B could be gained in much higher quality if modification A remained in aqueous suspension at room temperature (25°C). Sharp needles of good purity and higher crystallinity were obtained with maximum lengths of approximately 40 μm (Sudo et al., 1991a). After 3 weeks, complete disappearance of modification A-related peaks in the powder X-ray diffractogram was seen. The X-ray diffractogram is depicted in Fig. 4 (starting material, 'modification B'). Identity of the material was again confirmed by IR spectroscopy.

Therefore it is assumed that B is a real modification, but the crystals are too thin for single crystal X-ray structure analysis. Furthermore the needle-shaped crystals were found to disturb powder X-ray patterns by forming textures in the sample holder (see also Bauer et al., 1990).

3.1.3. Modification C

Modification C was gained quite reproducibly after the protocol in the literature (Hegedüs and Görög, 1985), and in better purity if seeding crystals were used in a second crystallisation step. The needles could easily be distinguished from those of modification B by their colour in the interference contrast microscope. This may also be an effect of their thickness, which is some 10-fold that of modification B. No needles thicker than ca. 15 μm in diameter could be crystallised, because of which the structure of this substance could not be elucidated by single crystal XRD either. Therefore it cannot be excluded for sure that modifications B and C are of the same crystal structure as was suspected by Tudor et al. (1991).

3.1.4. Modification D

Modification D was found not to crystallise under the conditions given in the patent of Kreidl et al. (1981) nor the protocol given by Parkanyi et al. (1984). Instead modifications A, B, C or M1 or mixtures thereof were obtained, but not in the case of D. By altering concentration of the starting solution and temperature treatment (see Section 2.1.), crystals of D of some 10 μm in size were formed, the purity and dimension of which could be greatly increased by a second crystallisation step. The explicit X-ray structure of modification D has been elucidated by Parkanyi et al. (1984). The expected theoretical plot of the powder X-ray pattern is given in Fig. 1 in comparison with the XRD pattern of the material obtained. Again a 'hill' in the background was observed (Fig. 1), which could result from amorphous proportions. It was always subtracted for a straight baseline and by comparing Bragg angles, modification D was identified.

3.1.5. Monohydrates

From the three monohydrates described in the literature (Hegedüs and Görög, 1985) the (pseudo-) modification M1 is easily accessible and its structure can be characterised definitely by its X-ray powder diffraction pattern (Kojic-Prodic et al., 1980; Harsanyi et al., 1981) and IR spectrum.

Very often during preparation of M1, particularly when the original solution was cooled down rapidly, a mixture of modifications M1 and anhydrous A or C was gained instead of the pure hydrate which was concluded from the IR spectra (data not shown).

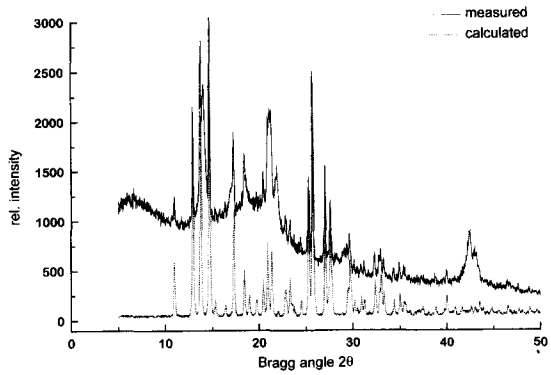

Fig. 1. X-ray powder diffraction pattern of cimetidine modification D: comparison of measured data and those calculated from the crystal structure.

3.2. Stability during processing and storage

As there are no reports published on polymorphic transitions of cimetidine during manufacturing and storage of solid dosage forms, the above mentioned modifications were analysed in the presence of humidity and solvents and under thermal and mechanical stress.

3.2.1. Water loss and water uptake during storage at ambient temperatures

The monohydrate M1 is described to be unstable upon storage at ambient conditions: it would transform into one of the water-free forms by water loss (unpublished data cited in Sudo et al., 1990). First, the water sorption isotherme of the pure monohydrate M1 was determined using an apparatus previously described by Schepky (1982), modified after Trautmann (1990). Water uptake was found to be very small (maximum of 1.4% water uptake at 84% relative humidity). Additionally the water-content of a sample of M1 stored at ambient temperatures in an evacuated desiccator over silica gel for 6 months was analysed using Karl-Fischer titration: 7.4% (m/m) water content was found ($n = 3$; theoretical value 6.7%) at the end of the period. According to the IR spectrum it was still in the form of M1. It was thus concluded that the pure monohydrate is of fair stability in terms of water loss and uptake at room temperature. Impure M1, as judged from IR spectra, in contrast to the above mentioned findings, however, lost its water of crystallisation relatively quickly (within 2 months at ambient conditions and even faster in a desiccator) and in this case all the substance transformed into modification A (identified from the IR spectrum). This may indicate that the water loss described by Sudo et al. (1990) may have occurred due to impure starting material.

3.2.2. Thermal stress

Thermal stress was applied in order to study high-temperature stability of the polymorphs.

3.2.2.1. Modification M1. When heated above approximately 65°C on a hot stage polarisation microscope it was observed that the pure (pseudo-)

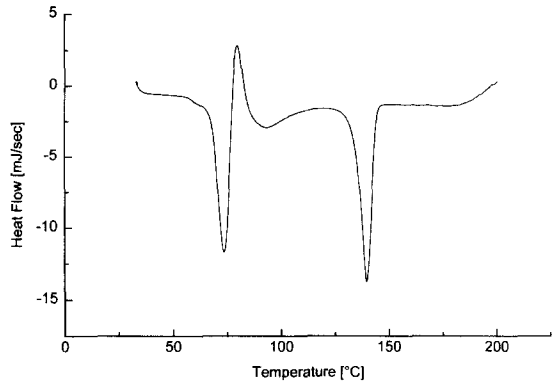

Fig. 2. DSC trace of cimetidine monohydrate M1. Endothermic peaks at 73.6°C (water vaporisation) and at 139.8°C (melting); scan rate 5 K/min, closed aluminium cup.

modification M1 readily transformed under loss of its water of crystallisation. Products of this transformation were studied in detail by heating samples of one single batch of pure M1 to temperatures of 90–110°C in the DSC oven using different temperature programs (heating rate 1 K/min or 5 K/min, holding time 5 min) and the resulting material was analysed by IR spectroscopy. It was found that modifications A, B or C or mixtures thereof were formed in an irreproducible manner, whereas impure M1 transformed to the modification already enclosed as an impurity. As can be seen from a typical DSC scan of modification M1 given in Fig. 2, an endothermic transition appears with onset temperatures of 70.6 ± 2.55°C, peak temperatures of 75.7 ± 2.16°C and heats of transition of 140.5 ± 21.1 mJ/mg (mean and standard deviation, $n = 10$). This peak is interpreted as monohydrate to anhydrate transition. In many cases a second peak was observed in the temperature range of 135–155°C, which was assigned to the melting of the anhydrous form.

3.2.2.2. Water-free modifications. In order to prove which of the anhydrous forms A, B, C or D is most stable at high temperatures, their behaviour during heating was observed on a hot stage polarisation microscope as well. There was no transformations, but in all cases spontaneous and clear melting of the respective crystals was observed and the glassy product did not recrys-

tallise during months of storage at room temperature. In the DSC each scan of all the anhydrous modifications at different heating rates (10 K/min; 5 K/min; 1 K/min) showed a single neat peak without any extra peaks or shoulders. Representative DSC scans of modifications A and D are given in Fig. 3. The corresponding onset temperatures, peak temperatures and heats of fusion are summarised in Table 4 together with data for modifications B, C and M1. In agreement with the literature (Table 1(a)) all of the four modifications were found to have very similar melting points (between 141 and 143°C) and heats of fusion (between 135 to 155 mJ/mg). The differences observed are all regarded to be smaller than the reproducibility of the method (Burger, 1982). Additionally, all substances were heated in the DSC following predefined temperature programs (Tables 2 and 3) which were designed to incubate the materials as close to their melting points and as long as possible without melting. The resulting substances were then analysed by IR spectroscopy 24 h later. No hints on transformation of any of the anhydrous modifications were found in the IR spectra (data not shown). Under these conditions A, B, C, and D are monotropic.

The above mentioned formation of mixtures of two anhydrates upon dehydration of M1 as well as yielding mixtures of modifications (mainly A, B, and/or C) when crystallising can be explained by the anhydrates as being more or less isoenergetic. Thermodynamic stability can also be estimated from true densities and equilibrium solubilities, but the values reported in the literature (Table 1(b, c)) are also within the tolerance of the respective methods (Burger, 1982).

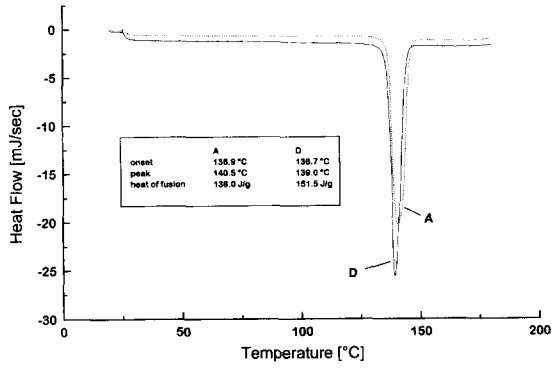

Fig. 3. DSC melting curves of modifications A and D; scan rate 5 K/min, closed aluminium cup.

3.2.3. *Stability in the presence of water and other solvents*

Transformation from one modification to the other may be easier in aqueous slurry and would be of interest for wet granulation. Pure modifications A, B, C and D were therefore incubated in water at room temperature and eventual transformations were monitored by light microscopy and IR spectroscopy. Apart from the transformation of modification A to B (as mentioned above as a means of preparing nice B-crystals; Section 3.1.2) no other transformation was observed within 12 months. However, it was observed that an aqueous slurry of a 1:1 mixture of modifications A and D transformed to modification C after very long time periods (more than a year) and much quicker upon heating above 50°C as revealed by means of IR spectra, X-ray patterns and the characteristic needles in the light microscope.

A physical mixture of modifications A and D was incubated in an ethanol–water mixture (50% v/v) at room temperature. It readily transformed to D rather than C as reported for aqueous medium. In a high shear mixer, additional transformation mechanisms would probably increase the transformation tendencies observed.

3.2.4. *Mechanical stress by grinding*

Micronisation of dry drug substances in order to gain good peroral bioavailability can be of extremely high energy and last for relatively long periods of time. Transformations induced by grinding are summarised in Table 5. In contrast to stability against thermal stress, modification C readily transformed to modification B upon minor mechanical treatment, i.e. trituration by hand using an agate mortar and pestle for less than 2 min as revealed by IR spectroscopy. This transformation is of particular importance because this treatment has to be done as a matter of routine, e.g. for standardising particle size for DSC studies and for X-ray powder diffraction. The transformation could be avoided if trituration of the substance

Table 1
Comparison of published data of physico-chemical properties of modifications of cimetidine

Reference	Method	A	B	C	D	M1
(a) Melting points (°C)						
Bavin et al. (1984)	USP XX	140–143.5				
Shibata et al. (1983a)	DSC: 20 mg 5 K/min; peak	149–152		152–154		81–83
Parkanyi et al. (1984)					141–143	
Sudo et al. (1991b)		141–143	142–145	145–146		
Prodic-Kojic et al. (1979)	Kofler micro-heating stage, 4 K/min	141–144	142–145	145–146		70–85
Kajfez et al. (1977)		142–143				
(b) True densities (g/cm^3)						
Bavin et al. (1984)		1.2815				
Shibata et al. (1983a)				1.351 D_m	1.310 D_m 1.320 D_x	1.333 D_m 1.310 D_m 1.337 D_x
Hädicke et al. (1978)		1.30 meas. 1.31 calcul.				
Parkanyi et al. (1984)					1.321 D_x	
Kojic-Prodic et al. (1980)						1.330 calcul.
(c) Equilibrium solubilities in water (g/l)						
Bavin et al. (1984)		5.0 (20°C) 6.15 (25°C) 11.4 (37°C)				
Shibata et al. (1983b)		5.4 (25°C)		4.7 (25°C)	5.0 (25°C)	5.8[a] (25°C)
Prodic-Kojic et al. (1979)		1.2% (35°C)[b]				
Sudo et al. (1991a)		4.3 (20°C)[b]	3.3 (20°C)[b]			

[a] Calculated in the form of the anhydrous form.
[b] estimated from published graph.

was carried out at very low temperatures in the presence of liquid nitrogen.

After Sudo et al. (1991b) transformation from B to A is not observed during trituration. In our opinion, however, in their diagram a clear-although not yet significant-trend appears after treatment per hand for 20 min. In the present study the same trend was found when modification B was ground in a mortar-mill: after a few hours of grinding (10 h), modification B had transformed completely to modification A. The respective XRD patterns after 0, 15, 60 and 600

Table 2
Temperature programs followed in transformation studies

Modification	Heating rate	Maximum temperature	Retention time
A	5 K/min	137°C	1 min
B	5 K/min	137.5°C	1 min
C	5 K/min	141°C	2 min
D	5 K/min	137°C	5 min

Table 3
Storage temperatures and conditions

Modification	Maximum temperature	Retention time
A	130°C	10 h
B	130°C	10 h
C	130°C	20 h
D	130°C	10 h (brown)

Table 4
Crystal habit and melting behaviour of cimetidine polymorphs (mean and S.D., $n = 3$)

Modification	A	B	C	D	M1
Crystal habit	Platelets	Fine sharp needles	Needles	Prismatic	Pyramidal
Melting behaviour onset (°C)	136.8 ± 0.1	133.5 ± 0.3	137.8 ± 0.4	136.7 ± 0.4	70.6 ± 2.55
Melting behaviour peak (°C)	140.4 ± 0.2	140.4 ± 0.1	144.3 ± 0.3	139.1 ± 0.3	Decomposition
Heat of fusion (J/g)	139.3 ± 5.2	140.2 ± 5.3	145.0 ± 7.0	148.6 ± 8.4	—

min of grinding are depicted in Fig. 4. The velocity of transformation, however, could not be quantified because an increasing amount of amorphous material was formed during the procedure. This can be estimated from the increase of the baseline at low Bragg angles and decreasing intensities of the maxima. The 'hill' in the baseline has been corrected as described above. Even extended grinding of modification A for another 24 h, which would also increase the temperature of the sample markedly but not quantifiably, did not give rise to another transformation but to further amorphisation. DSC curves of both the starting material and the same material after 34 h of grinding, are compared in Fig. 5. The shift of the melting peak to lower temperatures and its broadening can be assigned to the increased fraction of amorphous cimetidine after grinding. The obtained data, however, did not allow for quantification of the proportion of amorphous material (see also Hüttenrauch, 1978).

In summary, shear stress, temperature rise and grinding amorphisised substances C and B and led to modification A in both cases. Similar transformations of drug substances in the dry state resulting in the most stable forms were described for chloramphenicol palmitate by Kaneniwa and Otsuka (1985). They determined dissolution properties of original modifications and ground products also, but no reference is made to particle size effects which in addition to amorphisation do enhance dissolution rates (Kuhnert-Brandstätter and Burger, 1972). Therefore dissolution rates are regarded difficult to interpret and were not studied here. The mechanisms of transformation during grinding of other drugs were described by Otsuka et al. (1994): for cephalexin, chloramphenicol palmitate and indomethacin they found it going through amorphous states of the material followed by transformation to another polymorph which would only start upon nucleation by crystals of the product. Therefore artificial nucleation of cimetidine modification A by admixing some crystals of modification D (0.1%) was initiated. Subsequently a transformation of modification A to D was observed during grinding, which was completed after 84 h. This polymorphic transformation was also accompanied by the respective temperature increase and considerable amorphisation. A 1:1 mixture of modifications A and D transformed completely to D within 6 h. Pure modification D did not show any sign of transformation and was stable, with the exception of amorphisation, during grinding for more than 30 h.

In summary, A is more stable than B and C, but less stable than modification D when it comes to mechanical stress. The tendency of recrystallisation of amorphous material in the above described ground modification A was below the detection limit during storage at ambient conditions for 1 year as estimated by the X-ray patterns, IR spectra and DSC traces (data not shown).

3.2.5. High pressure (tableting)

The existence of high-pressure induced polymorphism is well documented for many inorganic substances and also for some drugs (e.g. Chan and Doelker, 1985). In order to find out whether there is a high-pressure form of cimetidine, all the modifications were compressed in a manually operated hydraulic-driven press without using any excipients under a load of 10 t (flat punches of 12 mm in diameter) for 10 min. It is known for other substances that often only a small proportion of

Table 5
Behaviour of cimetidine polymorphs under stress

Storage at room temperature	A	B	C	D	Pure modification: stable mixture
Transformations of Modification	A	B	C	D	M1
Dry storage at ambient conditions	—	—	—	—	Pure modification: stable mixture M1+A, B or C: →A, B or C
At increased temperature	—	—	—	—	Pure M1: irreproducible mixture M1+A, B or C: →A, B or C
Storage at room temperature in water	3 weeks → quantitatively		—	—	—
Mechanical treatment	← grinding within hours	← trituration within minutes			n.d.
	grinding, seed crystal of D → within hours				
Compression 10 t, 5 min	—	—	—	—	—

seeds may be formed during compression which would later on give rise to transformation of the whole tablet (Kala et al., 1982). Samples were taken from the upper edge of the tablets, where the zone of most stress is expected to be located, immediately and 14 days after compression and analysed by IR spectroscopy and X-ray powder diffraction. None of the substances A, B, C, D nor M1 showed any indication of polymorphic changes. The degree of crystallinity (indicated by the X-ray powder diffraction pattern and sharp peaks in the IR spectrum) increased under the applied compressional forces when samples of considerable content of amorphous substance (extensively ground material) were compressed.

3.3. Tabletability

In order to evaluate the mechanical properties of modifications, Kopp et al. (1989) recommended the preparation of disks of zero porosity by a melting technique which would provide evaluation of bending strength independently of particle size, porosity and crystal habit. In the case of cimetidine such disks could not be yielded because the material would not recrystallise upon melting. Therefore, in order to simulate 'realistic' processing properties, 'normal' tablets of all modifications, without using any excipients, were produced on a single-punch tablet press under defined standard conditions. Properties of the tablets were tested as described above. The results are summarised in Table 6. It was observed that the modifications B and C are of extraordinarily poor flow properties because they are needle-shaped. The corresponding tablets exhibited good breaking strengths. The observed differences, however, may also be due to different proportions of amorphous material in the crystalline phases. As York (1992) mentioned, high breaking strength is commonly attributed to the proportion of amorphous material being of extended plastic flow during compression. Even traces would affect the compressional behaviour. Modification D was found to be extremely difficult and it was not possible to gain any tablets at any force level without lamination, even if the punch velocity was reduced by operating the tablet press by hand. Tablets of modification A were very soft with the moderate compressional forces used in the test, hardness could be much improved using somewhat higher forces. Harder tablets than from any other material in the test were produced from the monohydrate M1 at the chosen force level (5 kN).

4. Conclusions

Five crystalline phases of cimetidine were prepared and studied. The two water-free modifica-

Table 6
Tableting behaviour of cimetidine polymorphs

Tablets made of Modification	A	B	C	D	M1
Breaking strength (Skt.)	<1	6	3	—	8
Comment	Better with higher compression forces	Poor flow properties	Poor flow properties	Sticking, capping, no tablets	Good flow and tableting properties

tions A and D and the pseudomodification M1 (monohydrate) could be crystallised and their identity confirmed by X-ray powder diffraction, because their explicit structures are known. The other two anhydrous crystalline phases (B and C), the explicit structures of which are not known, are likely to be modifications also, because they could be distinguished from the other modifications and from each other.

Under all conditions of heating of dry samples of anhydrous forms no polymorphic transition was observed. They showed straightforward melting behaviour almost at the same temperature and heat of fusion in the DSC. All four modifications are therefore regarded as isoenergetic within the accuracy of the method. In the presence of water, when the activation energy for the transition is decreased, the only transformation observed was from A to B. When ground extensively, amorphisation and polymorphic transformation was observed: not only modification C transformed to B, but B also to modification A. The latter could only transform to D upon nucleation. Therefore D is regarded as being most stable under tribomechanical treatment.

In contrast to other findings (Sudo et al., 1990), the monohydrate in this study was stable during long-term storage at ambient conditions.

4.1. Choice of 'best' form for tablets

For industrial tablet production B and C will not be used due to their poor bulk flowability. With D no reasonable tablets could be obtained at all whereas modification A, which is used in all the commercial products, is reasonably tabletable. The tabletability of the monohydrate was particularly good. Therefore it may be assumed that the

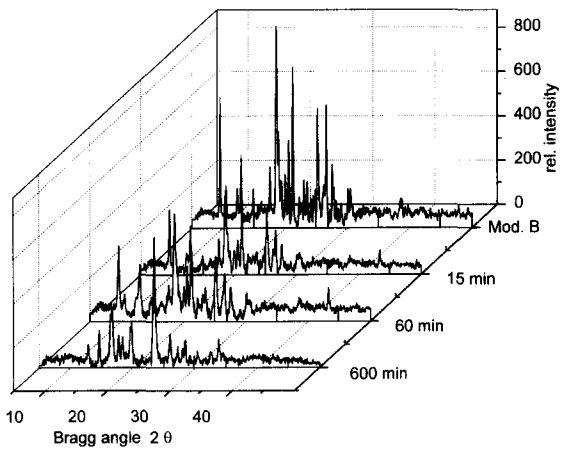

Fig. 4. Polymorphic transformation of modification B to modification A during grinding: X-ray powder patterns after 0, 15, 60 and 600 min in a mortar mill.

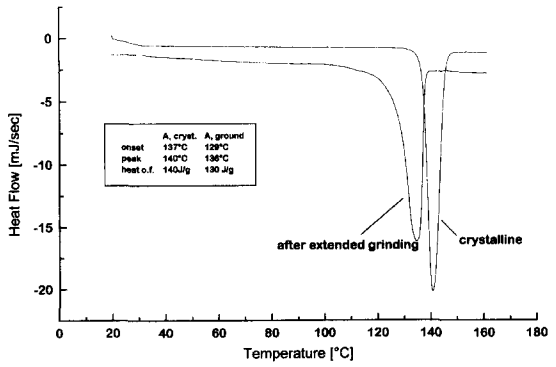

Fig. 5. Effect of extensive grinding on DSC melting traces of modification A: crystalline and partially amorphous material; scan rate 5 K/min, closed aluminium cups.

monohydrate makes very good tablets if polymorphic transition can be avoided, i.e. if crystallised in a suitable particle size distribution and processed by direct compression. Furthermore, it would appear favourable due to its known high dissolution rate and good therapeutical effectiveness in vivo (Shibata et al., 1983a; Kokubo et al., 1987).

Acknowledgements

Acknowledgement We wish to thank Prof. Y.T. Sohn (DukSung Women's University, Seoul), our students B. Witzigmann and H. Schlack; Dr J. Finnefroh and T. Wehrstein (Kristallographisches Institut, University of D-Freiburg) for X-ray powder diffraction, G. Röscheisen (Department of Pahramaceutical Technology, University of D-Tübingen) for tableting, Allphamed for donation of the drug, and Ciba Ltd, CH-Basle for financial support.

References

Bauer, A., Braun, G. and Müller, F., Measurement of rock-salt crystal orientation upon tableting. *Acta Pharm. Technol.*, 36 (1990) 85–90.

Bavin, P.M.G., Post, A. and Zarembo, E. in: Analytical Profiles of Drug Substances and Excipients (K. Florey, ed.), Academic Press, Orlando, Florida, 1984, Vol. 13, pp. 127–182; Vol. 17, p. 797.

Bavin, P.M.G., Sly, J.C.P., Tovey, G.D. and Ward, R.J., Cimetidin A, Verfahren zu seiner Herstellung und seine Verwendung als Histamin-H_2-Rezeptor-Antagonist. *Patent GB 39065-76* (1976).

Borka, L., Review on crystal polymorphism of substances in the European Pharmacopoeia. *Pharm. Acta Helv.*, 66 (1991) 16–22.

Burger, A., Zur Interpretation von Polymorphie-Untersuchungen. *Acta Pharm. Technol.*, 28 (1982) 1–20.

Burland, W.L., Duncan, W.A.M., Hesselbo, T., Mills, J.G., Sharpe, P.C., Haggie, S.J. and Wyllie, J.H., Pharmacological evaluation of cimetidine, a new histamine H_2-receptor antagonist, in healthy man. *Br. J. Clin. Pharmacol.*, 2 (1975) 481–486.

Burns, K., Prout, K. and Durant G.J., Crystal and Molecular structure of N-Nitrosocimetidine nitrate. *J. Chem. Soc. Perkin Trans.*, 2 (1983) 1239–1242.

Chan, H. and Doelker, E., Polymorphic transformations of some drugs under compression. *Drug Dev. Ind. Pharm.*, 11 (1985) 315–322.

Greenaway, F.T., Brown, L.M., Dabrowiak, J.C., Thompson, M.R. and Day, V.W., Copper (II) complexes of the antiulcer drug cimetidine. *J. Am. Chem. Soc.*, 102 (1980) 7782–7784.

Haleblian, J. and Mc Crone, W., Pharmaceutical Applications of Polymorphism. *J. Pharm. Sci.*, 58 (1969) 911–929.

Hädicke, E., Frickel, F. and Franke, A., Die Struktur von Cimetidin, einem Histamin H_2 Rezeptor Antagonist. *Chem. Ber.*, 111 (1978) 3222–3232.

Harsanyi, K., Domany, G., Fuchs, O., Toldy, L., Fekete, G., Hegedüs, B., Morasz, F., Rado, A., Lang, T., Lazar, A., Csongor, E., Balogh, T., Borvendeg, J., Reiter, J., Somogyi, T. and Bidlo, M., Cimetidinmonohydrat und Verfahren zur Herstellung desselben, *Patent BE 893610* (1981).

Hegedüs, B. and Görög, S., The polymorphism of cimetidine. *J. Pharm. Biomed. Anal.*, 3 (1985) 303–313.

Hüttenrauch, R., Molekulargalenik als Grundlage moderner Arzneiformung. *Acta Pharm. Technol. Suppl.*, 6 (1978) 55–127.

Kajfez, F., Lisini, A., Toso, R., Bein, B. and Sunjic, V., Study of physico-chemical properties of (cimetidine) and it S-oxid. *Acta Pharmacol. Jugoslav.*, 27 (1977) 199–207.

Kala, H., Traue, J., Haak, U., Moldenhauer, H., Kedvessy, G. and Selmeczi, B., Zur Zeitabhängigkeit der Modifikationsumwandlung des Sulfanilamids bei der Tablettenkompression. *Pharmazie*, 37 (1982) 674–675.

Kamiya, H., Morimoto, K. and Morisaka, K., Dissolution behavior and bioavailability of cimetidine-hydrochloride. *Int. J. Pharm.*, 26 (1985) 197–200.

Kaneniwa, N. and Otsuka, M., Effect of grinding on the transformation of polymorphs of chloramphenicol palmitate. *Chem. Pharm. Bull.*, 33 (1985) 1660–1668.

Kojic-Prodic, B., Ruzic-Toros, Z., Bresciani-Pahor, N. and Randaccio, L., 2-Cyano-1-methyl-3-{2-[(5-methyl-1H-imidazol-4-yl)methylthio]ethyl}guanidine Monohydrate. *Acta Crystallogr.*, B36 (1980) 1223–1225.

Kokubo, H., Morimoto, K., Ishida, T., Inoue, M. and Morisaka, K., Bioavailability and inhibitory effect for stress ulcer of cimetidine polymorphs in rats. *Int. J. Pharm.*, 35 (1987) 181–183.

Kopp, S., Beyer, C., Graf, E., Kubel, F. and Doelker, E., Methodology for a better evaluation of the relation between mechanical strength of solids and polymorphic form. *J. Pharm. Pharmacol.*, 41 (1989) 79–82.

Kreidl, J., Farkas, M., Harsanyi, K., Benke, B., Rado, A., Domany, G., Hegedüs, B., Csongor, E., Deutsch, I. and Pethö, H., Cimetidin Z und Verfahren zur Herstellung desselben und von Cimetidin A sowie das erstere enthaltende Arzneimittel, *Patent BE 894464* (1981).

Kuhnert-Brandstätter, M. and Burger, A., Untersuchungen zum Auflösungsverhalten polymorpher, pseudopolymorpher und amorpher Phasen von Arzneimitteln. *Pharm. Ind.*, 34 (1972) 187–190.

Otsuka, M., Otasuka, K. and Kaneniwa, N., Relation between polymorphic transformation pathway during grinding and the physicochemical properties of bulk powders for pharmaceutical preparations. *Drug Dev. Ind. Pharm.*, 20 (1994) 1649–1660.

Pharmazeutische Bestimmungsliste, 1994/95, IMP Neu-Isenburg 1994, ISSN 0171–6255.

Parkanyi, L., Kalman, A., Hegedüs, B., Harsanyi, K. and Kreidl, J., Structure of a novel and reproducible polymorph (Z) of the histamine H_2-receptor antagonst Cimetidine, $C_{10}H_{16}N_6S$. *Acta Crystallogr.*, C40 (1984) 676–679.

Pirttimäki, J., Laine, E., Ketolainen, J. and Paronen, P., Effect of grinding and compression on crystal structure of anhydrous caffeine. *Int. J. Pharm.*, 95 (1993) 93–99.

Pounder, R.E., Williams, J.G., Russelll, R.C.G., Milton-Thompson, G.J. and Misiewicz, J.J., Inhibition of food-stimulated gastric acid secretion by cimetidine. *Gut*, 17 (1976) 161–168.

Prodic-Kojic, B., Kajfes, F., Belin, B., Toso, R. and Sunjic, V., Study of crystalline forms of N-Cyano-N′-Methyl-N″-{2{[(4-methyl-1H-imidazol-5-yl)methyl]thio}ethyl} guanidine (Cimetidine). *Gazz. Chim. Ital.*, 109 (1979) 535–539.

Röscheisen, G., Optimierung von Schmiermitteln für Brausetabletten, *Ph.D. Thesis*, University of Tübingen, Germany, 1994.

Schepky, G., Ein Hygrostat mit einfacher und störungsarmer Probenauswaage. *Acta Pharm. Technol.*, 28 (1982) 87–88.

Shibata, M., Kagawa, M., Morisaka, K., Ishida, T. and Inoue, M., Structure of cimetidine monohydrochloride-monohydrate. *Acta Crystallogr.*, C39 (1983b) 1255–1257.

Shibata, M., Kokubo, H., Morimoto, K., Morisaka, K., Ishida, T. and Inoue, M., X-ray structural studies and physicochemical properties of cimetidine polymorphism. *J. Pharm. Sci.*, 72 (12) (1983a) 1436–1442.

Sudo, S., Sato, K. and Harano, Y., Solubilities and crystallization behaviour of cimetidine polymorphic forms A and B. *J. Chem. Eng. Jpn.*, 24 (1991a) 237–242.

Sudo, S., Sato, K. and Harano, Y., Growth and solvent-mediated phase transition of polymorphic forms A and B. *J. Chem. Eng. Jpn.*, 24 (1991b) 628–632.

Sudo, S., Sato, K., Harano, Y. and Ogo, Y., *Solid Phase Transition of Cimetidine Polymorphic Forms A and B.* Mem. Fac. Eng., Osaka City University, Vol. 31, 1990, pp. 61–67.

Trautmann, H., Stofftransport durch pharmazeutisch relevante Membranen, *Ph.D. Thesis*, University of Freiburg, Germany, 1990.

Tudor, A.M., Davies, M.C., Melia, C.D., Lee, D.C., Mitchell, R.C., Hendra, P.J. and Church, S.J., The application of near-infrared Fourier transform Raman spectroscopy to the analysis of polymorphic forms of cimetidine. *Spectrochim. Acta*, 47A (1991) 1389–1393.

Verma, A.R. and Krishna, P., *Polymorphism and Polytypism in Crystals*, Wiley, New York, 1966.

York, P., Crystal engineering and particle design for the powder compaction process. *Drug Dev. Ind. Pharm.*, 18 (1992) 677–721.