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Note

X-Ray powder diffraction determination of the relative amount of crystalline acetaminophen in solid dispersions with polyvinylpyrrolidone

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Abstract

A powder X-ray diffraction technique has been developed to quantify the relative amounts of crystalline acetaminophen in powder mixtures with polyvinylpyrrolidone prepared by blending and recrystallisation. Four methods were used to prepare solid dispersions of acetaminophen and PVP: (a) mechanical mixing in a tumbling mixer or planetary ball mill, (b) co-precipitation, (c) freeze-drying and (d) recrystallisation. Changes in X-ray powder diffraction properties and the differences in solubilities showed that the amount of crystalline acetaminophen only decreased in mixtures where both acetaminophen and polyvinylpyrrolidone were soluble (ethanol) or partially soluble (water). The decrease in the amount of crystalline material was the result of the formation of a glass-like, amorphous solid solution. The formation of this amorphous material could be followed by X-ray diffraction analysis of powdered samples.

Keywords: X-Ray diffraction; Crystallinity; Acetaminophen; Polyvinylpyrrolidone; Solid dispersions

Numerous workers have shown that dispersing a drug in polyvinylpyrrolidone (PVP) will markedly enhance the dissolution rate and/or the compressibility of the drug (Lipman and Summers, 1980; Horn and Dittert, 1982). Presumably this is a result of the presence of an amorphous

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form of the drug, or the formation of solid solutions (Shefter and Cheng, 1980) which could alter the degree of crystallinity of the acetaminophen in powdered samples (Suryanarayanan and Mitchell, 1985).

The degree of crystallinity can be determined by X-ray powder diffraction (XRD) analysis. Some of these studies were done to assess the degree of crystallinity of digoxin powder (Black and Lovering, 1977) and to determine phase transformations as a result of mechanical processing (Junginger, 1977). Bernabei et al. (1983) studied the effect of crystallinity on the enzymatic hydrolysis of chloramphenicol palmitate by XRD. Ryan (1986) reported the optimization of crystallinity in lyophilized solids using XRD. XRD analysis was also used in studies that looked at the effect of the degree of crystallinity on solid state stability (Imaizini et al., 1980) and the dissolution rate (Gubskaya et al., 1995) of drugs.

The objective of this study was to explore the use of X-ray powder diffraction analysis (XRD) to determine the amounts of crystalline acetaminophen present in solid dispersions of acetaminophen and polyvinylpyrrolidone (PVP) prepared by conventional powder mixing and recrystallisation methods. Four methods were used to prepare solid dispersions of acetaminophen and PVP: (a) mechanical mixing in a tumbling mixer or planetary ball mill, (b) co-precipitation, (c) freeze-drying and (d) recrystallisation. According to powder X-ray, PVP is amorphous (Wade and Weller, 1994) and acetaminophen is crystalline (Lin and Duncan-Hewitt, 1994). Therefore the decrease in the amount of crystalline acetaminophen present in the solid dispersions was followed by collecting XRD profiles of the mixtures (Black and Lovering, 1977).

Acetaminophen (paracetamol or 4-hydroxyacetanilide, MW = 151.2) and PVP (PVP-40T, average MW = 40 000, MW of a single vinylpyrrolidone molecule = 111.1) were obtained from Sigma (St. Louis, MO). The powders were dried and stored in a vacuum dessicator at 25°C over phosphorous pentoxide. All solvents used were of analytical quality and water fit for chromatography was used. Mixtures of acetaminophen and PVP, each with a total weight of 50 g, were prepared by mixing for 2 h in a Turbula Model T2C mixer (Bachofen, Switzerland) at a speed of 90 rev./min. Mixing was also done in a planetary ball mill (Pulverisette 7, Fritzch, Germany) for 15 min at speed setting eight.

Co-precipitation of mixtures from ethanol, in which both acetaminophen (95.16 $mg \cdot ml^{-1}$) and PVP are extremely soluble, was accomplished by evaporation in a rotary evaporator. Freeze-drying of suspensions of acetaminophen in a cold aqueous solution of PVP, in which acetaminophen is poorly soluble (2.43 $mg \cdot ml^{-1}$ at 10°C), was also used to prepare co-precipitates, as was crystallization from suspensions of PVP in an acetaminophen/dioxane solution, in which acetaminophen is very soluble (76.65 $mg \cdot ml^{-1}$).

The solubilities of acetaminophen in the solvents were determined by placing excess amounts of acetaminophen in 10-ml test tubes. To each tube, 10 ml of solvent was added and the tube was sealed. The tubes were rotated at 700 rev./min for 24 h in a water bath controlled at 25°C. The acetaminophen concentrations were determined spectrophotometrically at 254 nm.

XRD profiles were obtained in a temperature-controlled room at 22°C, with a Phillips 1710 automated diffractometer. The measurement conditions were: Cu Kα; Filter, Ni; Voltage, 40 kV; Current, 20 mA; Slit, 0.1 mm; Scanning speed, $2°2\theta\ min^{-1}$. Counts per second were related to a step scan through the peak at this speed corrected for background. Exactly 200 mg samples were weighed to the nearest 0.01 mg into aluminum XRD sample holders with Sartorius model BP211D balance (Sartorius, West Germany) taking care not to introduce a preferential orientation of the crystals. All samples were crushed with a glass pestle in a glass mortar and the sieve fraction between 150–300 μm was used. A decrease in the areas of two peaks, at 23.4 and 24.5°2θ in the X-ray pattern of acetaminophen, compared to the areas of the same two peaks in the original crystalline material, indicated a decrease in the amount of crystalline material present in the mixtures (Lin and Duncan-Hewitt, 1994). This method could not detect amorphous impurities produced through processing or even crystalline impurities below the 5% level.

After drying, or mixing, the total mixture was spread out in a flat tray and divided into three equal blocks. Three samples, each weighing ~100 mg, were taken randomly from each block and weighed. The remainder of each mixture was retained for XRD analysis. The acetaminophen concentration in each sample was obtained by a UV spectroscopic method. The samples were dissolved and suitably diluted in 95% ethanol, whereupon the UV absorbance was measured at 254 nm. The acetaminophen content was calculated from a calibration curve in 95% ethanol and expressed as mass fraction acetaminophen.

The acetaminophen contents of all of the mixtures were close to the intended amounts and the standard deviations were small. The mean concentration taken across all of the mixtures was 99.61% of the amount added, with a standard deviation of 0.94%. This illustrated that the mixing processes distributed the acetaminophen evenly throughout the mixtures. Variation in XRD scattering due to incomplete mixing was, therefore, not expected. These experimentally determined content values were used to represent the total acetaminophen contents of the mixtures when calculating the amount of crystalline acetaminophen present in each mixture.

To determine if physical mixing changed the amount of crystalline acetaminophen, a sample of crystalline acetaminophen was milled in the planetary ball mill for 2 h and no significant change ($p = 0.0032$) was observed, the areas under the two peaks being initially 1845 ± 28 and 1835 ± 31 after 2 h. Physical mixing of acetaminophen and excipients, when both were completely dry, was not, therefore, expected to change the amount of crystalline acetaminophen in the mixtures. To substantiate this, a 1:1 mixture of acetaminophen and zinc oxide was mixed in the Turbula mixer for 2 h. The total of the areas under the two sharp peaks at 23.4 and 24.5°2θ was calculated to be 914 counts. The percentage of acetaminophen present in the 50% mixture, calculated from the decrease in peak area, was 49.2% (914 counts/1858 counts × 100). For an equivalent mixture of acetaminophen and PVP mixed in the Turbula mixer, the total area under the peaks was equal to 50.8% of the original pure sample. Mixing of acetaminophen and PVP in the Turbula mixer did not change the amount of crystalline acetaminophen per mixture.

The percentages of crystalline material, C, present in the samples (crystalline contents) were calculated from:

$$C\% = \frac{I_c}{I_x}(100) \quad (1)$$

where, I_c and I_x are the intensities of X-rays scattered from the crystalline regions (areas under the two sharp peaks at 23.4 and 24.5°2θ in the X-ray pattern of acetaminophen) in the mixtures and a crystalline acetaminophen sample, respectively (Lin and Duncan-Hewitt, 1994). These areas for acetaminophen in mixtures, I_c, were compared to the same areas in the XRD pattern of the original crystalline acetaminophen, I_x, to determine the decrease in the amount of crystalline material present in the mixtures. PVP was X-ray amorphous, as shown in both Fig. 1 and Fig. 2, with no distinct X-ray scattering in the region 20–25°2θ. PVP did not produce any different peaks as a result of processing that would interfere with the acetaminophen peaks of interest.

When I_c was plotted as a function of the percentage of crystalline acetaminophen present in physical mixtures of acetaminophen and PVP prepared in a Turbula mixer, a linear curve with a coefficient of determination $R^2 = 0.994$ was obtained. This 6-point calibration curve ranged from 10–100% acetaminophen and was done in triplicate. The calibration curve was linear over the entire concentration range. Because it was assumed that no change in the crystalline properties of the acetaminophen occurred, this graph was used as a calibration plot for determining the degree of crystalline acetaminophen present in other mixtures. The y-intercept of the line was 31.27 counts with a standard deviation of 28.92 counts and the slope was 18.81 with a standard deviation of 0.49.

The degree of crystallinity is defined as the percentage by weight of crystalline drug in a sample containing drug in both the amorphous and crystalline states (Suryanarayanan and Mitchell, 1985). The degrees of crystallinity (F%)

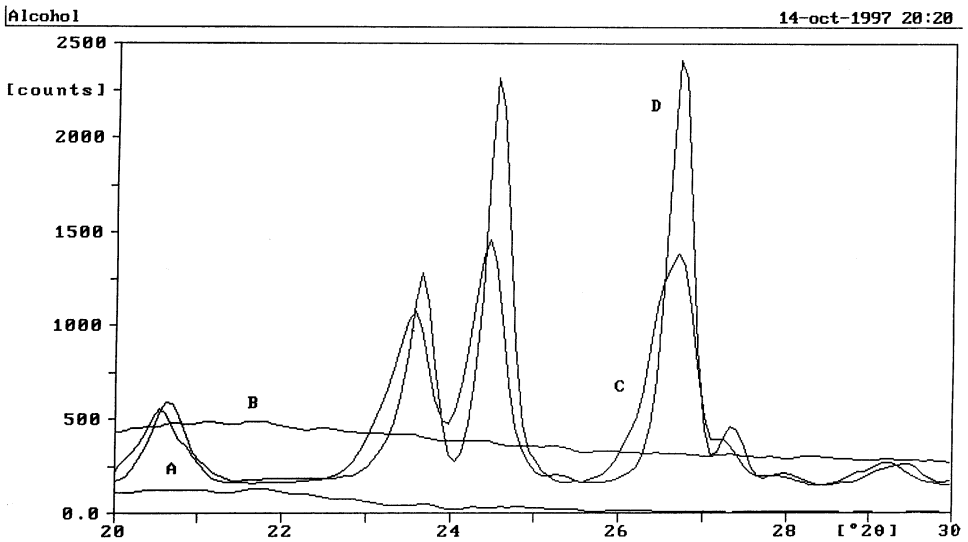

Fig. 1. Change in XRD patterns in the region between 20–25°2θ for acetaminophen/PVP mixtures recrystallised from ethanol.

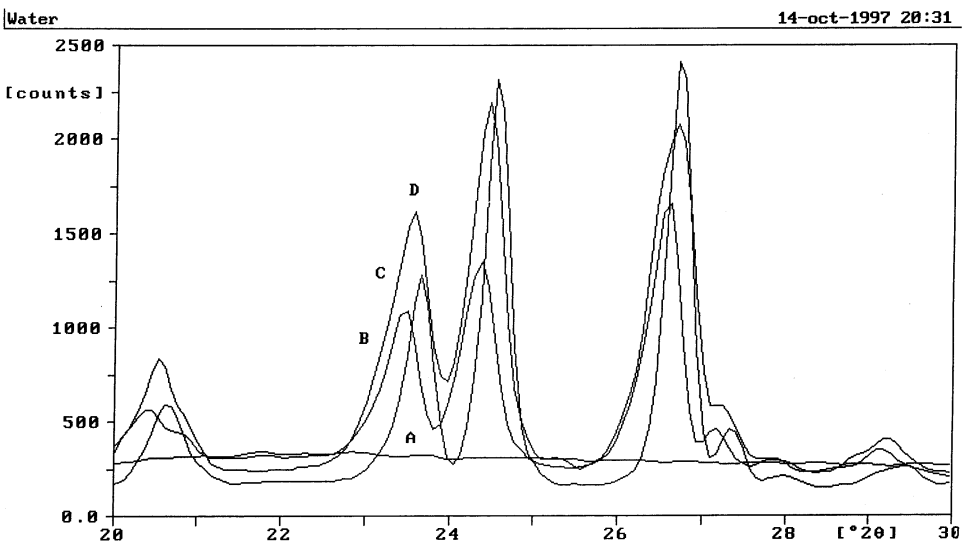

Fig. 2. Change in XRD patterns in the region between 20–25°2θ for acetaminophen/PVP mixtures recrystallised from cold water (10°C).

of the acetaminophen present in the mixtures were estimated by the following relationship:

$$F\% = \text{(Area under peaks of processed acetaminophen/Area under peaks of unprocessed acetaminophen with same composition)} \times 100 \quad (2)$$

The calibration data for mixtures prepared in Turbula mixer and the content uniformity values were used to calculate the areas under the peaks of unprocessed acetaminophen samples. The change in degree of crystallinity ($F\%$), according to Eq. (2) is shown in Fig. 3. Results for mixtures prepared in the Turbula or planetary ball mill, or recrystallised from ethanol, cold water or dioxane

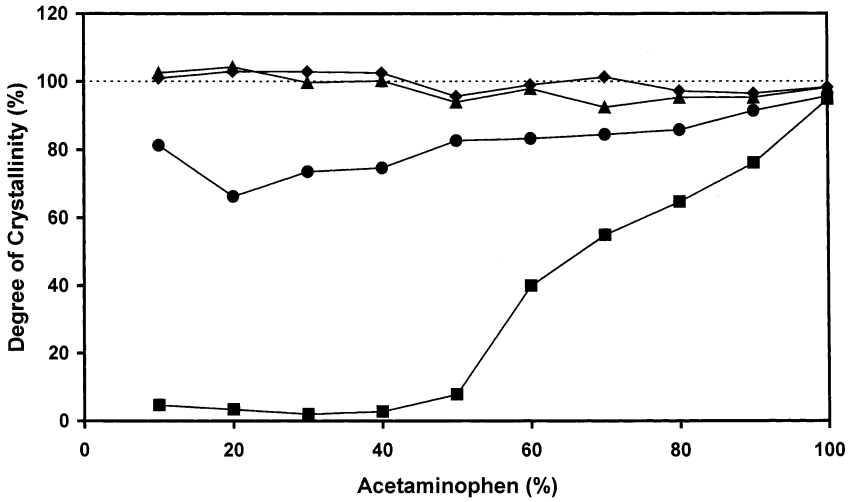

Fig. 3. Change in the degree of crystallinity (F%) as a function of acetaminophen concentration, in acetaminophen/PVP mixtures prepared by mechanical mixing or recrystallisation.

Table 1
Mean assay results and relative amounts of crystalline acetaminophen in solid dispersions

Acetaminophen[a] (%)	Ethanol (F%)	Cold water (F%)	Ball mill (F%)	Dioxane (F%)	Turbula (F%)
9.98 ± 0.4	4.67 ± 0.4	81.29 ± 1.2	102.48 ± 3.2	100.92 ± 2.3	98.56 ± 2.1
21.06 ± 0.8	3.38 ± 0.5	66.26 ± 2.1	104.19 ± 3.4	102.90 ± 2.7	100.03 ± 2.2
30.10 ± 0.2	1.99 ± 0.3	73.58 ± 2.4	99.68 ± 2.6	102.79 ± 3.1	101.10 ± 1.8
39.05 ± 0.7	2.74 ± 0.9	74.72 ± 3.1	100.21 ± 2.7	102.49 ± 3.2	98.65 ± 1.9
51.11 ± 0.6	7.77 ± 0.4	82.70 ± 2.6	93.89 ± 2.4	95.58 ± 2.7	98.67 ± 2.3
60.72 ± 0.3	39.93 ± 0.7	83.26 ± 1.9	97.82 ± 2.6	98.96 ± 2.8	99.06 ± 3.1
70.03 ± 0.2	54.97 ± 1.3	84.43 ± 3.2	92.46 ± 2.5	101.28 ± 2.6	102.13 ± 2.4
79.45 ± 0.4	64.71 ± 2.1	85.84 ± 3.5	95.26 ± 1.9	97.19 ± 3.1	101.23 ± 2.9
90.34 ± 0.6	76.16 ± 2.3	91.40 ± 2.6	95.32 ± 3.4	96.52 ± 3.2	99.67 ± 1.8
100.00 ± 0.65	94.77 ± 3.1	95.65 ± 2.4	98.19 ± 3.2	98.31 ± 3.1	99.89 ± 1.7

All values are ± S.D.
[a]Mean UV spectrophotometric results.

(in which the degree of solubility of acetaminophen differs) are shown.

When no change in the degree of crystallinity was observed, as shown in Table 1 for acetaminophen/PVP mixtures prepared with the Turbula mixer, F% was 100% irrespective of the percentage of acetaminophen present in a mixture. No significant deviation of F% from 100%, was observed for the mechanical mixtures prepared in the planetary ball mill, or the dispersions prepared in dioxane. Recrystallisation of acetaminophen, without PVP, did not change F%, because, as shown in Fig. 3, F% for pure acetaminophen was 100 irrespective of solvent. No amorphous material or different crystal forms as described by Chow and Grant, 1988, 1989 were obtained when recrystallisation was performed in any of these solvents. In physical mixtures with PVP and when PVP was suspended in an acetaminophen solution in dioxane, F% did not decrease because PVP was practically insoluble in dioxane. Acetaminophen was very soluble in dioxane (76.65 $mg \cdot ml^{-1}$). However, when PVP was not in solution it prevented the formation of solid solutions between acetaminophen and PVP.

In dispersions containing up to 50% w/w acetaminophen, crystallized from ethanol, either very small peaks or no peaks (Fig. 1) were observed in the X-ray patterns. Above 50%, a marked decrease in the total of the areas under the two sharp peaks at 23.4 and 24.5°2θ was still observed (Fig. 3). F% decreased in these solid dispersions either because acetaminophen was dissolved in the PVP or was precipitated in an amorphous state. Precipitates from water led to smaller decreases in F% (Fig. 2). In ethanol, both acetaminophen (95.16 $mg \cdot ml^{-1}$) and PVP were extremely soluble. Acetaminophen was poorly soluble (2.43 $mg \cdot ml^{-1}$) in cold water, while PVP was soluble.

Therefore, precipitation of acetaminophen in the presence of PVP decreased the degree of crystallinity of acetaminophen only when both were in solution (ethanol) or partially dissolved (water at 10°C). In cold water, the decrease in F% was less because the solubility of acetaminophen was less. The decrease in the amount of crystalline material was the result of the formation of a glass-like, X-ray amorphous solid solution. The formation of this glass-like amorphous material could be followed by XRD analysis of powdered samples.

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