

FACTORS INVOLVED IN QUANTITATIVE X-RAY ANALYSIS OF SOLID DISPERSIONS

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The increased dissolution rates of drugs from solid dispersion systems is often linked to a reduced crystallinity and the formation of amorphous high energy states (Simonelli, A.P. et al 1969). However, few attempts have been made to quantify these crystal changes. X-ray powder diffraction is often used to qualitatively show reductions in crystallinity (Chiou, W.L. 1977) but poor reproducibility hinders quantification.

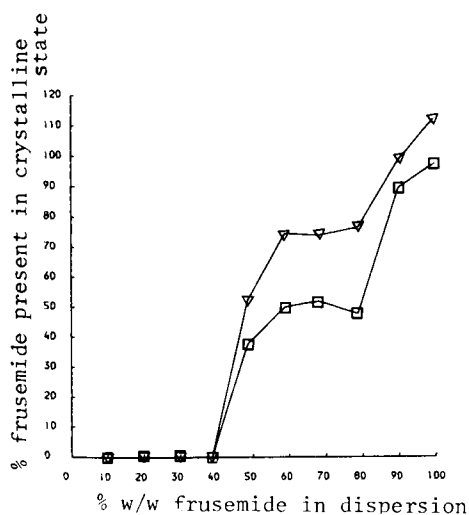
This work examines the experimental parameters that affect the precision of data derived from an x-ray analysis of the model drug frusemide B.P. (F) alone and in a series of solid dispersions with polyvinylpyrrolidone (Kollidon 25, BASF) (PVP), produced by slow evaporation of F/PVP methanolic solutions. X-ray diffraction spectra were obtained on a Philips PW 1120/00 generator ($\text{CuK}\alpha$ radiation) with a proportional detector probe.

The count losses of the detector, an important factor in quantitative x-ray analyses, were estimated from changes in intensity of the diffraction spectra as the current to the tube is varied. A linear relationship was found to exist using a singlet peak in the F spectra ($25.0^\circ 2\theta$). For quantification of the peak, some function of intensity is required. A comparison of the precision of the F peak height, area and weight of cut out peak area at two chart speeds (Table 1) shows that peak height at a chart speed of 25mm/min was the most reproducible function of peak intensity.

Fig. 1. Percentage of frusemide present in a crystalline state against percent of frusemide in dispersion.

(∇) x-ray diffraction;

(\square) DSC endotherm.



For quantification of the x-ray spectra both internal and standard techniques were compared. The internal standard method using zinc oxide (ZnO) was found to be more reproducible than an external standard technique using a pure crystalline F sample as the reference material. A calibration curve plotting the ratio of peak height of ZnO ($34.7^\circ 2\theta$) to F ($25.0^\circ 2\theta$) against mixes containing a fixed ZnO content (33.3% w/w) and varying amounts of crystalline F and amorphous PVP produced a straight line ($cc = 0.9887$) passing through the origin. This was used to assign % x-ray crystallinity measurements to the calculated ratio of ZnO/F intensities derived from solid dispersions containing 10-90% w/w F (Fig. 1).

Zero crystallinity for dispersions containing up to 40% w/w F was confirmed using a quantitative assessment of crystallinity from DSC endotherms. Above 40% w/w F, a similar trend of increasing crystallinity is observed. Information derived from quantitative x-ray analyses is proving valuable in current work directed at interpreting other functions of crystallinity and physicochemical data for solid dispersion systems.

Table 1. Parameters used to measure the intensity of diffraction spectra of frusemide ($25.0^\circ 2\theta$); \pm standard deviation (standard error): $n = 5$.

Measured Parameters	Chart Speed	
	10mm/min	25mm/min
Peak Height (mm)	179.0 \pm 19.0 (10.6%)	199.7 \pm 9.3 (4.7%)
Peak Area (mm ²)	701.4 \pm 87.6 (12.8%)	1716.0 \pm 145.4 (8.5%)
Peak Weight (mg)	-	131.3 \pm 7.3 (5.6%)

Simonelli, A.P. et al (1969) J. Pharm. Sci. 58:538-549

Chiou, W.L. (1977) J. Pharm. Sci. 66:989-991