Drug Development and Industrial Pharmacy, 27(6), 481–489 (2001)

RESEARCH PAPER

Polymorphic Changes of Thiamine Hydrochloride During Granulation and Tableting

K. Wöstheinrich and P. C. Schmidt*

University of Tübingen, Department of Pharmaceutical Technology, Auf der Morgenstelle 8, D-72076 Tübingen, Germany

ABSTRACT

Thiamine hydrochloride was granulated using an instrumented fluidized bed granulator (Hüttlin HKC 05-TJ). Granules consisting of pure thiamine hydrochloride were produced using an aqueous solution of thiamine hydrochloride as the granulating liquid. The effects of process variables such as inlet air temperature, spray rate, and amount of granulating liquid on granule properties are described. Particle size distributions of granules depended mainly on the amount of granulating liquid sprayed into the powder bed. Granules were tableted on a rotary tablet press at four different compression forces. Crushing strengths and disintegration times of all tablets were found to be very low after manufacture, but increased considerably after 4 months of storage at room temperature. Granular materials showed ''caking'' under the same storage conditions. These changes could be attributed to alterations of the polymorphic form of thiamine hydrochloride. The water-free form, being present directly after granulation, absorbs humidity very fast and is transformed into the monohydrate, which is stable at room temperature. Loss of water takes place during the drying phase of the granulation process and on storage of the substance at temperatures of 50°C and 80°C. During storage at room temperature while exposed to humidity, a transformation into the hemihydrate was observed. This polymorph is transformed during thermal analysis at about 190°C to a water-free form that is stable at higher temperatures.

* Corresponding author.

INTRODUCTION

Thiamine hydrochloride is widely used in tablets. High-dosage forms contain up to 500 mg of the active ingredient. The substance is a fine, white, poorly flowing powder. Direct compression of thiamine hydrochloride presents difficulties. Only by the addition of 79% of an easily compressible material like binders and/or fillers can direct compression of thiamine hydrochloride be performed (1,2). Wet granulation of the substance is described only for tablets with low concentrations of the active ingredient. The process ensures homogeneous distribution of the substance and improves flow and tableting properties of the mixture (3). Thiamine hydrochloride is sensitive to humidity and pH changes. The decomposition can be reduced by a decrease of moisture within the tablet, from 3% to 1% (4). Khandelwal et al. (5) recommend dry binders or alcoholic granulating liquids, which result in greater stability of the substance. Vitamin B complex tablets consisting of thiamine hydrochloride, pyridoxine hydrochloride, and cyanocobalamin show the best stability of thiamine hydrochloride after separate granulation of the active ingredients and coating of cyanocobalamin with ethylcellulose (6).

Thiamine hydrochloride shows five polymorphic forms (7). At room temperature, a water-free form exists besides the monohydrate (phase I) and the hemihydrate (phase II). The water-free substance (phase III) absorbs water very quickly when exposed to humid air and is transformed into the monohydrate (phase I; 8). During storage, the monohydrate is transformed into the hemihydrate (phase II; 9,10). As a result, crystals show caking. At higher temperatures (above 90°C), a transformation of both mono- and hemihydrate into a water-free phase III is described that is stable at higher temperatures (7). The polymorphic forms are summarized in Fig. 1. Polymorphs of pharmaceutical interest are the phases I, II, and III shown in Fig. 1.

The aim of this study was to investigate the possibility of polymorphic changes of thiamine hydrochloride during granulation and tableting. To avoid any influence from other chemicals, a binder-free agglomeration was carried out using aqueous thiamine hydrochloride solutions as the granulating liquid. The agglomeration was achieved by bridges consisting of recrystallized thiamine hydrochloride. The influence of process parameters such as inlet air temperature, spray rate, and amount of granulating liquid on granule properties was investigated. The laboratory-scale fluidized bed granulator provides a homogeneous movement of the powder bed by its fluidization device (11). The tableting properties of the granules were determined. To evaluate changes of granule and tablet properties during storage, thermoanalytical examinations were performed.

EXPERIMENTAL

Materials

Thiamine hydrochloride (Hoffmann-La Roche, Grenzach-Wyhlen, Germany) and a 5% aqueous solution of thiamine hydrochloride were used for the preparation of the granules. Tablets were compressed after the addition of 1% magnesium stearate (Bärlocher, Munich, Germany) as a lubricant.

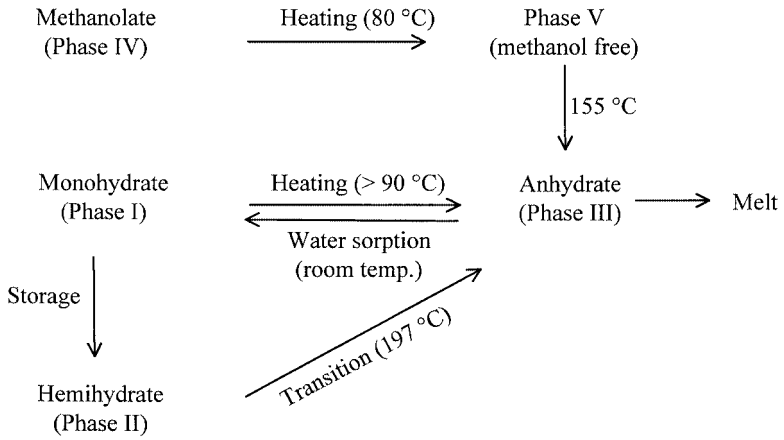

Figure 1. Polymorphic forms of thiamine hydrochloride according to Refs. 7 and 9.

Equipment

The following instruments were used: Hüttlin Kugelcoater HKC 05-TJ with two 3-component-nozzles (BWI Hüttlin, Steinen, Germany); Pt-100 temperature sensors; fan-wheel anemometer; combined relative humidity/NTC-temperature sensors; nickel-chromium-nickel temperature sensors; data logger Testo 454 and software ''comfort light,'' version 2.1 (Testo, Lenzkirch, Germany); control unit for the heater Jumo dTron 16 (Juchheim, Fulda, Germany); two piston pumps (LCP 4000, Biotek GmbH, Östringen, Germany); laser diffraction spectrometer Sympatec HELOS KA Compact with distribution unit RODOS (Sympatec, Clausthal-Zellerfeld, Germany); tapped density tester JEL ST2 (Engelmann AG, Ludwigshafen, Germany); mixer Turbula T2C (Willy Bachofen, Basel, Switzerland); rotary tablet press PH 103 (Korsch Pressen GmbH, Berlin, Germany); electronic balance AE 200 (Mettler-Toledo, Gießen, Germany); tablet hardness tester Schleuninger 6D (Schleuninger, Solothurn, Switzerland); tablet disintegration tester PTZ 1 (Pharmatest, Hainburg, Germany); and differential scanning calorimetry (DSC) system (Mettler TA 8100, Mettler Toledo, Gießen, Germany).

Methods

To evaluate the influence of process parameters on granule properties during fluidized bed granulation, the spray rates of the granulating liquid were kept constant at 6 g/min and 10 g/min. The temperature of the inlet air ranged from 50°C to 70°C. The mass of the starting material was 300 g. A 5% aqueous solution of thiamine hydrochloride was used as the granulating liquid. The amount of granulating liquid sprayed onto the powder bed was 200 g, 300 g, or 400 g. The atomizing pressure and the pressure used for the microclimate of the nozzles were kept constant at $3 \cdot 10^4$ Pa and 10^4 Pa, respectively. Sensor data were collected every 10 s and transferred from the data logger to the personal computer. A detailed description of the apparatus, its instrumentation, and the process control during granulation is given in Ref. 11.

Size distributions of both starting material and granules were determined using a laser diffraction spectrometer (Sympatec HELOS KA Compact) with a RODOS distribution unit. All results given are the mean of three determinations.

For the determination of the bulk density according to the 1997 Ph. Eur., 50 g of the granules were filled into a graduated 250-ml measuring cylinder, and the volume was determined. The same cylinder was then inserted into a JEL ST2 tapping device and tapped 1250 times (DIN EN ISO 787-11). For each reported value, two determinations of the bulk and tapped density were made. The *Hausner ratio*, defined as the ratio of tapped density to poured density, was calculated. The flow properties are described by the angle of repose; 150 ml of the material were allowed to flow through a funnel. The 10-mm orifice of the funnel was placed 7.5 cm above a plastic disk with a radius r of 5.0 cm. The height h of the cone obtained was measured. The angle of repose α was calculated as $\tan \alpha = h/r$. Three determinations were performed for each powder. All results are given in Table 1.

Ungranulated thiamine hydrochloride or granular materials and 1% magnesium stearate were mixed for

Table 1

Properties of Thiamine Hydrochloride Granules and the Starting Material

Granulation Parameters							
Inlet Air Temperature (°C)	Spray Rate (g/min)	Amount of Granulating Liquid (g)	Poured Density (g/ml)	Tapped Density (g/ml)	Hausner Factor	d_{50} (μm)	Angle of Repose (°)
50	6.2	200	0.439	0.549	1.251	87	38.0
50	9.9	200	0.397	0.481	1.211	122	38.4
60	6.3	200	0.413	0.485	1.174	85	34.1
60	9.7	200	0.407	0.495	1.216	82	35.2
60	10.0	300	0.435	0.515	1.184	107	33.0
60	9.9	400	0.420	0.485	1.155	126	33.1
70	6.3	200	0.459	0.549	1.196	67	36.1
Thiamine hydrochloride			0.279	0.476	1.706	26	62.9

Table 2

Properties of Thiamine Hydrochloride Tablets

Granulation Parameters				After Compression		After 4 Months of Storage	
Inlet Air Temperature (°C)	Spray Rate (g/min)	Amount of Granulating Liquid (g)	Compression Force (kN)	Crushing Strength (N)	Disintegration Time (s)	Crushing Strength (N)	Disintegration time (s)
50	6.2	200	12.11 ± 0.91	—	12	47.8 ± 3.63	155
			16.6 ± 1.68	18.1 ± 1.6	12	57.4 ± 9.69	175
			19.89 ± 2.29	21.5 ± 2.17	12	49.0 ± 4.8	210
			27.16 ± 2.55	29.3 ± 4.14	17	81.4 ± 6.5	205
50	9.9	200	12.23 ± 4.47	—	16	36.8 ± 3.63	185
			17.42 ± 1.62	16.0 ± 3.4	28	55.4 ± 5.03	190
			21.28 ± 1.89	21.3 ± 1.89	15	43.0 ± 4.47	210
			23.98 ± 2.30	22 ± 1.76	22	46.3 ± 1.95	225
60	6.3	200	11.4 ± 0.98	—	14	17.4 ± 1.14	210
			14.53 ± 1.18	11.8 ± 2.86	11	19.8 ± 3.03	255
			21.54 ± 1.87	16.7 ± 2.75	12	35.8 ± 4.21	260
			26.06 ± 2.29	19.5 ± 2.01	13	45.0 ± 3.32	245
60	9.7	200	8.75 ± 0.80	—	14	14.4 ± 1.52	175
			14.26 ± 1.44	11.8 ± 2.19	14	35.8 ± 4.97	270
			18.76 ± 1.91	16.0 ± 1.63	13	35.8 ± 4.99	290
			23.74 ± 1.95	17.4 ± 2.67	10	46.0 ± 2.65	300
60	10.0	300	11.23 ± 1.43	—	11	55.2 ± 3.11	240
			15.64 ± 0.84	14.2 ± 1.0	14	67.2 ± 9.63	285
			23.19 ± 1.95	18.9 ± 3.6	12	71.4 ± 3.13	290
			26.99 ± 2.62	23.4 ± 3.03	11	79.6 ± 17.49	280
60	9.9	400	9.52 ± 0.72	—	12	52.8 ± 4.55	195
			15.10 ± 1.45	13.2 ± 1.69	11	60.2 ± 9.63	260
			18.53 ± 1.98	15.8 ± 3.0	10	53.8 ± 3.96	240
			25.91 ± 2.12	21.4 ± 2.1	18	80.4 ± 10.48	275
70	6.3	200	12.06 ± 0.54	—	10	66.6 ± 2.7	185
			14.94 ± 0.72	11	14	80.6 ± 3.29	235
			20.56 ± 1.27	12.2	12	83.0 ± 26.1	270
			28.25 ± 2.09	20.0	9	101.6 ± 8.6	285

10 min using a Turbula T2C mixer at 42 rpm. Tablets were compressed using 10-mm beveled edge tooling on an instrumented rotary tablet press. The compression forces ranged from 10 to 25 kN in intervals of 5 kN. During a period of 20 s, all compression forces were recorded, and mean value and standard deviation were calculated. To monitor tablet uniformity, the masses of 10 tablets per compression force level were determined. The crushing strength of each of 10 tablets was analyzed using a Schleuninger Tablet Hardness Tester 6D. Disintegration times of each of 6 tablets were determined in purified water at 37°C using a Pharmatest PTZ 1 apparatus. Crushing strengths and disintegration times were determined 2 days after compression and after a storage period of 4 months. All results are given in Table 2.

The thermoanalytical behavior of thiamine hydrochloride granules and tablets were investigated using a Mettler TA 8100 DSC system. Tablets were powdered before the experiment using a mortar and pestle. The determinations were performed at a heating rate of 10 K/min using a 40-µm standard aluminum pan. The sample masses ranged from 4 mg to 6 mg.

Storage of thiamine hydrochloride was performed in sealed glass vessels at temperatures of 50°C and 80°C. For the storage of granules and tablets over 4 months, the samples were kept in sealed glass vessels at room temperature (20°C–25°C).

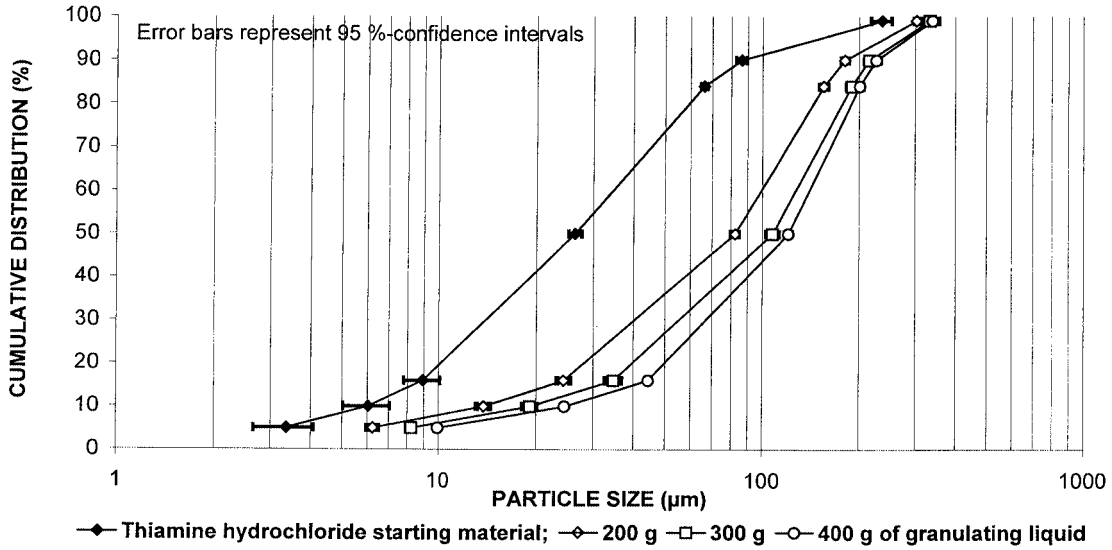

Figure 2. Particle size distributions of thiamine hydrochloride starting material and three granulations prepared with different amounts of granulating liquid ($N = 3$). Spray rate 10 g/min; inlet air temperature 60°C.

RESULTS AND DISCUSSION

The particle size distributions of both starting material and granules are shown in Fig. 2. The substance is a fine white powder with a mean particle size of 26 µm and has very poor flow properties (Table 1).

For an inlet air temperature of 60°C and a spray rate of 10 g/min, Fig. 2 shows the particle size distributions of granules obtained by spraying in 200 g, 300 g, and 400 g of the aqueous granulating liquid. Since thiamine hydrochloride, in a concentration of 5%, is the ingredient of the granulating liquid, the amount of the starting material (300 g) increases by the granulating process to a total of 310 g, 315 g, and 320 g, respectively. The mean particle size d_{50} of the granules increases with increasing amounts of granulating liquid (Table 1). The cumulative distributions are shifted to higher particle sizes when more granulating liquid is used.

The influence of spray rate and inlet air temperature on the particle size distribution is shown in Fig. 3. The amount of granulating liquid for these experiments was kept constant at 200 g. Only a very slight decrease of the particle sizes of the granules produced at spray rates of about 6 g/min was shown when the inlet air temperatures were increased from 50°C to 60°C and 70°C. The spray rate did not show a significant influence on the particle size distributions. As the granulating liquid did not contain any binder, the agglomeration of fine particles to bigger agglomerates took place only by the mechanism of recrystallization. On the surface of the particles, small amounts of material were dissolved by the granulating liquid. The dissolved material recrystallized and formed bridges between particles that consisted of pure thiamine hydrochloride. Storage of the granules for 4 months at room temperature led to strong caking of the material. While the granules showed excellent flowing behavior directly after granulation, after the storage, they stuck to the glass vessels. This behavior was attributed to the change into the hemihydrate (phase II) on storage, which was supported by DSC data (Figs. 4 and 5).

Figure 6 shows the crushing strength of thiamine hydrochloride tablets as a function of the compression force directly after compression and after 4 months of storage at room temperature. As tablets compressed at 10 kN did not break properly in the hardness tester directly after compression, determination of the crushing strengths of these tablets could not be performed. Differences between the granular materials did not affect the properties of the tablets. All tablets showed very low crushing strengths, less than 30 N (Table 2). Storage for 4 months at room temperature led to a significant increase of the crushing strength and disintegration time of the tablets. Granules prepared with 200 g of granulating liquid led to tablets with crushing strengths between 14 N and 46 N. Tablets with crushing strengths between 53 N and 80 N were obtained by increasing the amount of granulating liquid to 300 g and 400 g. Between these two batches, the crushing strength of the tablets differed only slightly.

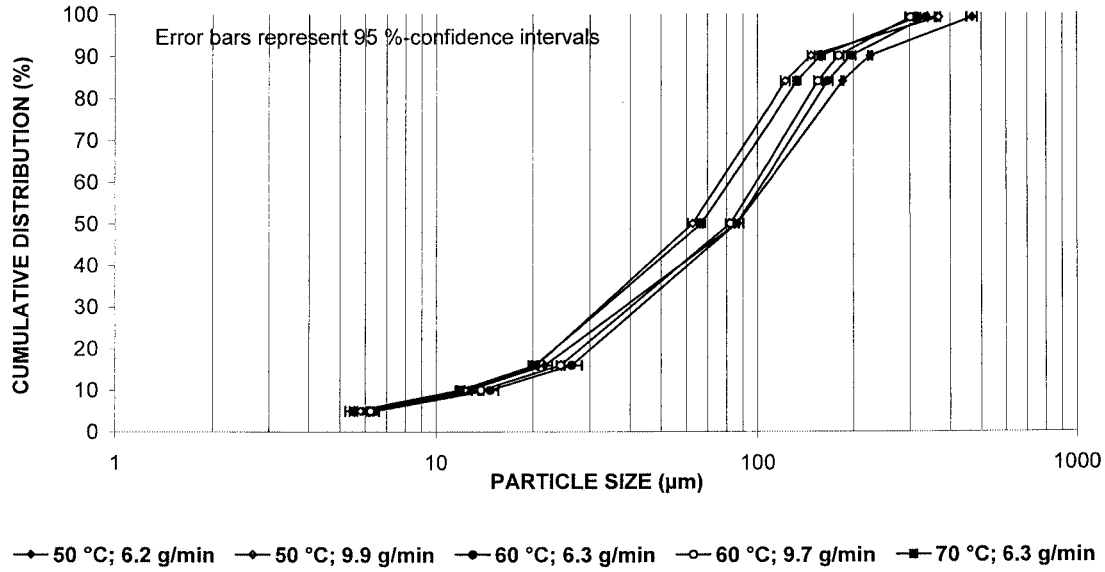

Figure 3. Particle size distributions of granulations prepared with inlet air temperatures of 50°C, 60°C, and 70°C and using two different spray rates ($N = 3$).

Disintegration times of tablets directly after compression were less than 1 min (Table 2). After storage for 4 months, the disintegration time increased to a maximum of 6 min.

To evaluate the different properties of both granules and tablets after compression and after a storage period of 4 months, thermoanalytical experiments were performed. Figure 4 shows the DSC diagram of thiamine hydrochloride. An endothermic peak at 141°C indicates the loss of water of the monohydrate. Melting and decomposition take place at a temperature above 248°C (not shown in Fig. 4). Storage of the substance at temperatures of 50°C and 80°C over 4 months leads to a loss of water. As a result, the peak indicating the loss of water of crystallization disappears, and only the melting peak at 248°C can be detected.

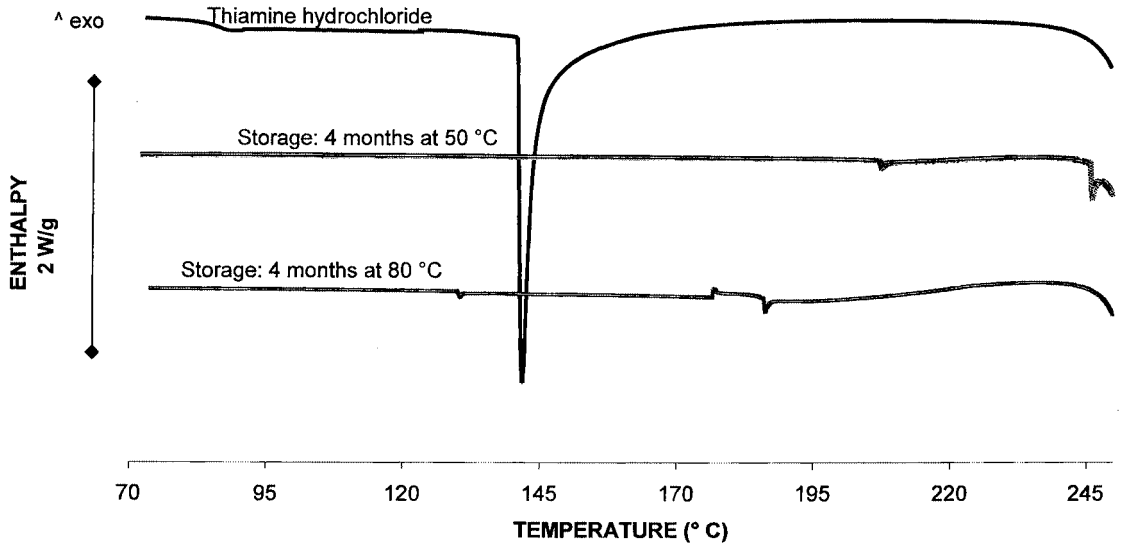

Figure 4. DSC curves of thiamine hydrochloride, tablets after manufacture, and granules after granulating process.

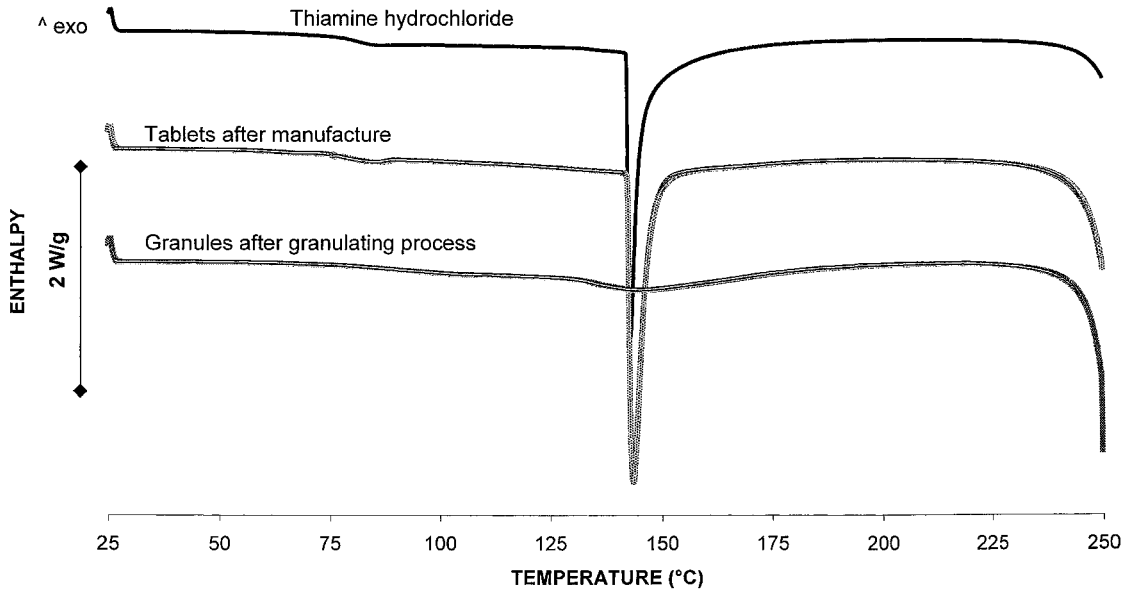

Figure 5. Crushing strength of thiamine hydrochloride tablets directly after compression and after 4 months of storage ($N = 10$). The granules used for tableting were prepared with 200, 300, and 400 g of granulating liquid.

The thermoanalytical behaviors of granules after the granulating process and of tablets after compression are given in Fig. 5. In comparison to the starting material, the granulated material showed only a very small peak at 141°C, indicating the loss of water of crystallization during the drying phase in the fluidized bed. Tablets after compression showed the same behavior as the starting material. During preparation of the tableting mixture and during tableting, the material was exposed to the humidity in the air. As a result, a conversion into the monohydrate took place by the absorption of water. These results correspond to experiments by Watanabe and Nakamachi (7).

Both granules and tablets hardened during storage for 4 months at room temperature. The granules showed cak-

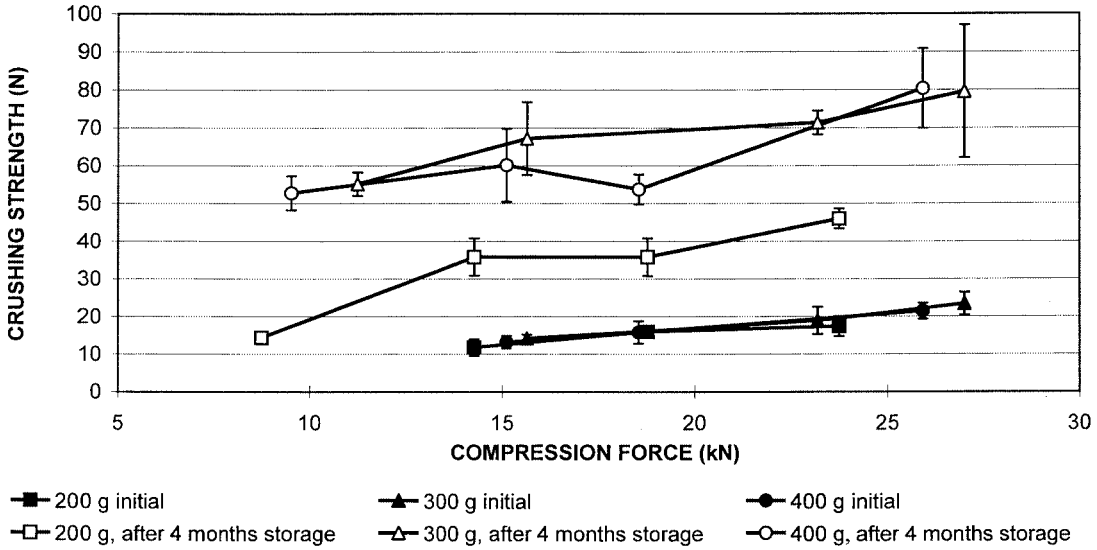

Figure 6. DSC diagram of thiamine hydrochloride and the same substance after 4 months of storage at 50°C and 80°C.

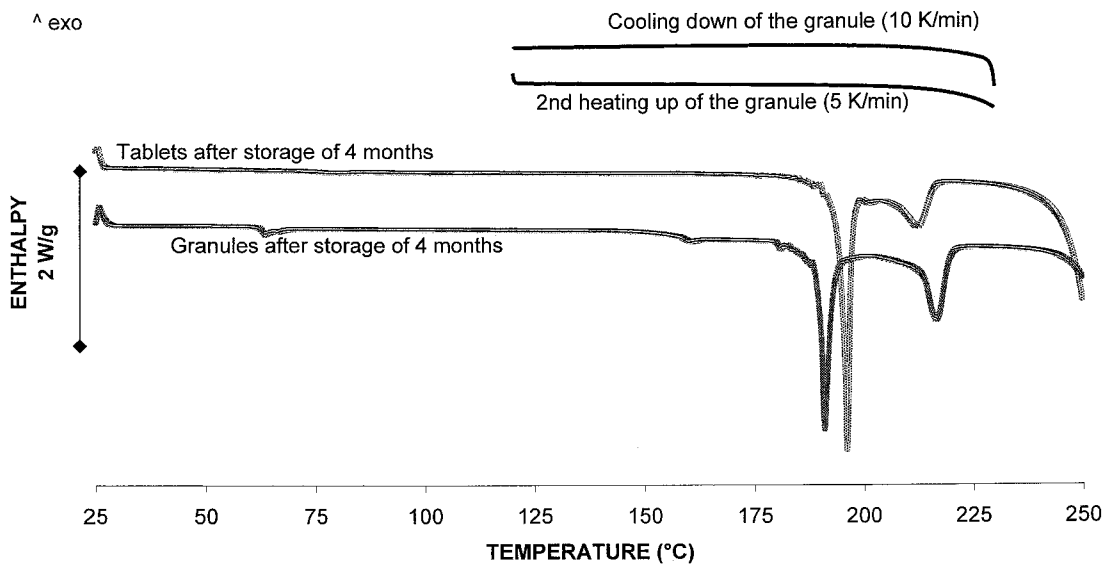

Figure 7. DSC diagrams of tablets and granules after 4 months of storage at room temperature and changes of the modification of the granules after cooling and a second heating process.

ing. The corresponding DSC diagrams showed, at a temperature around 185°C, the loss of water of the hemihydrate (Fig. 7). This polymorph is described as being the stable form both in the solid state and in suspension in a saturated solution (10). The second peak indicates the conversion into the water-free form III, as described in Ref. 7. Because during repeated heating of the same sample no peaks could be detected, the material totally lost its water during the first heating process (Fig. 7). Polymorph III is stable at higher temperatures and melts with decomposition at 248°C.

CONCLUSIONS

Thiamine hydrochloride tablets showed very low crushing strengths and short disintegration times directly after compression; these increased considerably during prolonged storage at room temperature. These changes could be attributed to changes of the polymorphs.

When exposed to humidity, the water-free substance absorbed water very quickly and was transformed into a monohydrate (form I). The water was removed very fast during the drying phase of the granulation process and during prolonged storage for 4 months at 50°C and 80°C. Transformation of the water-free form into the monohydrate could be observed during tableting.

Stored at room temperature for 4 months, the monohydrate (form I) was transformed into a hemihydrate (form II), which is the stable form. This transformation was accompanied by caking of crystals and an increase of the crushing strength and disintegration time of the tablets.

REFERENCES

1. Udeala, O.K.; Aly, S.A.S. Some Physical Properties of Directly Compressible Thiamine Hydrochloride Tablets. Drug Dev. Ind. Pharm. **1988**, *14*, 499–521.
2. El Sabbagh, H.; El Shaboury, M. The Use of Directly Compressible Vehicles for the Preparation of Vitamin B1 Tablets. Pharmazie **1984**, *39*, 237–239.
3. Khandelwal, B.; Shukla, A.K.; Asthana, J.G. Formulation and Stability Studies of Thiamine Hydrochloride Tablets. Indian Drugs **1978**, *15*, 177–180.
4. Tardif, R. Reliability of Accelerated Storage Tests to Predict Stability of Vitamins (A, B1, C) in Tablets. J. Pharm. Sci. **1965**, *54*, 281–284.
5. Khandelwal, B.; Shukla, A.K.; Asthana, J.G. Study of Physical Parameters of Thiamine Hydrochloride Granules. Indian Drugs **1978**, *15*, 173–176.
6. Hussein, A.M.; Kassem, A.A.; Darwish, W. Manufacture and Stability of a Tablet Containing Thiamine, Pyridoxine and Cyanocobalamin. Part I. Physical Stability. Bull. Fac. Pharm. **1970**, *8*, 213–221.
7. Watanabe, A.; Nakamachi, H. Polymorphism of Thiamine Hydrochloride. Yakugaku Zasshi **1976**, *96*, 1236–1240.

8. von Bruchhausen, F.; Dannhard, G., Eds. *Hagers Handbuch der Pharmazeutischen Praxis, Bd. 9., Thiaminhydrochlorid*, 5th Ed.; Springer Verlag: Heidelberg, 1993; 867–868.
9. Al-Rashood, K.A.M.; Al-Shammary, F.J.; Mian, N.A.A. Analytical Profile of Thiamine Hydrochloride. Anal. Profiles Drug Subst. **1989**, *18*, 413–459.
10. Watanabe, A.; Tasaki, S.; Wada, Y.; Nakamachi, H. Polymorphism of Thiamin Hydrochloride II. Crystal Structure of Thiamine Hydrochloride Hemihydrate and Its Stability. Chem. Pharm. Bull. **1979**, *27*, 2751–2759.
11. Wöstheinrich, K.; Schmidt, P.C. Evaluation and Validation of a Fully Instrumented Hüttlin HKC 05-TJ Laboratory-Scale Fluidized Bed Granulator. Drug Dev. Ind. Pharm. **2000**, *26*, 621–633.