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FACTORS INFLUENCING POLYMORPHIC TRANSITION OF HYOSCINE N-BUTYL BROMIDE.

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ABSTRACT

Two crystalline forms of hyoscine N-butyl bromide (HBB) were identified and characterized by DSC, x-ray powder diffraction, scanning electron microscope and i.r. spectrophotometry techniques. DSC was the most useful method in differentiating the two polymorphs. The stable and metastable forms of HBB showed no significant variation in their x-ray and i.r. spectra. Melting points were 123.4 $\pm$ .5°C and 143.6 $\pm$ .9°C for the metastable and the stable forms respectively. Their purities exceeded 99% and their heat of fusion was obtained. While crystallization from methanol produced the metastable form, other solvents precipitated the stable form. Compression force transfered the metastable form into the stable form. Such transfere depended on the applied pressure. Mild trituration and ball milling had a negligible effect on crystalline transitions. Although storage at room temperature and at 55°C converted the drug into its stable form, the two

crystalline forms coexisted in the commercial samples of the same batch or different batches.

INTRODUCTION

The effect of different polymorphic forms on the solubility and oral bioavailability is well recognized (1). Recent studies have been focused on the polymorphic transitions under various mechanical and industrial processings. The influence of trituration on thirty two drugs was assessed. Further, caffeine , maprotiline hydrochloride and sulphabenzamide were selected to study their polymorphic transitions under compression (2). Such transformation was evident in sulphabenzamide and depended on the zone of the tablet and the force applied. The excipient's presence prevented such transitions to a certain extent (3). Although this important polymorphism effect was recognized, the official compendia still lacks specific information concerning this matter. Accordingly, the awarence of the consequence of polymorphic transition on the formulated product has to be carefully investigated prior to the product development. During the development of Hyoscine N-Butyl Bromide formulation, no consistency in the melting point and i.r. spectrum of the starting material was observed. Such observation caused the search for polymorphism existence in HBB. The presence of these polymorphic forms necessitate the assessment of their influence on various industrial processes and the implication of such phenomena on the product's formulation.

MATERIALS AND METHODS

Hyoscine-N-Butyl Bromide B.P. (99% purity) was provided by the Jordanian Pharmaceutical Manufacturing Co., Naor, Jordan, (JPM). All organic solvents used were of analar grade (BDH), U.K.

Crystallization of Hyoscine N-Butyl Bromide from Various Organic Solvents :

Warm saturated solution of HBB was cooled and left in conical flasks. The precipitated crystals were filtered and dried prior to investigation.

Thermal Analysis:

Differential scanning calorimetery thermographs were recorded using Mettler TA 3000 DSC 20 unit. The heating rate was $10^{o}C\ min^{-1}$ and the sample size ranged between 4-10 mg. TGA analysis was carried out using the same instrument.

Crystal Characterization by Scanning Electron Microscope :

Leitz scanning electron microscope was used to compare HBB crystals obtained from various solvents. The crystalline powder was placed on a metallic support and coated with golden layers under vacuum.

X-Ray Powder Diffraction :

Phillips diffractometer PM 9920/05 was used to obtain diffraction pattern.

Infrared Analysis :

i.r. spectra were obtained with a Perkin Elmer 598 infrared spectrophotometer using the liquid paraffin-mull technique.

Batch to Batch Variation and In Batch Variation :

Samples from four different commercial batches of HBB were examined for their polymorphic types. Samples from different containers of the same batch, each containing 1 kg, were monitored for the presence of polymorphic forms.

Effect of Compression :

500 mg of HBB powder of unified particle size were compressed using hydraulic press at 5, 10 and 15 tons of pressure for 30 minutes. Samples were obtained from the lower and upper surface of these discs. Further, tablets of HBB were compressed on a Manesty single punch machine and samples were obtained from the upper and lower tablet surface . Additional two samples were taken from the core of each tablet. These samples were screened for their polymorphic transitions using D.S.C.

Effect of Trituration and Milling :

The two polymorphic forms were manually triturated and milled in a porcelain mortar separately. Their thermal behaviour and i.r. spectrum were recorded during these processes.

Effect of Ball Milling :

50 G of the HBB were placed in the Erweka ball mill and samples were withdrawn at various intervals and tested for polymorphic transiton.

Effect of Storage at Room Temperature and at 55°C :

Freshly crystallized HBB samples from methanol were stored in a closed flask in an oven , which was set up at 55°C. Samples were withdrawn at 30 minutes intervals and their thermographs and i.r. spectra were recorded. Additional HBB samples were stored at room temperature and their polymorphic transitions were recorded daily.

RESULTS AND DISCUSSION

Thermographs of some HBB commercial samples were found to contain two endothermic peaks at the proximity of 123°C and 143°C, Figure (1). Accordingly , the commercial samples were recrystallized from various solvents, and under different crystallization conditions, Table (1). Two polymorphs were obtained, one melted at 123.4 ± 0.5°C and was crystallized from methanol. The other polymorph obtained from the rest of solvents used,melted at 143.6 ± 0.9°C. Their melting points coincided with the endothermic peaks obtained from the commercial samples, indicating that these two polymorphs existed in the commercial bulk material.Crystallization from ethanol was a complex, it was not consistent which may be due to the sensivity of its crystallization process. However,in many carried out crystallizations, there were endothermic peaks, reproduced in its DSC thermograph at 82°C, 105°C and 142°C , Figure (2). When crystals were melted and rechecked these peaks disappeared and only the peak at 142°C prevailed and a loss of the weight in the proximity of 3% followed the melt,indicating solvate formation at 105°C. Nevertheless, crystallization from

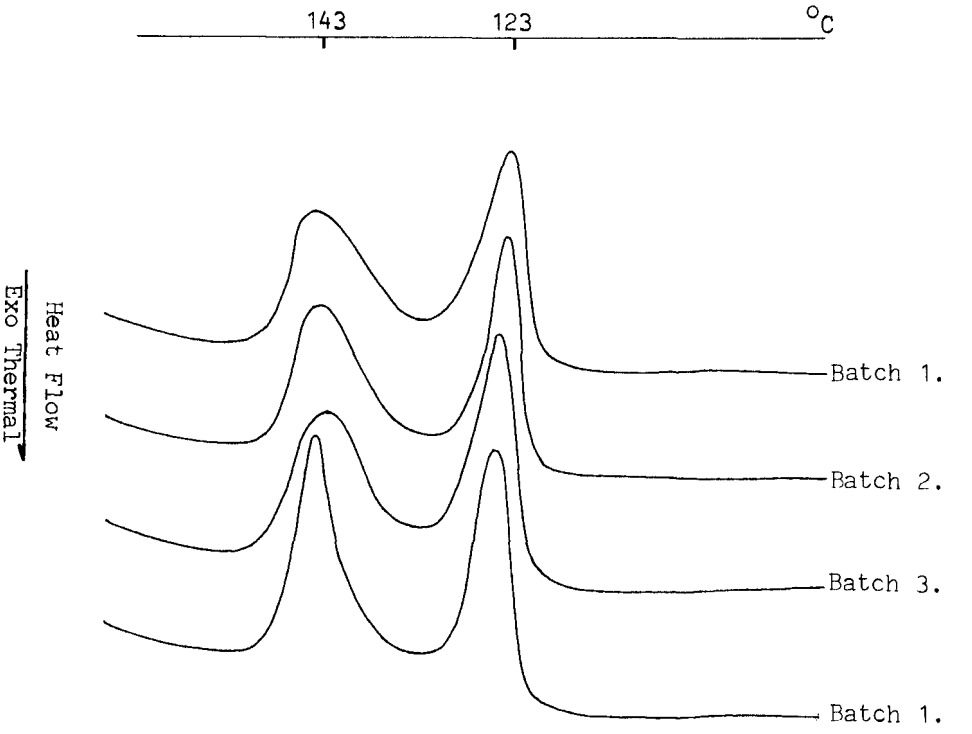

FIGURE 1

Typical commercial HBB samples from different batches of the same source. Thermograph was obtained at 10°C min^{-1}.

TABLE (1)

SOLVENTS USED IN CRYSTALLIZATION AND THE CRYSTALLINE FORMS PRODUCED.

Solvent	Melting Point(°C)	Number of Crystal Forms	Solvates	Crystallization Time(Hrs.)	Condition for Crystallization
Methanol	123.4	1	-	6-12	Cool Evaporation.
*Ethanol	142.0	1	(1)105°C	6-24	" "
Butanol	144.1	1	-	6-12	" "
Isobutanol	143.8	1	-	6-12	" "
Propanol	144.2	1	-	6-12	" "
Isopropanol	144.1	1	-	6-12	" "
Hexanol	143.6	1	-	6-12	" "
Octanol	143.4	1	-	6-12	" "
Acetonitrile		1		4-12	Room Temp.
Chloroform	142.6	+	-	5 days	" "
Water	143.6	1		24 days	" "

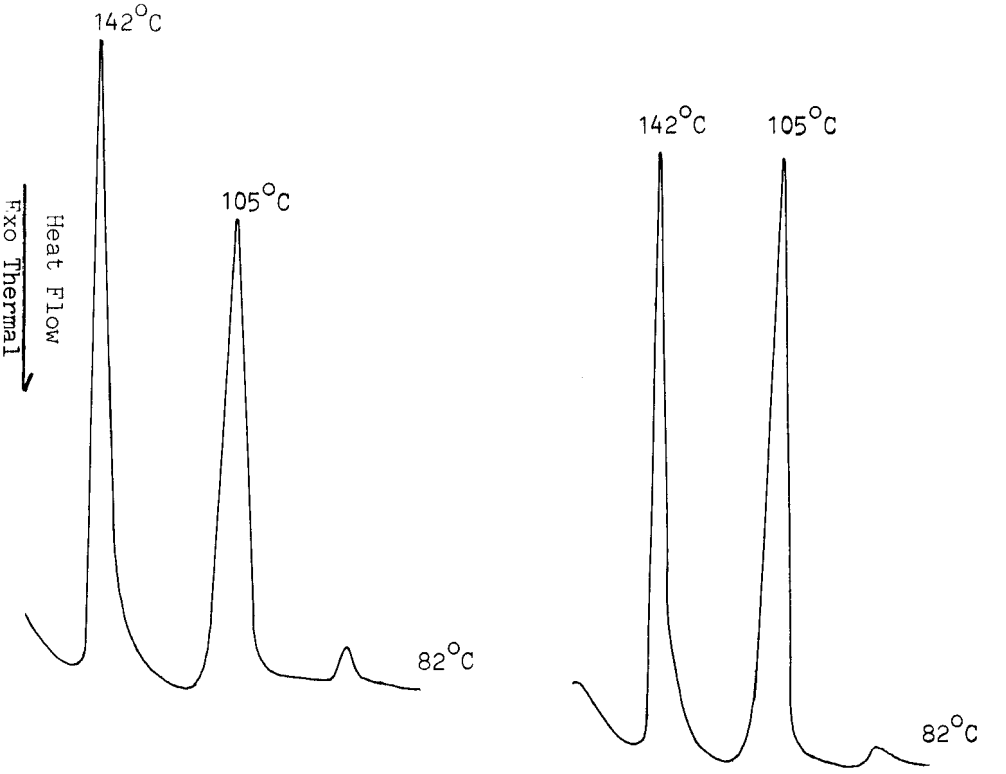

FIGURE 2

Shows the reproducibility in obtaining the ethanol solvate of HBB. Thermograph was obtained at $10^{\circ}C\ min^{-1}$.

ethanol still needs further investigations. The ESM photographs, showed different crystal habits, Figure (3). The crystallized drug from methanol showed irregular bulky flakes,while crystals obtained from ethanol were thin platy flakes. Regular crystalline tabular shape was precipitated from acetonitrile-drug solution. X-ray powder diffraction is shown in Figure (4) for the two polymorphic forms. The gross difference was small but indicated that the two polymorphic forms were crystalline.

a- Original commercial powder.

b- Powder crystallized from methanol.

c- Powder crystallized from ethanol.

d- Powder Crystallized from acetonitrile.

FIGURE 3

ESM photographs of HBB starting materials crystallized from various solvents.

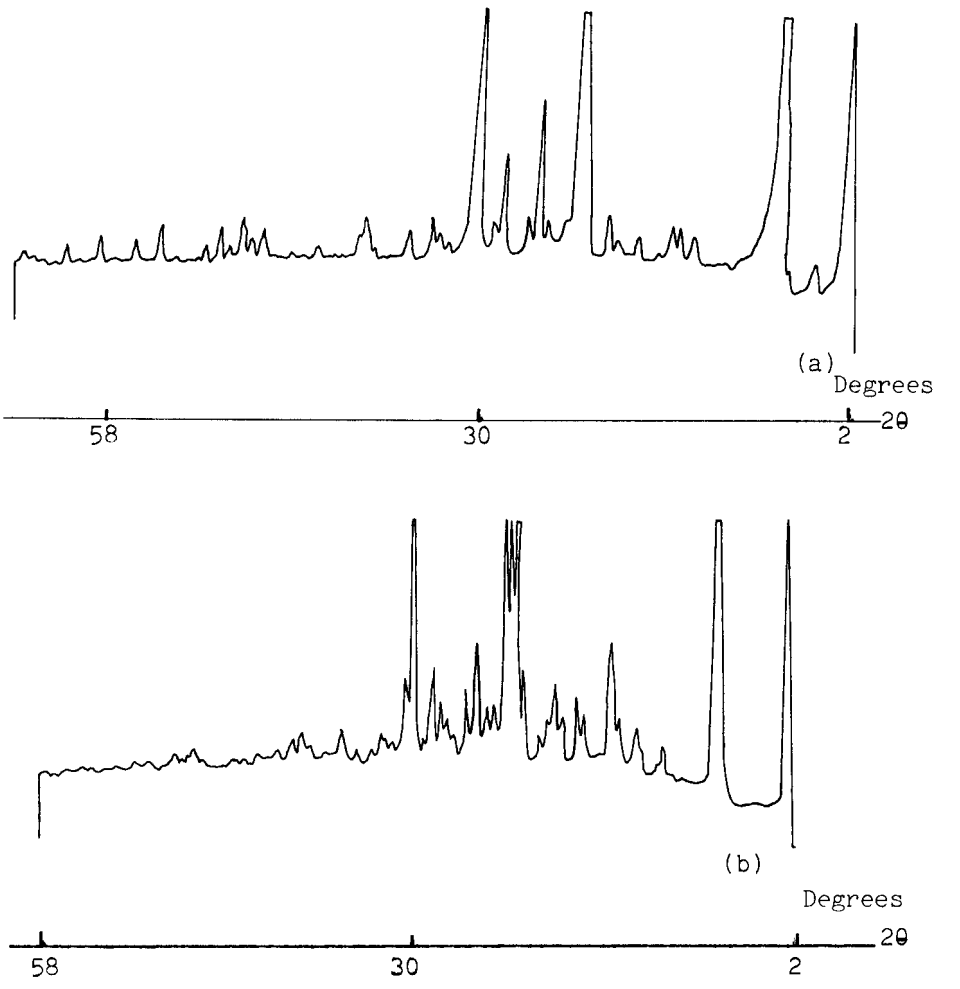

FIGURE 4

X-ray powder diffraction of a: material recrystallized from methanol form II. b: material recrystallized from acetonitrile form I.

Examination of liquid parafin mull, i.r. spectrum of HBB crystallized from different solvents exhibited principal peaks at wave numbers 1175, 1721, 1052, 874, 1072 and 709 cm^{-1}. Minor differences were observed in i.r. spectra of the two polymorphs. In the region 1720-1730 cm^{-1} the crystalline form with the lower

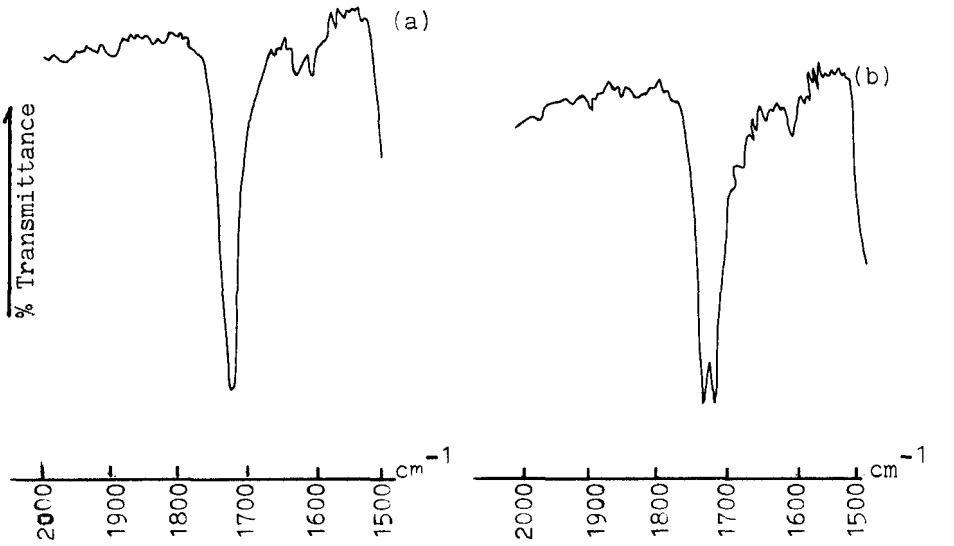

FIGURE 5

Infrared spectra of liquid paraffin mulls crystallized from a: methanol b: acetonitrile .

melting point (123.4°C) gave a singlet at 1721 cm^{-1}, while the polymorph with the higher melting point (143.6°C) gave a doublet at the same wave number, Figure (5). It was observed that the pressure used in preparing the KBr discs could introduce polymorphic transitions. This may be misleading in judging certain raw materials,as the melting point would not correspond to the actual i.r. spectrum. Indeed the use of the halide discs caused confusion concerning the reported i.r. spectrum of HBB (4). The drug polymorphic conversion could be attributed to the flexible lattice which allowed the molecule to adopt new conformation (5).

Four different commercial batches from the same source were screened for their endothermic peaks. Three batches tested were

mixtures of the two crystalline forms. However, DSC scan of one of the batches tested, showed a single endothermic peak corresponding to the higher recorded melting point (143.6°C). This made the sample in compliance with the cited drug specification regarding the melting point (4) . Furthermore, the i.r. spectrum prepared in liquid paraffin mulls showed a doublet at 1721 cm^{-1}. Fourteen samples were collected from different containers of the same batch. These samples were mixtures of the two previously recognized crystalline forms. Such results indicated the evident variation in the composition of the commercial HBB. The difference was observed among various batches and in the different containers of the same batch. The mixture of these two polymorphs would yield a lower melting point when compared with the reported values (4). Consequently, the inclusion of additional information concerning the polymorphic nature of HBB in the official compendia would be appreciated. The DSC method proved to be a useful technique in differentiating the two polymorphs. This may be developed for quantitative measurement of HBB polymorphic mixtures.

The purity of the crystals obtained from methanol and acetonitrile was determined, based on the derived Van't Hoff's equation:

$$T_o - T_s = \frac{RT_o^2 X_2}{\Delta H_f} \quad \text{.....(1) .}$$

Where : ΔH_f is the enthalpy of fusion, T_o, T_s are melting points of the pure and of the sample respectively. T_o-T_s is the depression in the melting point due to impurities. X_2: is the mole fraction of impurities, R is the gas constant.

In freshly prepared crystals from methanol, the percentage of mole fraction purity was 99.1% and its heat of fusion was 22.54 K.J. $mole^{-1}$. Crystals obtained from acetonitrile had 99.03% purity and their heat of fusion was 44.22 K.J. $mole^{-1}$.

It was shown explicitly,that HBB existed in two crystalline forms. The first melted at 123.4 $\pm$ 0.5°C ,with a singlet in its i.r. spectrum at 1721 cm^{-1} and was designated as form II. The second form melted at 143.6 $\pm$ 0.9°C.and had a doublet at 1721 cm^{-1} and was designated as form I.

Figure (6) illustrated the effect of compression on form II of HBB. Compression for 30 minutes under 5 tons produced large transition to form I. Further increase in the compression force to 10 and 15 tons was enough for the total transformation of form II to I. As form II had the lower melting point it would have the least stress value at the temperature of compression. However,the stable form showed no changes under compression. These tests were repeated using Manesty single punch machine. The tablet was forced to cap and samples from the tablet contacting the upper punch, the tablet core and lower surface showed a transformation to the stable polymorphic form. Mild trituration, ball milling and reduction of the particle size did not have significant polymorphic transition when both forms were processed. But milling at high speed mills converted the drug into a plastic mass.

Storage of the form II at room temperature and in a desicator in a dark place showed that this form needed more than 180 days to be converted to the stable form as illustrated in Figure (7). Such

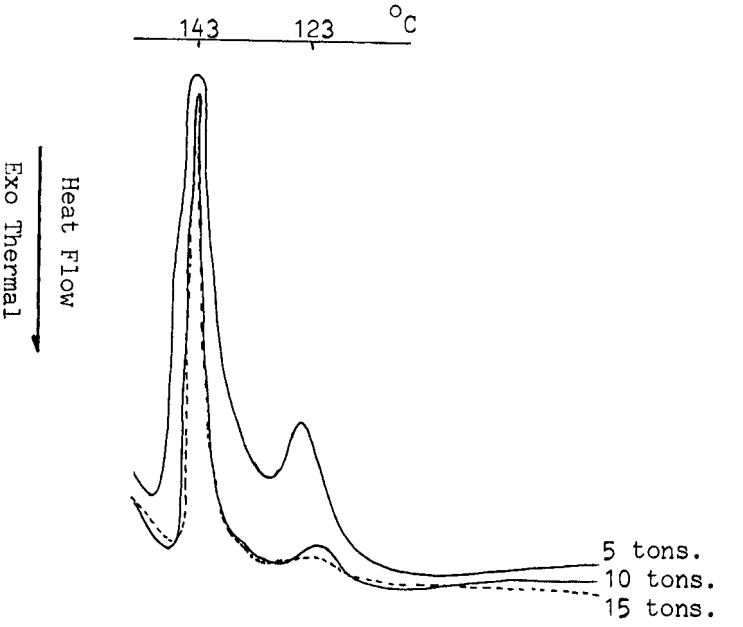

FIGURE 6

The transformation of HBB metastable polymorph (II) into the crystalline stable form(I)under compression monitored by DSC.

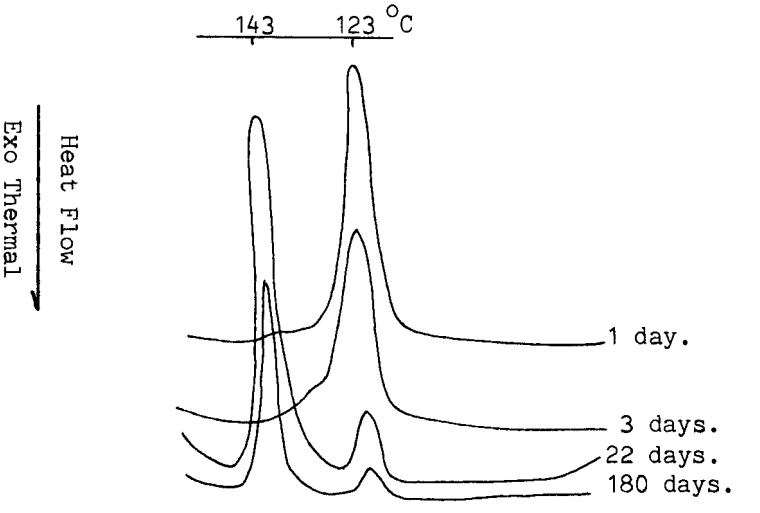

FIGURE 7

The polymorphic transition of the metastable HBB polymorph(II)to the stable form(I)at room temperature monitored by DSC.

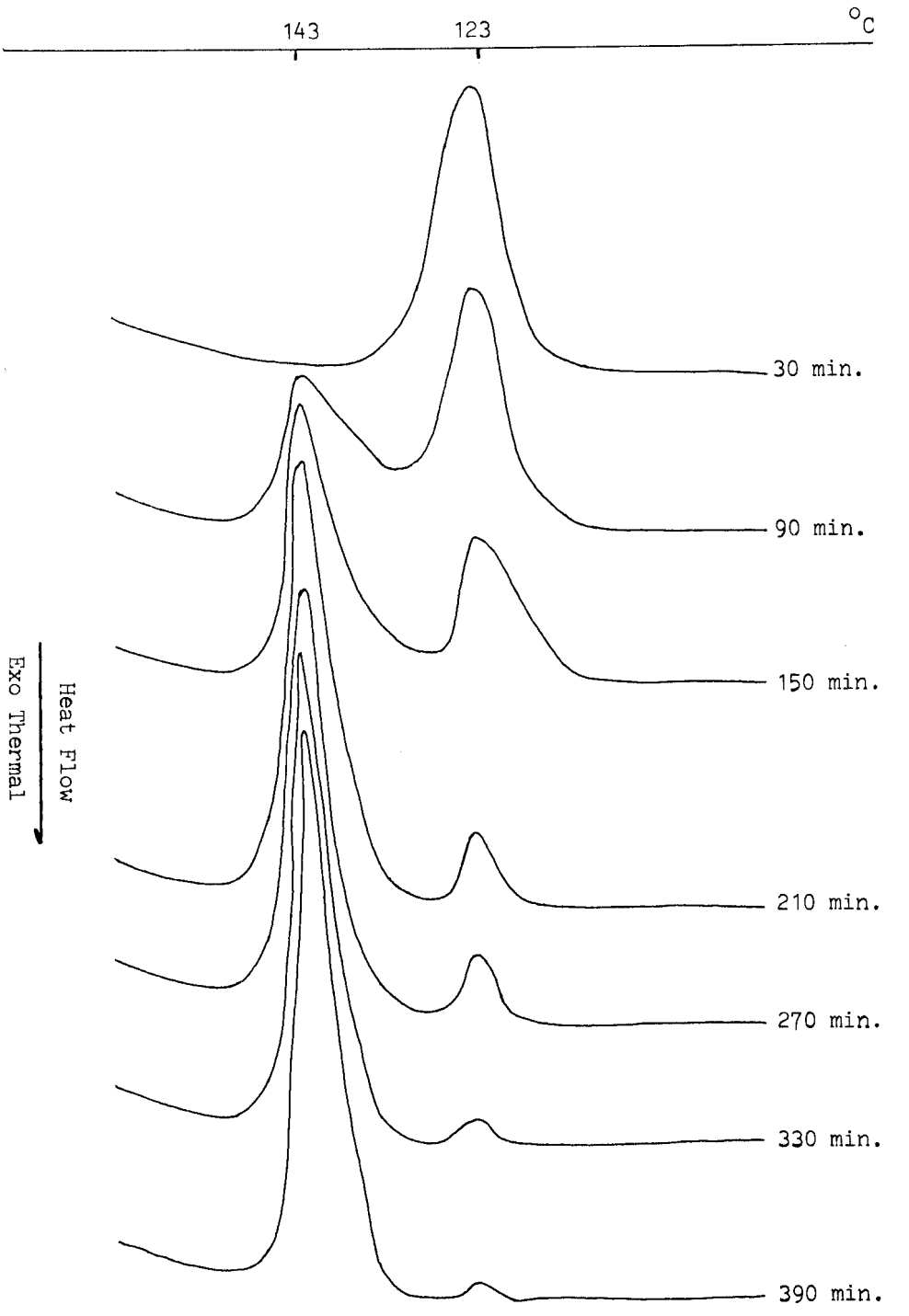

FIGURE 8

Polymorphic transition from HBB metastable form to the stable form at 55°C monitored by DSC.

TABLE (2)

TRANSFORMATION OF FORM II TO FORM I AT 55°C.

Time in Hours	Area % of Form I	Area % of Form II
0.5 hr.	0.00 %	100.00%
1.5 hrs.	26.40 %	73.60%
2.0 hrs.	72.65 %	27.34%
3.5 hrs.	86.67 %	13.33%
4.5 hrs.	94.96 %	5.03%
6.5 hrs.	98.22 %	1.78%
1 day	100.00 %	0.00%

phenomena is known to occur in many organic compounds. Storage at 55°C converted the form II into the form I. This process was clearly time dependant as the total conversion needed more than 6 hours to be completed. The DSC graphs showed that form II changed simultaneously to form I Figure (8). The percentage of such tansformation was calculated and is shown in Table (2).

Results obtained may be used in obtaining kinetics of transformation, as kinetic theory predicts that if the transformation from one polymorphic structure to another is opposed by a potential barrier of magnitude B, the speed of transformation is proportional to $1/_{e}B/KT$ (6). Accordingly, the transformation speed would be a function of the thermal energy of the atoms available to surmount that barrier.

CONCLUSION

Individual polymorphs were identified as stable form I melted at 143.6°C and metastable form II melted at 123.4°C. It was shown

that polymorphic transition took place from the metastable to the stable form under various processings or storage conditions. Nevertheless the coexistence of HBB two polymorphs in the commercial bulk material would raise discrepancies in the identification of the drug. The nature of such coexistence needs more attention, and the study of factors effecting this polymorphic transitions in solid phase is required to be explored.

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REFERENCES

1. A. Burger, Topics in Pharmaceutical Sciences. D.D. Breimer and P. Speiser, eds, Elsevier, 1983, P. 347.

2. H.K. Chan and E. Doelker, Drug Dev. and Ind. Pharm., 11, (2 & 3) 315 (1985).

3. H.K. Chan and E. Doelker, 4th Int. Conf. on Pharm. Tech., 1, 115 (1986).

4. Clark's Isolation and Identification of Drugs. A.C. Moffat, Consulting Editor, The Pharmaceutical Press 1986, p. 675.

5. E.G. Salole and F.A. Al-Sarraj., Drug Dev. Ind. Pharm., 11, (4) 855 (1985).

6. J.K. Haleblian, J. Pharm. Sci., 64, (8) 1269 (1975).