

CRYSTALLOGRAPHIC AND CHEMICAL STABILITY OF MODIFIED PHENYLBUTAZONE CRYSTALS CONTAINING LOW LEVEL POLYMER ADDITIVES

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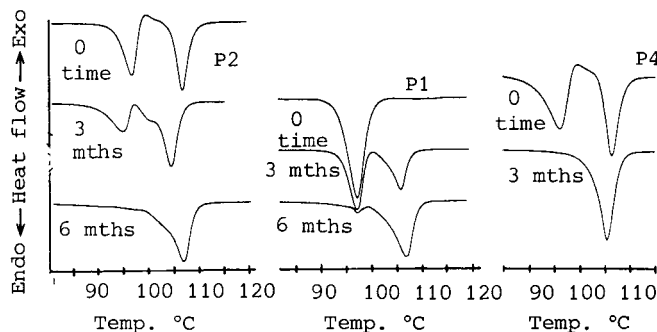
Al-Meshal & York (1984, 1985) have examined the effects of incorporating low levels of polymers on the solid state and physicochemical properties of phenylbutazone (PBZ) crystals. Improvements in dissolution behaviour have been related to complexation and crystal disruption phenomena. This communication considers the crystallographic and chemical stability of the modified materials stored as powders in sealed glass containers for 6 months. The samples, see Table 1, were prepared as previously reported (Al-Meshal, 1985). A published HPLC assay for identified decomposition products (Fabre et al, 1982) was modified to use a Partasil-10 ODS reverse phase column (25 cm x 4.6mm i.d.) examining at 237  $\mu\text{m}$  and operating at 188 bars, sensitivity 0.08, flow rate 2 ml  $\text{min}^{-1}$  (Pye Unicam LC-XPD and UV detector). The mobile phase was 42:58 methanol (HPLC grade): distilled water using salicylic acid as internal standard. A calibration curve ( $r=0.9997$ ) was used to estimate the concentration of the only detected decomposition product,  $\alpha$ -carboxy-N-caproyl-hydrazobenzene (CCH), which is formed by hydrolysis of phenylbutazone (Awang et al, 1973)

Table 1: Sample composition, preparation route and chemical stability data.

Sample	Sample code	% w/w polymer in sample	Preparation route	% w/w CCH			
				Storage (months) 3		Storage (months) 6	
				Storage temp( $^{\circ}\text{C}$ )			
				37	50	37	50
PBZ	PBZ	0.00	As supplied	0.0	0.0	0.0	0.0
PBZ + HPMC*	P1	2.20	Crystallised	3.8	13.0	6.3	18.0
PBZ + HPMC	P2	1.90	Spray-dried	2.1	4.4	3.2	10.0
PBZ + Poloxamer 188	P3	1.06	Crystallised	17.4	33.0	20.5	54.4
PBZ + Poloxamer 188	P4	1.05	Spray-dried	5.9	15.6	8.4	20.0

(\*HPMC = Hydroxypropyl methylcellulose (Pharmacoat 606))

Figures in Table 1 show that whilst PBZ remained unchanged over the period of study, the degree of decomposition for modified materials was lower for those containing HPMC and was influenced by sample preparation conditions. Associated changes in crystallographic form of stored samples were monitored by differential scanning calorimetry (DSC-Du Pont 1090/910) using 5 mg samples in pierced, crimped aluminium pans, scanned at  $10^{\circ}\text{C min}^{-1}$  under nitrogen. Representative DSC thermograms for samples stored at  $50^{\circ}\text{C}$  in Figure 1 demonstrate for sample P2 the conversion of the metastable  $\beta$ -polymorph of phenylbutazone to the stable  $\delta$ -form. For sample P1 the complex formed on crystallisation, which exhibited a single endotherm at  $97^{\circ}\text{C}$  is increasingly broken down over longer storage times. However, sample P4, originally in  $\beta$ -polymorphic form was totally converted to the  $\delta$ -stable form after 3 months storage at  $50^{\circ}\text{C}$ . Thus the type of polymer additive and sample preparation route, which influence the crystallographic form of the sample, play major roles in directing the hydrolytic degradation process. Different degrees of decomposition were observed for samples containing similar low levels of the same polymer but prepared by alternative processes.



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