The effect of particle size reduction on digoxin crystal properties

The similarity of the digoxin molecule to compounds such as aescin, digitonin and spironolactone, which are known to have dissolution and absorption properties dependent on particle size and perhaps polymorphic form (Rosoff, Schulman & others, 1967; Bauer, Rieckmann & Schaumann, 1962; Shaldon, Ryder & Garsenstein, 1963), led us to study the effects of grinding on the properties of digoxin crystals. The crystalline saponin aescin is very poorly soluble in water, but upon grinding becomes very soluble due to the formation of an amorphous phase (Rosoff & others, 1967). Grinding of digoxin during manufacturing procedures may similarly give rise to more soluble forms of digoxin.

We have examined infrared spectra, dissolution rates and equilibrium solubilities of various samples of digoxin and carried out differential thermal analysis and X-ray powder diffraction on several samples before and after dry grinding in a mortar or ball-mill. The dissolution profiles of the samples are shown in Fig. 1b and initial dissolution rates are listed in Table 1. Between the slowest dissolving sample (British Chemical Reference Standard) and the fastest (Swiss micronized, mortar ground) there is an eighteen-fold difference in initial rates of solution. The dissolution profiles suggest the existence of a freely soluble amorphous layer on the crystals which is rapidly removed after about 30 min in the dissolution medium. (The presence of this layer is supported by the fact that typical infrared spectrum of the ground sample loses the extra band to give a spectrum of the unground sample.) The rate of solution then decreases and the more slowly rising portion of the curve represents the dissolution of the crystalline material. Equilibrium solubility values are not attained until several days have elapsed. The equilibrium solubilities are not identical, suggesting that different forms of the digoxin crystal have been examined (Table 1). This view is substantiated by the formation of a substantially amorphous sample of digoxin on ball-milling for 5 h a micronized sample of digoxin (Sandoz). A comparison of all other samples including the unmilled micronized material by X-ray diffraction showed differences which may be accounted for by differences in grain size or in crystallinity. The solubility evidence seems to point

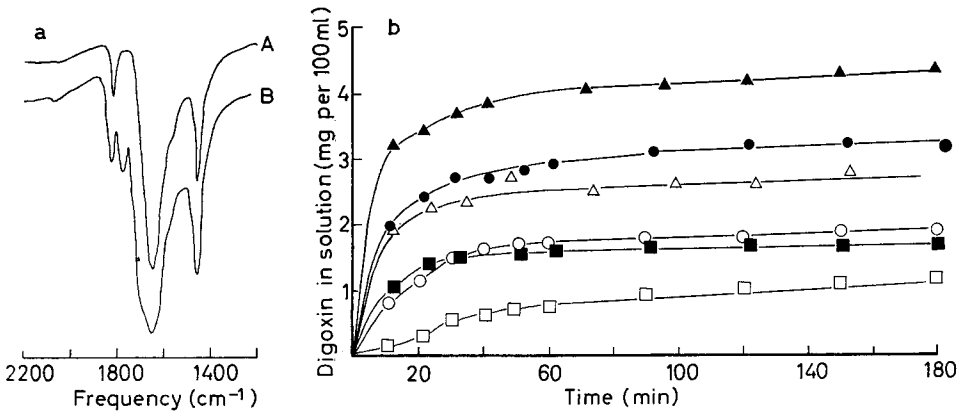

FIG. 1a. Infra-red spectra of A unground, B mortar ground Swiss micronized (Sandoz) digoxin.

1b. Dissolution of digoxin samples (25 mg) into 250 ml of 0·005% polysorbate 80 stirred at 37° ± 0·2°. Closed symbols represent mortar ground samples. Open symbols original samples. □ ■: British Chemical Reference Substance; ○ ● Swiss Standard (Courtin & Warner); △ ▲: Swiss micronized ground (Sandoz, through Courtin & Warner).

Table 1. *Melting points and equilibrium solubilities of several digoxin samples.*

Sample	Source	Melting point*	Solubility[1] mg dl^{-1}	Initial rates of solution[2] mg $dl^{-1}min^{-1}$
British Standard	Courtin & Warner	235·5°	5·4	0·11
Swiss Standard	,, ,,	228·5°	4·35	$0·07_8$
Swiss Micronized	Sandoz	225·5°	7·0	0·18
Swiss Standard ground	Mortar ground	—	5·75	$0·18_5$
B.C.R.S.	British Pharmacopoeia Commission	241°		$0·01_8$

1. Solubility after 5 days in water. 2. Rates of solution of 25 mg digoxin in 250 ml of 0·005% polysorbate 80 at 37° between t = 0 and t = 10 min. Concentration of digoxin determined by ultraviolet spectrophotometry. * From differential scanning calorimetry traces.

to the cause being changes in the ratio of crystalline and amorphous material in the digoxin samples.

The infrared spectra of samples before and after grinding exhibit the growth of a band at 1780 cm^{-1}; the rest of the spectrum is the same. Representative spectra are shown in Fig. 1a. The melting behaviour of the samples is markedly different; samples which dissolve rapidly tend to have lower melting points (Table 1). Endothermic transitions at around 170° occur in the differential thermal analysis traces, well below the melting points. These may be due to the amorphous fraction of the sample.

The wide spread in melting points quoted for digoxin in the national pharmacopoeias and compendia* may well reflect differences in sample crystallinity. Shaw, Carless & others (1973) have shown that particle size reduction can markedly affect the plasma levels of digoxin. It now appears that the method of particle size reduction may also have an influence on the dissolution behaviour of the drug. There is therefore an obvious need for a specification for digoxin which not only controls surface area but also exercises some control over the crystal properties of the material.

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* French Pharmacopoeia 1965: Melts higher than 270°; Merck Index 265° (decomp.) U.S.P. XV: Melts above 235°. B.P. 1958: *ca* 240°; B.P.C. 1954: *ca* 235° Martindale 26th Edition 240°. Dictionary of Organic compounds: melts with decomp. at 265°.