The recrystallization of amorphous digoxin

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The bioavailability of poorly soluble drugs may be enhanced if the drug can be administered in the amorphous form, novobiocin being a well known example (Mullins & Macek, 1960). Florence & Salole (1976) showed that crystalline digoxin can be reduced to the amorphous state by comminution and, whilst comparing the rate at which crystalline and amorphous drug dissolved from compressed discs, observed that the appearance of the surface changed during the experiment (Salole & Florence, 1976). Although the apparent equilibrium solubility of digoxin usually increases as the rate of dissolution increases and the particle size decreases, we thought other factors might also be operating, and we postulated that the physical state of the drug, whether crystalline or amorphous, might be one of these. We therefore devised procedures to measure the degree of crystallinity in the drug and then set out to measure the dissolution rate and apparent equilibrium solubility of samples differing in degree of crystallinity, hoping to relate these properties, but found instead that rapid recrystallization took place. We also observed that drug samples having the same degree of crystallinity differed in apparent equilibrium solubility. Thus it appears that factors other than, or in addition to, the degree of crystallinity contribute to the apparent equilibrium solubility.

Amorphous digoxin was prepared as previously described (Black & Lovering, 1977). Specimens for recrystallization rate measurement were prepared by placing 40 mg of amorphous digoxin on a 0·8 μm Millipore filter paper and wetting by running 40 ml of distilled water through the filter. The moist drug was pressed into the cavity of the brass X-ray sample holder, covered with Parafilm M to prevent evaporation, mounted in a diffractometer and scanned from $2\theta = 8°$ to $2\theta = 7°$ immediately, and at appropriate time intervals until recrystallization was complete. X-Ray equipment and techniques were as previously described (Black & Lovering, 1977). The time between wetting the drug and the first X-ray measurement was 2 to 3 min.

The degree of crystallinity at various times during recrystallization, C_t, was calculated from,

$$\frac{h_t}{h_\infty} = \frac{C_t}{C_\infty} \quad \ldots \quad \ldots \quad \ldots \quad (1)$$

where h_t is the height, at time t, of the peak at $2\theta = 7{\cdot}70°$ (d = 5·3 Å, Mo target) with respect to the trough at $2\theta = 7{\cdot}05°$ and h_∞ is the height of this peak at the end of the experiment when crystallization is complete. C_∞ is the degree of crystallinity at the end of the experiment. C_∞ was obtained by drying the sample at room temperature (25°) and measuring the degree of crystallinity as previously described (Black & Lovering, 1977). The degree of crystallinity during recrystallization of amorphous drug could not be read directly from a graph of area ratios *vs* degree of crystallinity because of X-ray scattering by the moisture in the sample. However, re-analysis of previous data showed that the height of the peak at $2\theta = 7{\cdot}70°$, increased linearly with the degree of crystallinity, although in moist samples the absolute peak heights varied from one experiment to the next.

The degree of crystallinity increased from 0 to 75% within 25 min of wetting and levelled out at about 85 to 90% within 60 min (Fig. 1). Amorphous digoxin also recrystallized in 0·1M hydrochloric acid, benzene and ethanol but not in iso-octane or carbon tetrachloride. Although the results obtained could be interpreted as initial dissolution followed by spontaneous recrystallization, it is also possible that the phenomenon is analogous to solid state or mesomorphic state transitions without actual dissolution.

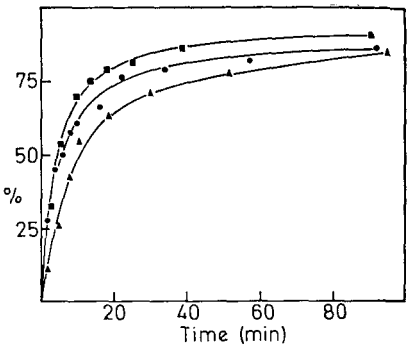

FIG. 1. Degree of crystallinity (%) *vs* time (min). Experimental points from three experiments are represented by the different symbols.

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