indication of the roundness of the spheres, increased dramatically if extrusion forces were higher than 1260 N.

The most important parameters influencing the extrusion forces were the solubility of the excipient and the amount of fluid phase used as was shown in previous work (Baert et al 1991). When an excipient was added to the binary mixtures of microcrystalline cellulose, the ratio microcrystalline cellulose/water can vary from 1·22 to 1·63 in the case of dicalcium phosphate, from 1·09 to 2·00 in the case of α-lactose monohydrate and from 1·00 to 2·08 in the case of β-lactose, in order to obtain spheres with the defined quality. The lower limit of microcrystalline cellulose concentration that can be used in order to obtain good spheres depended on the solubility of the third compound. A lower limit of 12, 15 and 31·5% of the mixture was observed in the cases of β-lactose, α-lactose monohydrate and dicalcium phosphate dihydrate, respectively. The largest quantity of excipient that can be used depended also on the solubility of the third excipient and values of 63, 55 and 21% of the mixture for β-lactose, α-lactose monohydrate and dicalcium phosphate, respectively, were recorded, representing an amount of 85, 79 and 40% on dry pellet base, respectively. It should be emphasized that the experiments have been performed on a gravity feed extruder and with fixed parameters during the spheronization process. Nevertheless formulators may apply these observations in the case of sphere formulation development with additives or active ingredients of different solubility.

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Effect of compressional forces on piroxicam polymorphs

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Abstract—The effect of compressional force on the polymorphic transition in piroxicam has been examined, using pure polymorph, by differential scanning calorimetery, powder X-ray diffractometry and by determination of dissolution rates from tablets of the individual polymorphs. The needle shaped polymorph was found to undergo transition to the cubic polymorph during compression.

Mechanical processes such as size reduction and compression have been reported to bring about polymorphic changes in drugs. Nogami et al (1969) reported transitions of metastable forms of barbitone to a stable polymorph during tableting. Summers et al (1976) reported reduction in transition temperature due to dislocations in crystal boundaries during compression. Ibrahim et al (1977) reported transition of metastable polymorphs of phenylbutazone to stable polymorphs by mechanical stress. Similar observations were made by Chan & Doelker (1985), Takahashi et al (1985), Debord et al (1987) and Otsuka et al (1989).

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Piroxicam, a long-acting non-steroidal anti-inflammatory drug (NSAID) is available in monohydric and anhydrous forms. Influence of water of hydration of this drug on its tableting behaviour has been reported by Huettenrausch & Fricke (1989). The existence of the needle shaped and cubic polymorphs has been reported by Mihalic et al (1986).

We have studied the effect of compression force on polymorphic transition of piroxicam. The results obtained from other studies including X-ray diffraction, IR spectroscopy, solid state ^{13}C NMR spectroscopy, and differential scanning calorimetry on pure polymorphs have been extended to this study wherever applicable. IR spectra of the powdered tablets were not recorded since the two polymorphs do not exhibit differences in the IR spectra.

Materials and methods

Materials. Piroxicam USP (Sekhsaria Chem. Pvt. Ltd, Bombay, India), absolute alcohol (Riedel de Haen, India), benzoic acid AR, lactose USP, starch IP, magnesium stearate IP, conc. hydrochloric acid (all from Qualigens, India) were purchased from the companies stated.

Table 1. Compression hardness of tablets made from piroxicam polymorphs.

Polymorphs of piroxicam	Hardness of tablet (kg cm^{-2})	Code
Needle shaped (α)	6	LT α 6
Needle shaped (α)	8	LT α 8
Needle shaped (α)	9	LT α 9
Needle shaped (α)	10	LT α 10
Needle shaped (α)	11	LT α 11
Cubic (β)	6	LT β 6
Cubic (β)	8	LT β 8
Cubic (β)	9	LT β 9
Cubic (β)	10	LT β 10
Cubic (β)	11	LT β 11

Methods. Preparation of polymorphs of piroxicam. The method suggested by Mihalic et al (1986) was used for this purpose. The needle-shaped polymorph (abbreviated here as polymorph α) was obtained by rapid cooling of saturated ethanolic solution of piroxicam, while the cubic polymorph (abbreviated here as polymorph β) was obtained by slow cooling of the alcoholic solution of piroxicam.

Compression of pure polymorphs. The two polymorphs in their pure state were compressed in a hydraulic press at pressures of 80 and 130 kg cm^{-2}. The pellets were then subjected to differential scanning calorimetric analysis (DSC). For comparison, benzoic acid was compressed at the same pressures and analysed by DSC.

DSC of pure polymorphs. Thermal analysis system model DT-40 (Shimadzu Corp., Japan), with DSC and thermogravimetric analysis (TGA) modules and equipped with a Chromatopac CR6A integrator was used for DSC analysis. About 5–10 mg of the sample was weighed in an open aluminium cup and heated at a rate of 10°C min^{-1} using an empty aluminium cup as reference in an inert atmosphere of nitrogen (flow rate 30 mL min^{-1}). The instrument was calibrated using indium.

Piroxicam tablets—their preparation and evaluation. Tablets, each containing 20 mg of piroxicam were prepared from each of the polymorphs, by granulation, using starch, lactose and magnesium stearate as excipients, followed by compression on a Jaguar 10-station rotary tablet compression machine. Compression pressures were applied to obtain tablets having hardness values of 6, 8, 9, 10 and 11 kg cm^{-2} (measured using a Monsanto Hardness Tester). They were designated as shown in Table 1.

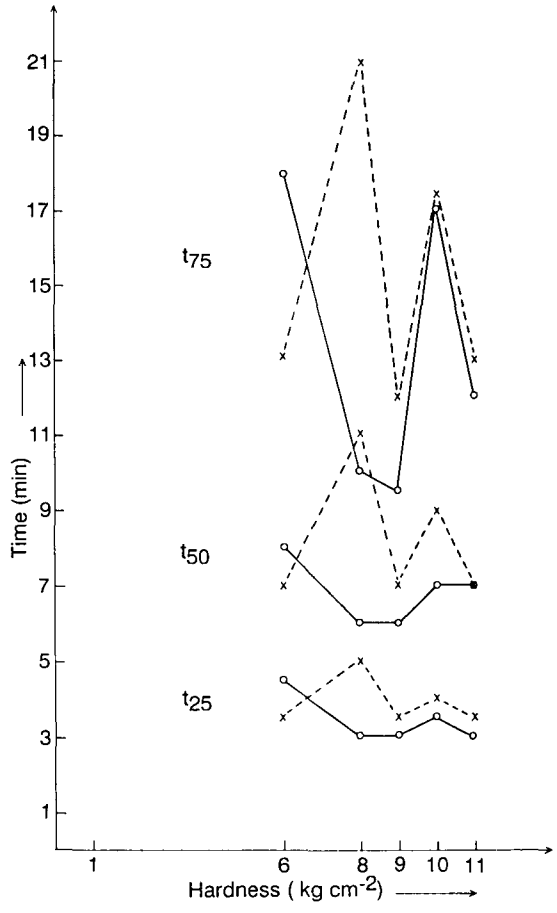

FIG. 1. Plot of compression hardness vs time to release of 25% (t_{25}), 50% (t_{50}) and 75% (t_{75}) of piroxicam. Polymorph α ○, polymorph β ×.

The tablets were then subjected to studies of their dissolution rates and powder X-ray diffraction analysis. Since the polymorphs also had excipients, it was not possible to record and interpret the IR spectra and DSC data.

Dissolution rate studies. The dissolution rate was determined using 6 tablets in a 6-station automated dissolution rate test apparatus, model DT-600 (Freund-Jasco, Japan) connected to a variable detector model UV-VIS 340 via a flow-through cell. The

Table 2. Differential scanning calorimetric data of piroxicam polymorphs and benzoic acid before and after compression.

	Piroxicam polymorphs				Benzoic acid	
	Needle shaped		Cubic			
	Hf* (J g^{-1})	mp (°C)	Hf* (J g^{-1})	mp (°C)	Hf* (J g^{-1})	mp (°C)
Uncompressed	62·36 ±0·20	209·7	64·20 ±0·14	205·7	101·49 ±0·25	121·9
Compressed at 80 kg cm^{-2}	79·26 ±0·43	203·5	57·05 ±0·30	212·5	110·01 ±0·19	121·7
Compressed at 130 kg cm^{-2}	71·40 ±0·15	207·1	31·48 ±0·15	204·1	101·44 ±0·19	121·2

*Mean ± s.d. (n = 3). Hf = heat of fusion. mp = melting point.

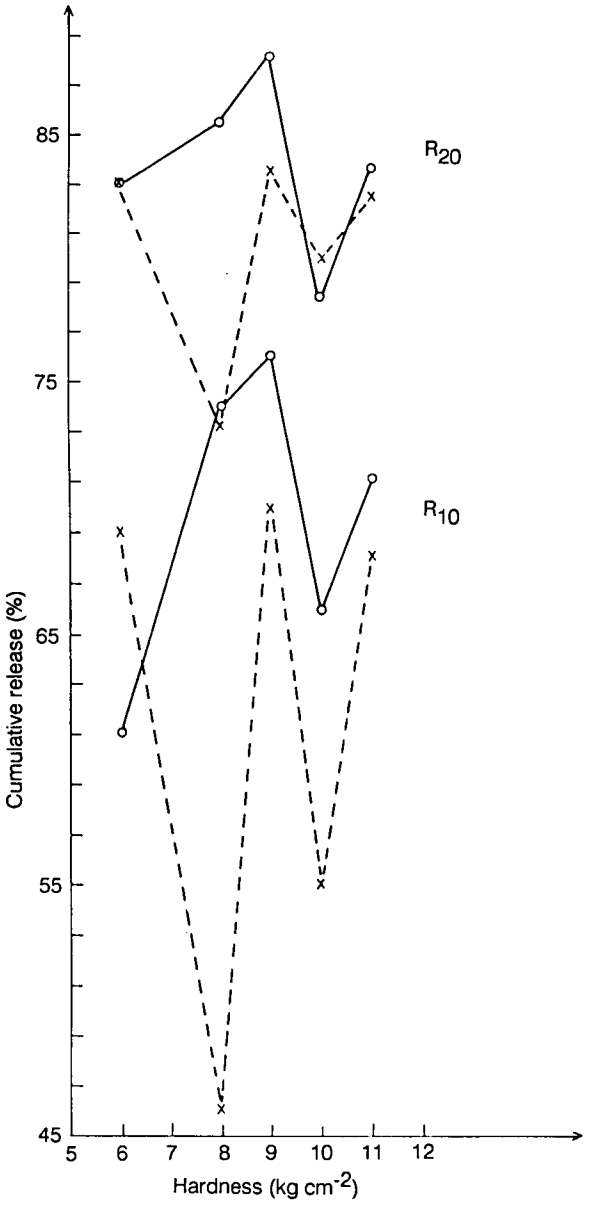

FIG. 2. Plot of compression hardness vs release of piroxicam in the first 10 (R_{10}) and 20 (R_{20}) min. Polymorph α O, polymorph β ×.

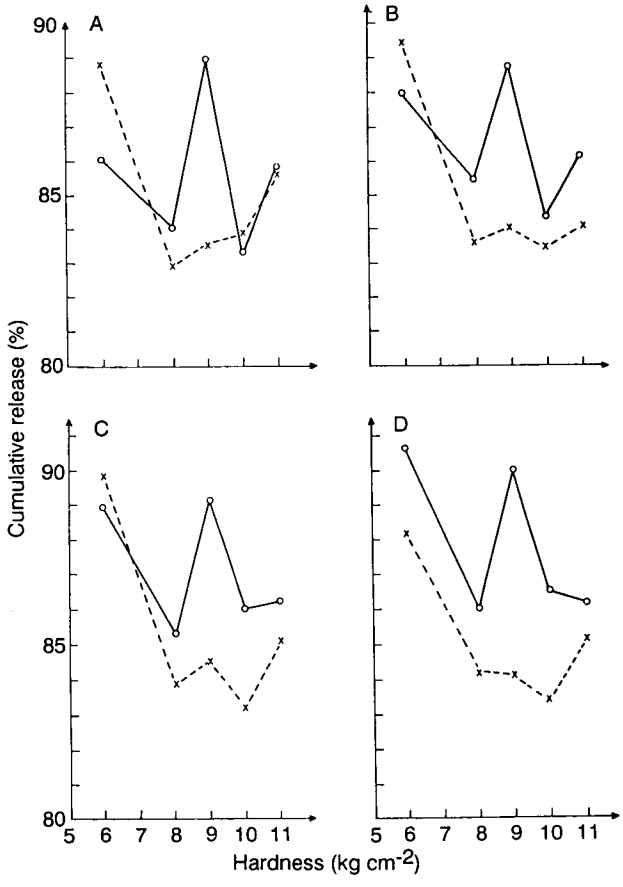

FIG. 3. Plot of compression hardness vs release of piroxicam in (A) 30 min (R_{30}), (B) 40 min (R_{40}), (C) 50 min (R_{50}) and (D) 60 min (R_{60}). Polymorph α O, polymorph β ×.

medium employed was 900 mL of 0·1 M hydrochloric acid at 37 ± 0·5°C agitated with a paddle at 50 rev min^{-1}. One tablet each was introduced into 900 mL of the medium. Samples (25 mL) were withdrawn at 10 min intervals during 1 h, the quantity withdrawn being replaced by the same quantity of fresh medium. The absorbance of the solution was measured at 334 nm. The values represent an average of six.

Powder X-ray diffraction analysis. Powder X-ray diffractograms were recorded at room temperature (24°C) with a PW 1140 diffractometer (Philips). The measurement conditions were: target, Cu K_α ($\lambda = 1{\cdot}5406^0$A); filter, Ni; voltage, 40 KV; current, 30 mA; receiving slit 0·2 mm; scan speed 2° min^{-1}.

Results and discussion

Effect of compression pressure on pure polymorphs. The DSC data obtained from uncompressed and compressed polymorphs of piroxicam, as well as benzoic acid are presented in Table 2. The melting point of polymorph α decreased on compression and slowly approached the melting point of polymorph β. Contrary to this the melting point of polymorph β was close to the melting point of the uncompressed polymorph. It was observed that polymorph α on compression showed heat of fusion values (79.26 and 71.40 J g^{-1}) much higher than the original value (71.40 J g^{-1}) (Table 2). On the other hand benzoic acid showed no alteration in melting point on compression at 80 and 130 kg cm^{-2}. Thus it can be concluded that polymorph α undergoes polymorphic transitions during compression, the high energy generated being utilized for inducing and accelerating the conversion.

Effect of compression pressure on polymorphs in the presence of excipients; hardness vs dissolution. Maximum release varied between 82 and 90%. Time taken for 25, 50 and 75% release (t_{25}, t_{50}, t_{75}, respectively), were extrapolated from cumulative release vs time profiles and plotted against hardness for interpretation of results.

Fig. 1 shows a comparison of t_{25}, t_{50}, and t_{75} values for the tablets containing polymorphs α and β. Polymorphs α and β in tablets showed similar patterns of hardness beyond 9 kg cm^{-2}. The time values to release increased with an increase in hardness from 9 to 10 kg cm^{-2} but decreased from 10 to 11.

The patterns followed by the two polymorphs below a hardness value of 9 kg cm^{-2} were exactly opposite to each other, thus indicating that polymorph α underwent transition to

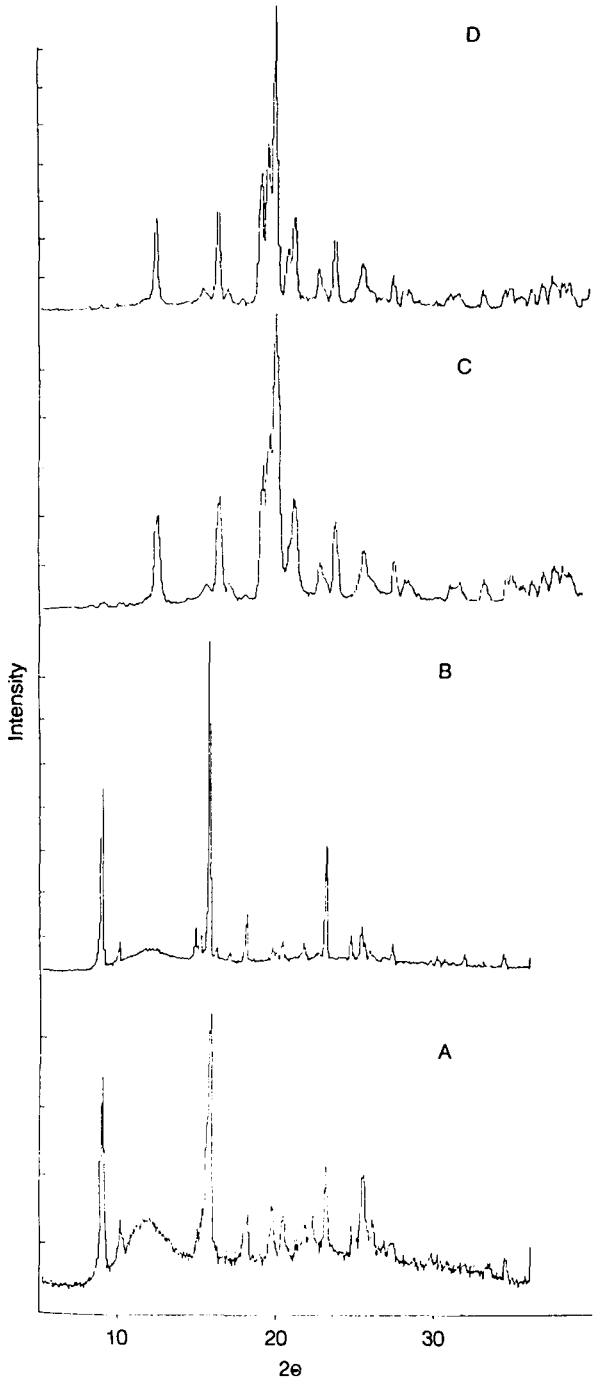

FIG. 4. Powder X-ray diffractograms of A, polymorph α, B, polymorph β, C, LTα9, and D, LTβ9.

polymorph β at a hardness value of 9 kg cm^{-2}. These findings are confirmed by R_{10}–R_{60} values recorded in Figs 2, 3. It is probable that a change in the polymorphic form is responsible for the change in dissolution pattern.

Powder X-ray diffraction analysis. The X-ray diffractograms of tablets of polymorphs α and β in the presence of excipients with a hardness value of 9 kg cm^{-2} are shown in Fig. 4. Polymorph β showed peaks at $2\theta^\circ = 9{\cdot}04$, 15·58, 16·47, 17·16, 18·02, 19·6, 27·55 and 31·76 which conformed to the peaks obtained with pure polymorph β indicating that polymorphic transition had not taken place during tableting. However, in the X-ray diffractogram of the tablet of polymorph α, peaks appeared at $2\theta^\circ = 9{\cdot}16$, 15·67, 16·47, 17·16, 19·605, 27·55, 31·78 and 34·64 as against the expected values of $2\theta^\circ = 15{\cdot}83$, 18·13, 21·75 and 22·24 for polymorph α. The values obtained closely approximated those obtained for polymorph β ($2\theta^\circ = 9{\cdot}04$, 15·58, 16·47, 17·16, 19·6, 27·55, 31·76). The absence of peaks of polymorph α in the compressed tablets and similarity to those of polymorph β confirmed the polymorphic transition that took place when polymorph α was subjected to compression at a tablet hardness of 9 kg cm^{-2}. The other peaks shown in Fig. 4 C, D were attributed to the excipients; hence no attempt was made to identify them.

Thus, the present investigations on the polymorphic transition from α to β polymorphs of piroxicam as a result of compression indicate that although polymorph α does not exhibit any polymorphic change under compression to a tablet hardness of up to 9 kg cm^{-2} it does at or above this value. The present dosage form of piroxicam in capsules would avoid this transition. At present it is uncertain whether these polymorphs would exhibit differences in their bioavailability or not.

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