Polymorphism of phenylbutazone by a spray drying method

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An effective method to improve the bioavailability of water-insoluble drugs is to use their polymorphism. There are two important factors relating to resulting crystal forms in obtaining polymorphs by recrystallization, namely, the solvent from which crystals are separated, and their crystallization velocity. Most of polymorphic studies have been carried out with recrystallization techniques rather than crystallization velocity. With the spray dryer, control of crystallization velocity may be possible by varying the drying temperature of the droplets sprayed from the atomizing nozzle, and this application will provide more extensive conditions for crystallization.

Phenylbutazone has been reported to have several polymorphs by the recrystallization technique (Matsunaga et al 1976; Ibrahim et al 1977; Chauvet & Masse 1978; Müller 1978). The forms were summarized by Müller (1978) as α, β, γ, and δ, among which form δ was stable, and form γ could not be isolated.

In the present investigation, a 5% w/v methylene chloride solution of phenylbutazone (form δ) was supplied to a minispray dryer. The temperature in the drying chamber was varied in seven steps in seven runs from 120 ° to 30 °C which is lower than the boiling point of the solvent under the atmospheric pressure, and the other operating conditions were maintained constant. The resulting crystalline samples were subjected to X-ray powder diffractometry, thermal analysis, i.r. spectrophotometry, photomicroscopy by hot stage method, and scanning electron microscopy.

From the above measurements, the sample obtained at 120 °C was identified as the original form. As the drying temperature dropped, the X-ray diffraction pattern changed gradually in diffraction angles and intensity, suggesting the intermix of the other crystal forms in the sample, and settled down a new profile shown as the bottom chart in Fig. 1 at the drying temperature of 30 °C. From the changes in diffraction pattern, samples obtained in this investigation were estimated to be composed of two or three crystal forms including a new form which differed from any of the known forms. This evidence was supported by DTA curves (Fig. 2) which showed that samples obtained at 80 ° and 70 °C with increasing temperature first fused at 91–92 °C with loss of heat, the liquid then recrystallized (exothermic peak) at 93 °C to form δ, which melted at 103 °C, thus corresponding to the thermal behaviour of form β. They were not single modifications but mixtures of forms δ and β, and a new form, among which form β was the most abundant. This phenomenon was confirmed from the remaining diffraction peaks of form δ, the occurrence of a new endothermic peak at 95 °C, and the result of scanning electron microscopy. Below 60 °C the endothermic peak at 91 °C began to disappear and the characteristic endotherm at 95 °C

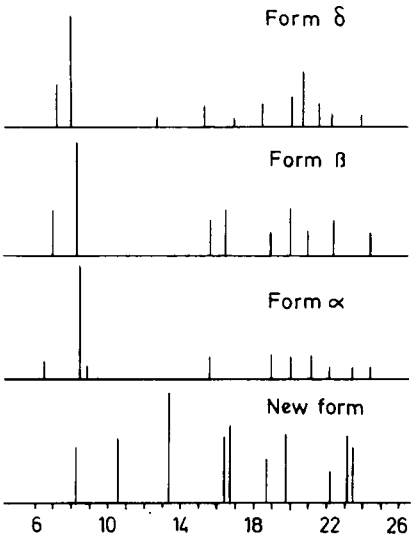

FIG. 1. X-ray diffraction patterns of polymorphic forms of phenylbutazone. Ordinate: relative diffraction intensity. Abscissa: diffraction angle (degrees).

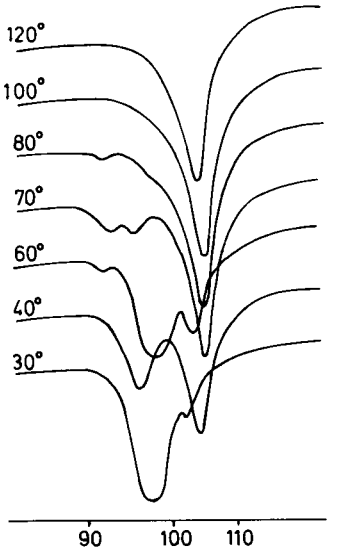

FIG. 2. DTA-curves of spray-dried phenylbutazone obtained at various drying temperatures. Numbers in the figure indicate drying temperature. Abscissa: temperature °C.

* Correspondence.

became progressively clearer as the drying temperature dropped. Changes in X-ray diffraction pattern also suggested that the fraction of new form in the sample increased at lower ranges of drying temperature. However, the new polymorph could not be isolated as a pure crystalline modification. Scanning electron photomicrographs showed that a small amount of crystals of form β still remained and these were surrounded by the new form crystals in the sample obtained at 30 °C. The assumption that the new form might be a solvate was disproved by the results of both elemental analysis and TG.

The dissolution rates by the disc method (Wood et al 1965) and the solubility of samples in the U.S.P. dissolution test solution (U.S.P. 1975) were measured at 37 °C. Their behaviour, depending on drying temperature, was in good agreement. The solubility of the sample obtained at 30 °C was 1·5 times higher than that of the sample obtained at 120 °C, and the bioavailability of the new form crystals would be expected to compare with the other known forms.

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Physical interpretation of parameters in the Rosin-Rammler-Sperling-Weibull distribution for drug release from controlled release dosage forms

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In recent years (see Langenbucher 1976; Gurny et al 1976; Goldsmith et al 1978) in vitro drug release has often been described in accordance with the general mathematical function originally proposed by Rosin et al (1933) and later by Weibull (1951). (The Rosin-Rammler-Sperling-Weibull RRSW distribution). This can take the following form when applied to drug release data:

$$\frac{C_{extr}(t)}{C_{extr}(\infty)} = 1 - \exp(-(t-\gamma)^{\beta}/\alpha) \quad .. \quad .. \quad (1)$$

Equation (1) gives the concentration $C_{extr}(t)$ in the extraction medium as a function of time t. α, β and γ are adjustable parameters which may be calculated to give a least squares fit to observed data. $C_{extr}(\infty)$ is the concentration in the extraction medium when all of the drug has been released at $t = \infty$. γ represents a change in the zero point for the time, and it is evident that equation (1) has a meaning only when $(t - \gamma) \geq 0$.

The flexibility of the distribution in equation (1) is obvious, and it has therefore also been applied to a large variety of distributions such as yield strength of fibres and steels, size of beans and insects (Rosin et al 1933). Thus the RRSW is not particularly designed to describe drug release, and there are no obvious physical reasons for using that particular distribution. This is a serious drawback of the method since it does not allow a prediction of a release profile for pellets of e.g. different sizes and with different coats. Besides, it is not possible to apply the parametric form in a simulation of in vivo release. In order to do so, it is necessary to consider a reasonable physical model for the release. In this study we describe the drug release as a quasi-stationary diffusion of drug through the coat which is the main obstacle for the release. We have considered pellets consisting of a core containing the drug and excipients surrounded by a uniform coat. For simplicity, it is assumed that the drug in the core is dissolved and that the diffusion coefficient in the coat is much smaller than in the core; thus we assume that the concentration of drug in the core at all times is uniform. It is also assumed that the drug concentration in the extraction fluid is uniform at all times due to effective stirring. We do not consider the initial swelling of pellets and dissolution of drug when dry pellets are put into an extraction medium. This may be accounted for by the introduction of a time lag (γ) as shown in equation (1).

Let us consider a spherical pellet where the radius of the core is b and the radius of the coated core is a; then the thickness of the coat is (a–b). Since we only consider radial diffusion, the diffusion equation for the coat is given by Fick's 2nd law (see Crank 1964),

$$\frac{\delta(rc)}{\delta t} = D\frac{\delta^2(rc)}{\delta r^2} \qquad b < r < a \quad .. \quad (2)$$

where D is the diffusion coefficient for the particular drug in the coat, r is the radius to a particular stage in the coat, and c is the concentration in the coat at that particular stage and time. We now impose stationarity upon the concentration profile in the coat, that is

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