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POLYMORPHIC TRANSFORMATION OF SOME DRUGS UNDER COMPRESSION

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ABSTRACT

The existence of various crystalline forms in drugs is a phenomenon frequently encountered (about 40% of the USP XX tablet monographs with dissolution tests are concerned with such compounds). Some studies concerning trituration or grinding of polymorphs have been published; surprisingly little information is available on the transformation under compression, although of great relevance. In this work, thirty-two drugs known to exist as polymorphs were submitted to a trituration test for possible transitions. Out of the eleven transforming substances (approximately 34%), three model drugs, namely caffeine, sulfabenzamide and maprotiline hydrochloride were chosen for tabletting tests. Differential scanning calorimetry and hot stage microscopy were used to investigate polymorphic changes on the upper and lower surfaces, middle region and side of the compacts. The relationships between the extent of transformation and the compression pressure, and the energy of compression were examined, as well as the effect of drug particle size.

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INTRODUCTION

Polymorphism of drugs is a problem frequently encountered, as shown by the fact that about 40% of the USP XX tablet monographs with dissolution tests are known to be concerned with drugs which exist in different polymorphic forms. An increasing amount of work has been done for more than 10 years on the existence of polymorphs in various organic compounds, and the differences in their physico-chemical and thermodynamic properties. Solubility, dissolution rate and bioavailability have been extensively investigated.

Compression behaviour of polymorphs have also been studied in connection with the mechanical properties of the finished tablets, but very little attention has been paid to the polymorphic transition of drugs under mechanical treatment. Several drugs have been studied for their transformation under trituration and to our knowledge, only about a dozen reports on polymorphic transformation of drugs under compression have been published (1-11).

The aim of this study is to evaluate the extent of this phenomenon because of the many technological and biopharmaceutical implications. For this purpose, 32 drugs which have been reported to possess different polymorphs are tested for their polymorphic transformation under trituration as a screening for their susceptibility.

Among them, three substances are chosen for quantitative work on tabletting: caffeine (12), a xanthine often incorporated in medical products; sulfabenzamide (13,14), a sulfonamide, and maprotiline hydrochloride (15),

a tetracyclic antidepressant. The relationship between the degree of polymorphic transformation and the energy of compression is investigated.

MATERIALS AND METHODS

Thirty two drugs were obtained from various commercial sources and tested for the presence of polymorphs using Differential Scanning Calorimetry (Perkin-Elmer DSC-4). As a preliminary scan, each was triturated by pestle and mortar (5,10 and 15 minutes) and retested by DSC for thermographic changes. Hot stage microscopy (Leitz model 350) was also used to view the crystals under heating. Caffeine, sulfabenzamide and maprotiline HCl were selected for compression trials and their polymorphs identified using the same methods plus IR spectroscopy (Perkin-Elmer model 298).

Individual forms were recrystallized from appropriate solvents and their water contents determined by the Karl Fischer titrimeter (Metrohm model 633). Two size fractions (0 - 125 μm and 63 - 250 μm) were isolated using a sieve shaker (Fritsch Analysette 3). Densities of the powders were determined by an air comparison pycnometer (Beckman model 930).

The enthalpies of fusion (ΔH_f) of the pure stable polymorphs and the enthalpies of transition (ΔH_t) of the pure unstable polymorphs during endothermic or exothermic transition from the unstable to a more stable form were calculated from the DSC thermographs, calibrated with indium (ΔH_f = 3.26 kJ mol^{-1}), at a heating rate of 10 K min^{-1}, sensibility 2 mcals s^{-1}, recorder chart speed 80 mm min^{-1}. Tablets of 12.0 mm diameter and 2 mm thickness at zero theoretical porosity of each polymorphic form were made on an instrument-

ed (16-17) single-punch machine (Korsch EK-0) at a speed of 30 cycles min^{-1}. The compression pressures were between 50 - 350 MPa. From the signals, two pieces of information among others were considered:

The upper punch work (UPW) (18), that is the work delivered by the upper punch, or gross input (G.I.), is given by:

$$UPW = \int_{D_S}^{D_M} UPF \cdot dD$$

UPF = upper punch force.

D = displacement of the upper punch, measured relative to the lower punch.

D_S = point at which the force rises from zero.

D_M = maximum displacement of the upper punch.

Similarly, the lower punch work (LPW) (18) is obtained from the lower punch force (LPF):

$$LPW = \int_{D_S}^{D_M} LPF \cdot dD$$

Samples of powder were taken from the upper, lower surfaces, the middle region and the side of the tablets and their new ΔH_f or ΔH_t values calculated from the DSC thermographs in order to determine the amount of unstable form being transformed during compression. If calculation of ΔH_f or ΔH_t is not possible, only DSC thermographs registered at a chart speed of 20 mm min^{-1} are presented. Generally, the weights used were approximately 1 mg for caffeine, 0.25 mg for sulfabenzamide and 0.40 mg for maprotiline hydrochloride.

Storage tests were also performed on the powders of the metastable forms to detect any transformation over time.

RESULTS AND DISCUSSION

- Trituration.

Out of the 32 commercially-obtained drugs tested, 11 (34%) were found to possess more than one modification and show polymorphic transformation under trituration demonstrated by their changes in thermographs (Tab. 1). Hot stage microscopy could reveal only the melting points of the stable forms and in some cases, sublimation and/or recrystallization to the same or a different form on cooling.

- Compression.

Caffeine

Caffeine was obtained through two commercial sources, both of which contained a mixture of the two forms A (transition temperature 141° C) and B (m.p. 236° C). Table 2 shows the preparation and properties of these two forms. The size fraction was 63 - 250 μm.

Tablets were made from both forms taking the density as 1.23 g cm^{-3}. Results of ΔH_t analysis of the monotropic transformation of form A to B show that the upper surface transforms rapidly under increasing pressure from about 100 to 150 MPa (Fig. 1a) and eventually attains a maximum transformation of about 25%. The middle region demonstrates similar rapidity of transformation, but to a lesser extent, i.e. under 18%. The change in the lower surface is much slower from 100 to 250 MPa and then followed by a faster change reaching a maximum transformation of about 18% also. The side of

TABLE 1

DRUGS TESTED FOR POLYMORPHIC TRANSITION UNDER TRITURATION

Drug	Polymorphic transformation*	Number of polymorphs before trituration**	Number of polymorphs after trituration**
Acetohexamide	-		
Azaperone	-		
Barbitone	+	2	1
Bumetanide	-		
Butobarbitone	-		
Caffeine	+	2	1
Chlorpropamide	+	3	2
Clenbuterol HCl	+	2	3
Diazepam	-		
Digitoxin	-		
Dipyridamole	+	2	1
Disopyramide	-		
Fluanisone	-		
Indomethacin	-		
Maprotiline HCl	+	3	1
Mebendazole	+	4	5
Mefenamic Acid	-		
Meprobamate	-		
Methylprednisolone	-		
Nafoxidine HCl	+	4	3
Pentobarbitone	+	3	2
Phenazone	-		
Phenobarbitone	+	2	1
Sulfabenzamide	+	2	1
Sulfaethidol	-		
Sulfadimidine	-		
Sulfamethoxazole	-		
Sulfapyridine	-		
Sulfisoxazole	-		
Theophylline	-		
Tolbutamide	-		
Trimethoprim	-		

* - Not observed, + observed.

** Not mentioned means no change in the number of polymorphs before and after trituration (depending on the source of material).

TABLE 2

POLYMORPHIC FORMS OF CAFFEINE

Form	Recrystallization Technique	Solvent	Water Content (%)	ΔH_f (kJ mol^{-1})	ΔH_t (kJ mol^{-1})
A	Evaporation under vacuum	Water; Propanol	2.24		3.36
B	Melting, recooling in liquid N_2	---	2.46	19.51	

the tablet transforms more slowly than that of the middle region at lower pressures but much faster from about 250 MPa onwards and reaches a maximum value of about 23%.

The graph of % caffeine transformed vs gross input (upper punch work) (Fig. 1b) has the curves of the four zones with similar shapes as in Fig. 1a. The same is true for the lower punch work and therefore not presented.

Thus, as the upper surface experiences on average the largest force on compression, it demonstrates a more rapid and higher degree of transformation. The middle region receives slightly weaker forces, but which in turn are stronger than that received by the lower surface at low pressures. However, from about 250 MPa onwards, the forces on the lower surface increase to a level high enough to give a second increase of the curve to reach a maximum value similar to the middle region. The side receives a weaker force than the middle at low pressures, but also after 250 MPa, the forces experienced are large enough to produce a second increase in transformation to achieve a maximum just under that of the upper surface.

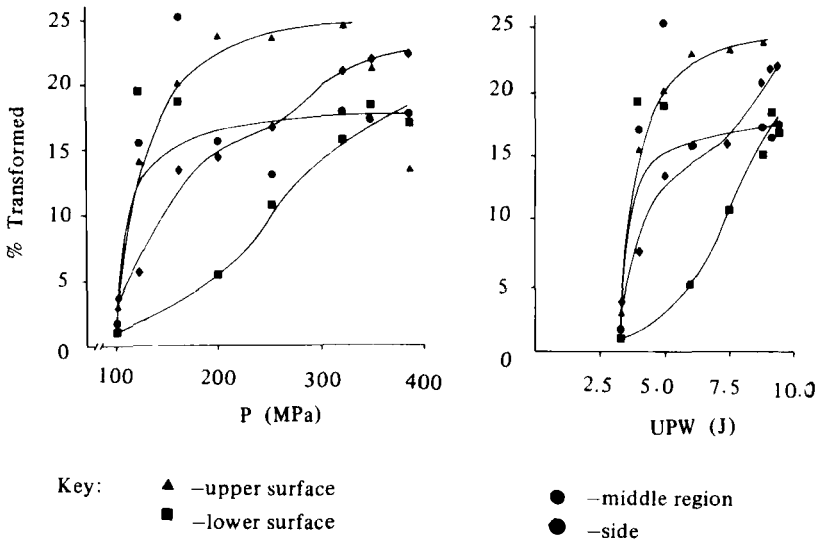

FIGURE 1

PERCENTAGE OF CAFFEINE FORM A TRANSFORMED VERSUS a) APPLIED PRESSURE P, b) UPPER PUNCH WORK UPW

This could probably be due to the large friction between the die wall and the powder both during compression and ejection of the tablet.

All these observations are in agreement with the differences in pressure and density distributions in tablets measured by many workers (19-22).

Values of the heat of fusion ΔH_f calculated from a tablet of form B compressed at 249 MPa confirm that there is no transformation of this stable form. Finally, both forms A and B are found to be stable on storage at room temperature.

Sulfabenzamide

Sulfabenzamide was also obtained from two commercial sources, both containing a mixture of the stable

TABLE 3

POLYMORPHIC FORMS OF SULFABENZAMIDE

Form	Recrystallization Technique	Solvent	Water Content (%)	ΔH_f ($kJ\ mol^{-1}$)
A	Evaporation under vacuum	Chloroform; Methanol; Ethanol; Propanol	1.08	29.50
B	Supersaturation	Water	1.92	---

form A (m.p. 181° C) and unstable form B (m.p. 171° C). (Tab. 3).

The enthalpy of fusion ΔH_f of form B cannot be calculated from the DSC thermographs because the peak of fusion is immediately followed by an exothermic peak, showing the monotropic transition of B to A, and then the fusion peak of form A.

Tablets of form B were made using a density of 1.32 g cm^{-3}.

The four zones of the tablets were tested by DSC and their thermographs compared at different compression pressures (Fig. 2 and 3). At about 50 MPa, there is already drastic diminution in the peak height of form B, showing extensive transformation to form A. The effect increases with stronger compression pressures; and within the same tablet, the extent of transformation at lower pressures is highest on the upper surface and the side. At higher pressures, the extent is largest on the side, the lower surface and the middle respectively.

The sieve fraction 63 - 250 µm seems to show the phenomenon more evidently probably due to better transmission of forces through the powder bed.

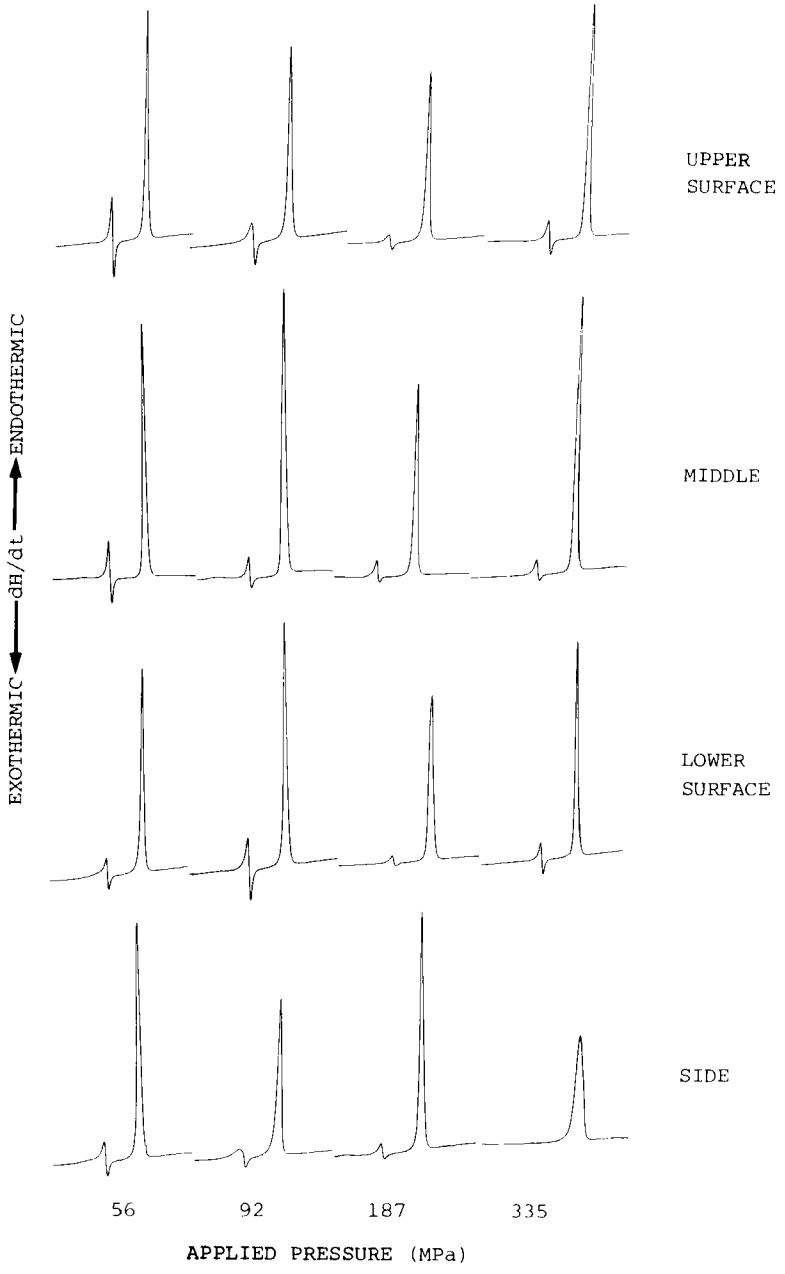

FIGURE 2
DSC THERMOGRAPHS OF SULFABENZAMIDE FORM B (0-125 μm) AT DIFFERENT PRESSURES

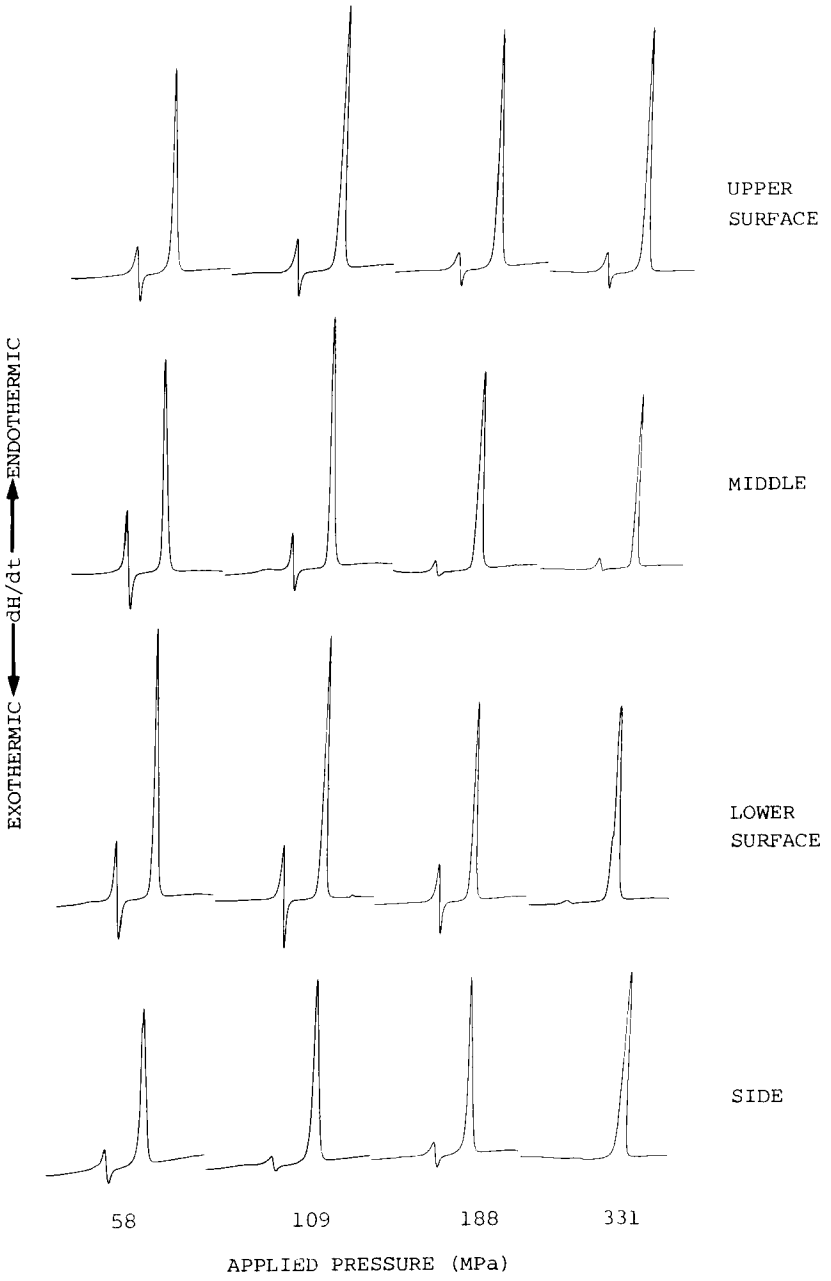

FIGURE 3
DSC THERMOGRAPHS OF SULFABENZAMIDE FORM B (63-250 μm) AT DIFFERENT PRESSURES

Storage test on form B revealed, however, a gradual transformation to form A, demonstrated by the decrease in the relative peak heights of B to A (Fig. 4).

Maprotiline hydrochloride

A maprotiline HCl sample was obtained from a commercial source and found to contain the metastable form I (m.p. 243° C) and stable form II (m.p. 239° C). Another metastable form III was fabricated (transition temperature 140 - 145° C) (15) (Table 4).

Tablets were made from forms I and III taking the density as 1.151 g cm^{-3}. Form III exhibits monotropic transformation to form II, while form I is stable under compression and does not transform at all.

The powder of form III (particle size 63 - 250 μm) was stored for more than one month before being used for compression; thereby, the ΔH_t value had already dropped to 1.58 kJ mol^{-1} spontaneously. Hence, the quantitative analysis of transformation after compression was done on the basic value of 1.58 kJ mol^{-1}. Calculated ΔH_t values (Fig. 5a) show that the middle region of the tablet achieves surprisingly the highest degree of transformation after a more rapid increase from 200 MPa onwards. The upper surface has a lower degree of transformation until about 200 MPa, followed by a rapid increase to reach a maximum of about 20%. The lower surface curve has the highest value at lower pressures but levels off after 200 MPa. The side shows little transformation, especially under 220 MPa. The graph of % transformation vs gross input (Fig. 5b) shows the same trends of changes.

For the powder of particle size 0-125 μm, the starting ΔH_t value for compression was 5.36 kJ mol^{-1} (1 week

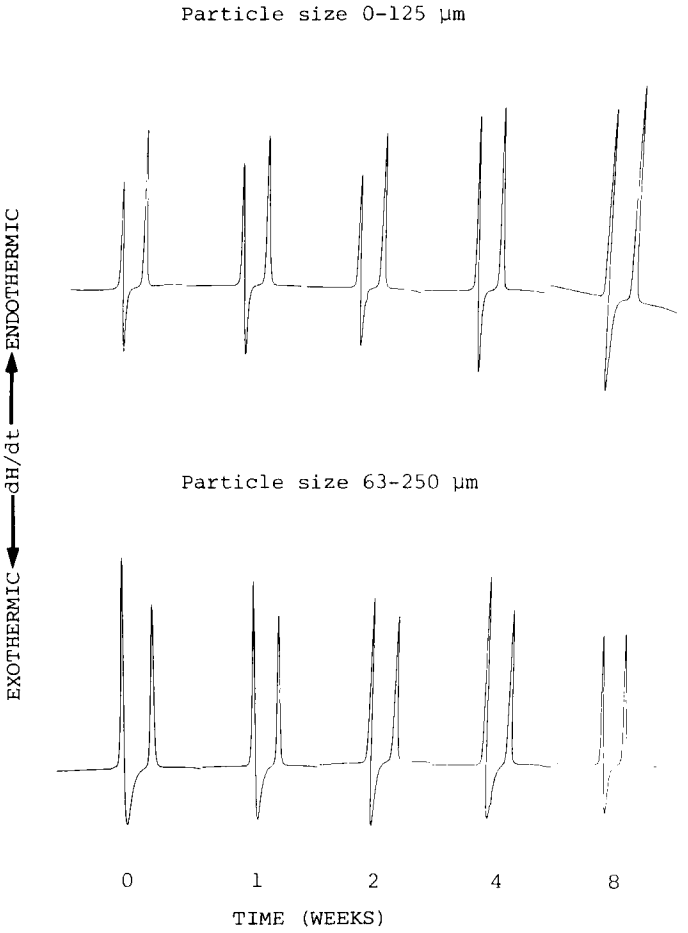

FIGURE 4
DSC THERMOGRAPHS OF SULFABENZAMIDE FORM B ON STORAGE

after fabrication). The profiles of transformation (Fig. 6a,b) for this fraction are completely different. Little transformation was observed for both the middle and the lower surface. The upper surface transforms steadily and levels off just under 200 MPa. The side transforms more slowly, but reaches a higher value of about 45%. The difference between these two size fractions could be explained on the analogy of the work by Summers (9) on

TABLE 4

PREPARATION AND CHARACTERISTICS OF MAPROTILINE HCl POLYMORPHS

Form	Recrystallization Technique	Solvent	Water Content (%)	ΔH_f (kJ mol^{-1})	ΔH_t (kJ mol^{-1})
I	Evaporation under vacuum	Water	2.64	28.86	---
II	Evaporation under vacuum	Methanol; Ethanol; Propanol	3.53	34.77	---
III	Melting,recooling in liquid N_2	---	2.56	---	6.44

barbitone granules and crystals. The former develops a lower pressure at the points of contact for a given applied axial force than the latter, because of its higher contact area due to surface roughness. It could, therefore, be deduced that for a powder of lower sieve fraction, ie. higher area contact between crystals, the pressure at the points of contact is lower, which would consequently produce less polymorphic transformation. However, the higher friction between the smaller size crystals and the die wall could explain the much higher degrees of transformation on the sides of the tablets made from the 0-125 μm fraction.

On the other hand, when comparing the upper punch work developed for the two fractions at the same applied pressure, there appears to be no correlation between the UPW values and the extent of transformation. The work involved in compressing the 0 - 125 μm is greater but the percentage transformed is smaller. This is not surprising because fine particles are known to be less

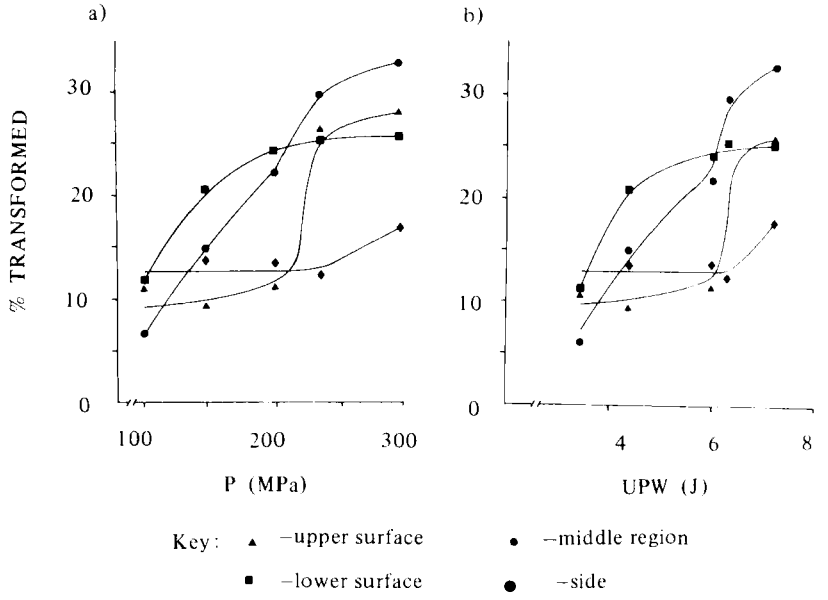

FIGURE 5
PERCENTAGE OF MAPROTILINE HYDROCHLORIDE FORM III TRANSFORMED VERSUS
a) APPLIED PRESSURE P, b) UPPER PUNCH WORK UPW
(PARTICLE SIZE 63-250 μm)

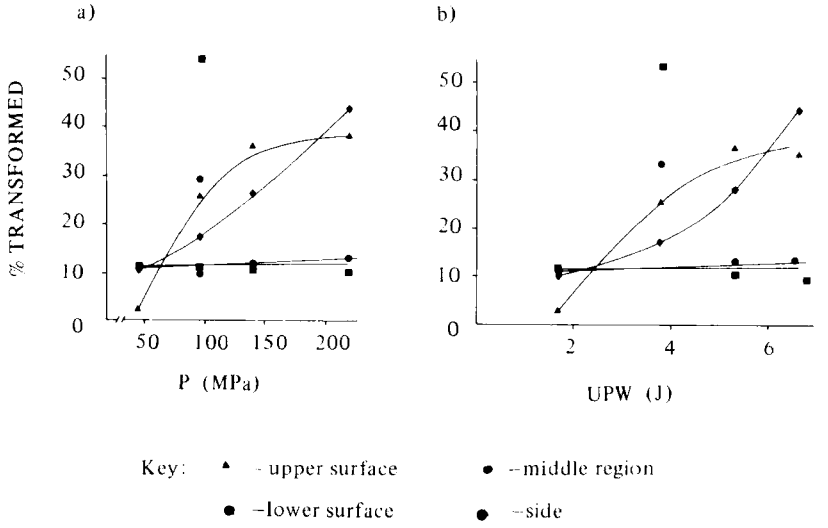

FIGURE 6
PERCENTAGE OF MAPROTILINE HYDROCHLORIDE FORM III TRANSFORMED VERSUS
a) APPLIED PRESSURE P, b) UPPER PUNCH WORK UPW
(PARTICLE SIZE 0-125 μm).

prone to plastic flow and to fragmentation and therefore more resistant to compression; it should be remembered that the gross input consists of several components, ie. the friction with the die wall, the amount of work required for the elastic and plastic deformation as well as the fragmentation of the particles (18).

CONCLUSION

The phenomenon of polymorphic transition under mechanical treatment was explained by Summers (9) who analysed from Cahn (23) that it occurs through a mechanism of nucleation and growth of a second phase within the first. Nucleation tends to proceed from dislocations in a crystal because of their higher free energy; hence, the energy for transformation is lower at these sites. Moreover, during compression, the plastic flow induces dislocational strains in a crystal, thereby, facilitating nucleation.

For a substance with different crystal forms, the form with the lowest melting point has the least intermolecular attractive forces and probably the least yield stress values at a given temperature. This could explain the polymorphic transition of a lower melting point metastable form to a higher melting point stable form, as demonstrated by the drugs studied.

Here, we have shown that tablets of caffeine, sulfabenzamide and maprotiline hydrochloride all transformed to different degrees from the unstable to the stable form. The extent of transformation depended on the zone of the tablet, the pressure applied and the particle size of the powder.

In future, the effect of lubrication and the protection by excipients against transformation will be

examined. The intrinsic dissolution rate of the compacts will also be studied in order to relate the *in vitro* availability to the amount of polymorphic transformation.

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