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The physicochemical properties of digoxin*

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Abstract: In a study of variations in the physicochemical properties of digoxin powder from several commercial sources, recrystallizations of digoxin were performed under several conditions. Polymorphs were not obtained whereas a pure amorphous form was formed under certain conditions. The amorphous form was more soluble and more stable under compression than was the crystalline form; nevertheless in contact with water it crystallized quickly. Traces of the crystalline form reduced the dissolution rate and stability of the amorphous form.

Variations in the thermal behaviour of commercial samples can be explained by the presence of variable proportions of the amorphous form and also by thermal decomposition that varies from one sample to another and generally occurs at 160°C and above.

Keywords: *Digoxin; solid-state properties; physicochemical characteristics; amorphous forms; polymorphs; dissolution rate.*

Introduction

It has been clearly demonstrated that the oral bioavailability of digoxin is highly variable from one manufacturer to another and even between batches produced by the same manufacturer [1–4]. Many factors are known to affect the bioavailability of the poorly soluble drug, such as the characteristics of the formulation, the particle size, the milling process and the grinding intensity [5–9]. It has also been established that crystalline digoxin may be transformed into solid products with different thermodynamic properties and hence with different dissolution characteristics [10–13]. Such behaviour suggests the existence of polymorphic, solvated or amorphous forms.

From the important work of Chiou and Kyle [11] and of Nürnberg and Dölle [12, 13], some questions remain to be answered, especially about the existence of polymorphic forms, and about the preparation and stability of an amorphous form. The aim of this work was to improve knowledge of the physicochemical properties of digoxin, especially by studying the solids obtained after recrystallization of the drug in several solvents.

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Materials and Methods

Materials

Seven samples of digoxin (S_I to S_{VII}) were obtained from commercial sources. They conformed to the specifications of the *British Pharmacopoeia* [14] and the *USP XX* [15]. Two samples were made in 1981, three samples in 1982 and two in 1983.

Additional samples were also obtained by recrystallization of S_{III} according to the following method. Saturated solutions were prepared in boiling solvents: ethanol; methanol; chloroform; chloroform–methanol (70:30, v/v); and ethanol–water (80:20, v/v). The solvents were slowly and rapidly evaporated. These samples were designated S_I^s to S_V^s, and S_I^r to S_V^r. All solvents were of analytical reagent grade.

Methods

Thermal analysis of original and recrystallized samples was performed using differential scanning calorimetry (DSC-2C, Perkin Elmer) at 10°/min and 20°/min and hot-stage polarizing microscopy (Mettler hot-stage FP5, FP52, Olympus polarizing microscope) at 10°/min. Each sample was embedded in a drop of silicone oil for better observation of escaping volatile substances.

The thermogravimetric study was performed on a thermobalance (TGS-2, Perkin Elmer) at 10°/min from ambient temperature to 280°C.

Infrared spectra were recorded in potassium bromide pellets (0.5%, w/w) (IR 580 Perkin Elmer).

X-Ray powder diffraction spectra were recorded using Philips X-ray diffraction equipment (PW 1720) and a Guinier–Hägg camera. Incident radiation was CuKα:λ = 1.5406 Å.

The dissolution rate study was performed using a continuous flow dissolution apparatus [16]: flow rate, 50 ml/min; dissolution volume, 400 ml; dissolution medium, water; sample weight, equivalent to 20 mg of digoxin; spectrophotometric determination at 222 nm.

The granulometric study was performed on 300 particles, using a microscope (BHC, Olympus).

Results and Discussion

The thermal behaviour observed by DSC and hot-stage microscopy presents marked variations among the seven original samples (Table 1). These observations are consistent with those previously reported and indicate very wide melting ranges and large variations in melting temperature [11]. The evolution of volatile substances was detected in all samples by the appearance of gas bubbles above 200°C (Table 1); simultaneously a gradual darkening of the crystals was observed.

The thermogravimetric study of the samples indicated that from about 160°C, a continuous loss of weight occurred, varying from one sample to another and reaching 25% in some instances. The variable loss of weight associated with the darkening of the powder supports the hypothesis of thermal decomposition rather than that of pseudopolymorphism [17] (Table 1).

The infrared spectra of the seven original samples are similar but not identical; the intensity and the width of the peaks and shoulders at 3540, 3520, 3440, 3100, 2900, 1800, 1720 . . . cm^{-1} differ from one spectrum to another. Sample S_{III}, with the more intense peaks, was chosen as the reference substance (Fig. 1).

Table 1
Thermal behaviour of the seven commercial samples of digoxin

Sample	TGS	Hot-stage microscopy*		DSC
	loss of weight (%)	Temperature of bubbling (°C)	Melting point (°C)	endotherms (°C)
S_I	17	>250	>250	230–170
S_{II}	25	210–228	>250	197–250
S_{III}	16	210–220	230–>250	220–250
S_{IV}	7	230–240	>250	220–267
S_V	19	210–230	235–247	220–267
S_{VI}	25	211–242	248–>250	215–260
S_{VII}	11	226–240	240–250	210–260

*Hot-stage maximum temperature: 250°C.

The X-ray powder diffraction spectra of the seven samples correspond to the spectrum recently published by Nürnberg and Dölle [12, 13]; the intensity of all the lines was not precisely constant.

These observations support the two hypotheses of Chiou and Kyle to explain such great differences of behaviour between different samples of digoxin [11]; these hypotheses were polymorphism and the existence of an amorphous form.

Generally the existence of polymorphs or amorphous forms can be confirmed by recrystallization in several solvents and characterization of the solids obtained; frequently mixtures of forms are found. The corresponding infrared and X-ray spectra and the thermal behaviour show differences caused by different solid states.

Thermogravimetric analysis of recrystallized samples did not reveal the escape of residual solvent after heating to 150°C; moreover the shape of the crystals was not markedly modified. Except for sample S^r_{III}, obtained by rapid evaporation of a saturated chloroformic solution, the recrystallized samples exhibited a wide melting range, large variations in melting temperatures and evolution of volatile substances from about 160°C as observed in the original samples. Sample S^r_{III} had a very peculiar thermal behaviour. At ambient temperature it seemed to be amorphous under the hot-stage polarizing microscope; this observation was confirmed by the absence of lines on the X-ray powder diffraction spectrum. On heating the sample on the hot-stage microscope, crystallization occurred at about 140°C. The thermogram obtained by DSC showed a weak exotherm between 130 and 140°C, corresponding to crystallization (Fig. 2). The X-ray powder diffraction spectrum was similar to those obtained with samples S_I to S_{VII}. Infrared spectra of the amorphous form obtained by the solvent method differed from those of samples S_I to S_{VII} but showed good agreement with those previously published [8, 10, 12] (Fig. 1) for triturated, micronized or spray-dried digoxin, which were considered as partially or completely amorphous.

The infrared spectrum varied according to the rate and the conditions of evaporation of chloroform and, in some instances, the typical peaks of S_{III} appeared.

The amount of drug dissolved after 2 h was markedly increased when the amorphous sample was used (Fig. 3) and yet the particle size distribution of the amorphous form showed a greater proportion of large particles (Fig. 4) than did the sample S_{III}.

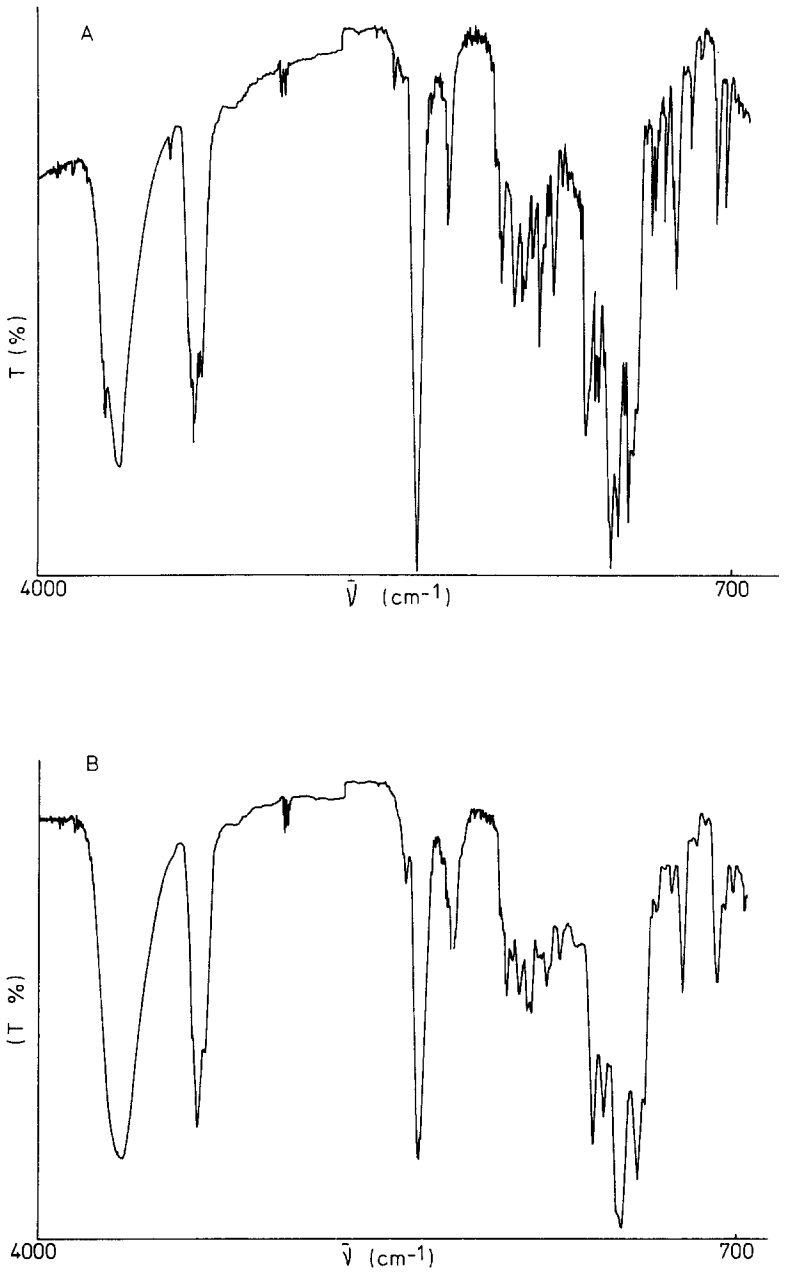

Figure 1A and B.

Figure 1C.

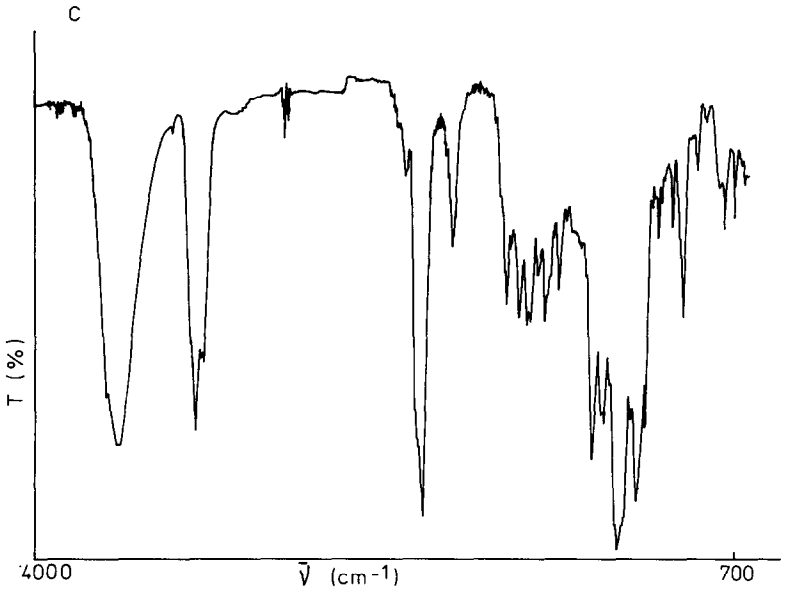

Figure 1
Infrared spectra of digoxin. A: Sample S_{III}; B: amorphous form; C: 50:50 (m/m) mixture of S_{III} and amorphous form.

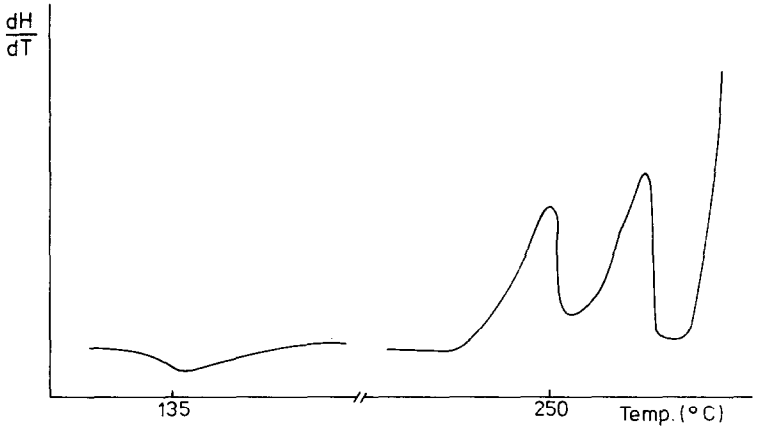

Figure 2
Thermogram (DSC) of the amorphous form.

Differences in the dissolution profile have also been observed after micronization or trituration of digoxin and were attributed to the formation of amorphous digoxin [8, 11].

Several conclusions can be drawn. First, preparation of polymorphs of digoxin by recrystallization is not easy. Thus it is difficult to explain the spectral differences between samples of digoxin by the existence of polymorphs or a mixture of polymorphs.

Second, an amorphous form may be obtained by evaporation of a saturated solution. Its rate of dissolution is greater than that of crystalline samples. Mixture of this amorphous form with the crystalline form modifies the infrared spectra (Fig. 1) and the dissolution profile (Fig. 3). These differences are similar to those observed between the

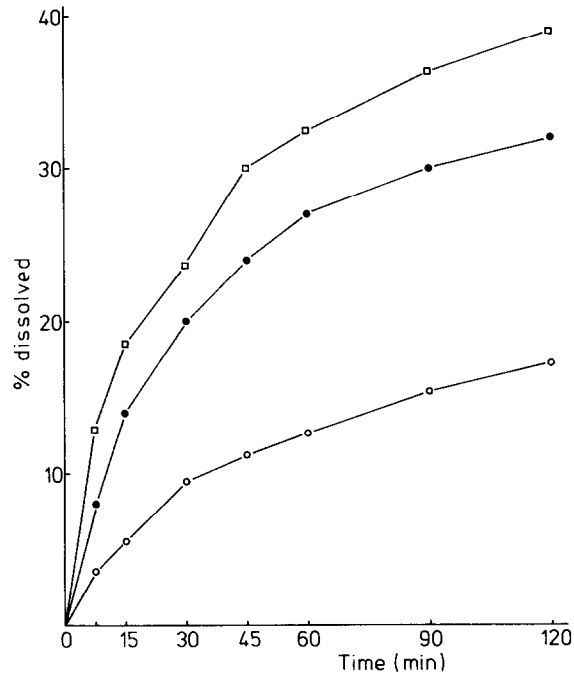

Figure 3
Dissolution rate of digoxin powder. ○ Sample S_{III}; □ amorphous form; ● 50:50 (m/m) mixture of S_{III} and amorphous form.

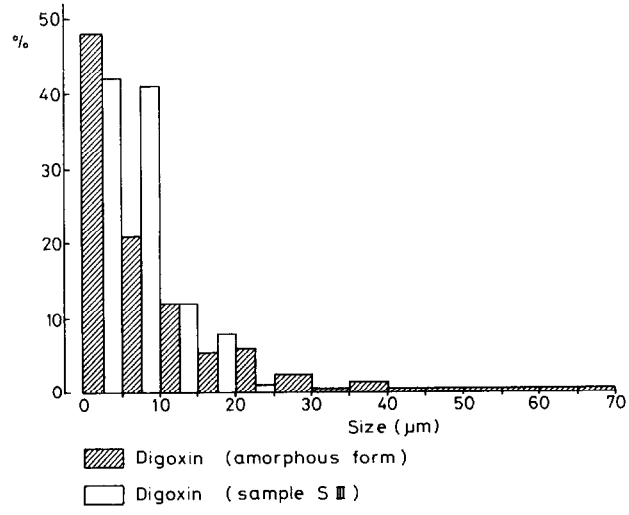

Figure 4
Particle size distribution of digoxin for Sample S_{III} and amorphous form.

original samples and confirm the hypothesis of a mixture of the amorphous and crystalline forms. The absence of an exotherm on the thermogram of some original samples is not inconsistent with that hypothesis; the exotherm observed on the thermograms for the pure amorphous form was relatively small and it disappeared when the proportion of amorphous form decreased. For a 50:50 (w/w) mixture, the exotherm was invisible.

Third, the important differences of thermal behaviour between the seven original samples and the recrystallized samples (except S_{III}) cannot be explained by the presence of variable proportions of the amorphous form. The thermal decomposition that gradually takes place during heating may be regarded as a more realistic explanation. The history of each sample (crystallization conditions, ageing of the powder, particle size, balling or milling) influences the temperature at which decomposition begins and the general thermal behaviour.

The consequences of the existence of this more soluble amorphous form are very important for the bioavailability of digoxin. Nevertheless the higher free energy of that form may affect the stability of the material. Therefore the second part of the work was devoted to a comparison of the stability of the amorphous and crystalline forms. The stability was determined by infrared spectrometry, hot-stage polarizing microscopy and X-ray powder diffraction spectra (Table 2).

After normal grinding in a mortar for 2 min, the amorphous form was produced from the crystal form, as previously described [8, 10]. But the infrared and X-ray spectra showed persistence of the crystalline form, even after grinding for 30 min.

Compression at 250 kg/cm^2 gradually transformed the crystals into the amorphous form. Nevertheless after 8 h, only 50% of the crystal form was transformed.

At ambient temperature, even under conditions of high relative humidity, amorphous and crystalline forms were very stable. But a 50:50 (w/w) mixture of these two forms underwent quick and quantitative crystallization. At 140°C, quantitative crystallization of the pure amorphous form took place in 30 min. That observation is in good agreement with the observations of thermal behaviour. Good stability of the amorphous form was observed in water at 37° or 25°C during 2 h (Fig. 3). The stability was greater than that reported by Nürnberg and Werthmann [9]; these authors report a reduction of the dissolved amount of digoxin after 5–30 min for the amorphous form. The discrepancy between the observations may be explained by the greater physical purity of the amorphous form produced by recrystallization.

Table 2
Comparative study of the physical stability of amorphous and crystalline digoxin

Test	Percentage transformation from amorphous crystalline form	Percentage transformation from crystalline to amorphous form
Manual grinding in a mortar	0% after 1 h	30% after 2 min
Compression at 250 kg/cm^2	0% after 8 h	50% after 8 h
Storage at 20°C	0% after 1 year	0% after 1 year
Storage at 20°C and 85% R.H.	0% after 30 days	0% after 30 days
Storage at 105°C	0% after 24 h	0% after 24 h
Storage at 140°C	100% after 30 min	0% after 24 h
Agitation in water at 25°C	50% after 2 h	0% after 72 h
Agitation in water at 37°C	50% after 2 h	0% after 72 h

Conclusions

An amorphous form of digoxin may be obtained by recrystallization; this form presents the same infrared spectrum, thermal behaviour and X-ray diffraction spectrum as that obtained by grinding. The use of a solvent method ensures the reproducible preparation of a purer amorphous form. Its good stability could permit the preparation of oral solid dosage forms. These points will be developed in a further paper.

From the results of this study of all the products obtained by recrystallization of the digoxin, it appears that the possibility of the existence of polymorphs or pseudopolymorphs can be discarded.

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