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OBSERVATIONS ON THE USE OF COMPRESSED DISCS IN DISSOLUTION STUDIES

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ABSTRACT

Intrinsic dissolution rates of crystalline and "amorphous" digoxin from compressed discs of the drug show a dependency on the initial particle characteristics, such as specific surface area. Scanning electron microscopy of disc surfaces show that pits appear at the boundaries between crystals although some fusion has obviously occurred. Presumably these edges act as preferential sites for dissolution. After some dissolution has occurred the disc surface appears microcrystalline and has by no means the same surface area as the starting surface. Some caution has therefore to be applied in the interpretation of dissolution results obtained from compressed discs.

INTRODUCTION

Non-disintegrating compressed discs have found extensive use in the determination of the intrinsic dissolution rates of drug samples[1,2] their theoretical advantage being that a constant area is presented to the solvent, therefore ruling out particle size effects. Compressed discs have been used to differentiate between polymorphs,[3,4] to estimate solubility[5] and effective surface area,[6] to determine thermodynamic parameters associated with polymorphic phase changes,[7,8,9] and to obtain interfacial energies[10]. During an investigation into the crystalline and

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amorphous forms of digoxin[11] we considered that compressed discs of the drug might afford a means of confirming whether a polymorphic change in digoxin occurs on comminution, as other evidence from our laboratories has suggested.[11,12] The results obtained were surprising in that the initial particle characteristics determined to some extent the dissolution rates obtained from the discs. The work has emphasised the need for caution in the interpretation of results from poorly soluble materials such as steroids. Some of the problems are discussed in this paper.

EXPERIMENTAL

MATERIALS AND METHODS

Digoxin: Commercial 'British Standard', 'Swiss Standard' and 'Swiss Micronized (Sandoz)' samples were obtained through Courtin & Warner Ltd., Lewes, Sussex. 'British Chemical Reference Substance Digoxin' was obtained from the British Pharmacopoeia Commission, London.

Digoxin exhibiting a blank X-ray diffraction pattern ("amorphous" digoxin) was obtained by milling a sample of British Standard digoxin in a Glen Creston Model M270 ball mill (1.3 cm I.D. x 2.8 cm Nylon 66 chamber, with one 1.03 g steel ball of 0.65 cm diameter.

Sodium chloride was of analytical reagent grade ('Analar', BDH).

Disc manufacturing procedure: about 180 mg of powder sample was weighed into the chamber of an evacuable die (1.3 cm diameter, Beckman Instruments Model K13), carefully levelled out and slowly compressed under vacuum to a pressure of 6.1 kg. $sq.cm^{-1}$ for 3 minutes.

Disc dissolution: a 700 ml wide-necked reaction flask (Quickfit FR 700F), fitted with a multi-necked lid (Quickfit MAF2/32)

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adapted to hold and support a stirrer shaft and motor (speed fixed at 60 r.p.m.), was used. A 4-bladed circular stirrer (4.3 cm diameter) was attached to the motor shaft. The bottom of the flask had been adapted to hold a Perspex holder into which the compressed disc fitted so that only one face was exposed to solvent. The assembly was suspended in a water-bath at 37°C. At zero time, 550 ml of degassed water previously equilibrated at 37°C were added to the flask. 2 ml samples were removed at intervals and assayed by the B.P. fluorimetric method for digoxin (British Pharmacopoeia 1973, Addendum 1975).

Scanning electron microscopy (SEM) was performed using a Cambridge stereoscan Mk. IIA scanning electron microscope, after samples had been coated with a palladium:gold 40:60 alloy to a thickness of 5-20 nm.

RESULTS AND DISCUSSION

The scanning electron micrographs show clearly that the virgin disc surface is not perfectly smooth; pits and fissures appear at the junction of many of the crystals in the surface layer (Fig. 1). The nature of the surface is seen to depend to some extent on the initial size of the powder which has been compressed, the finely ground samples showing few fissures. The exposed crystal edges might be expected to act as sites from which dissolution occurs rapidly. If this were so the dissolution patterns would be distorted. Fig. 2a shows a disc surface after it has been immersed in solvent for several minutes; the nearly smooth surface of this sample has given way to a heterogeneous crystal mass, of much larger surface area than the initial disc surface. Levy and Gumtow[13] have reported that preferential dissolution leading to a pitted surface and thus increased dissolution occurs on surfaces of discs of mixtures of aspirin and hydrophobic tablet lubricants, but not on the surfaces of discs of drug alone. In the case of digoxin the observation of uneven dissolution might be predicted from

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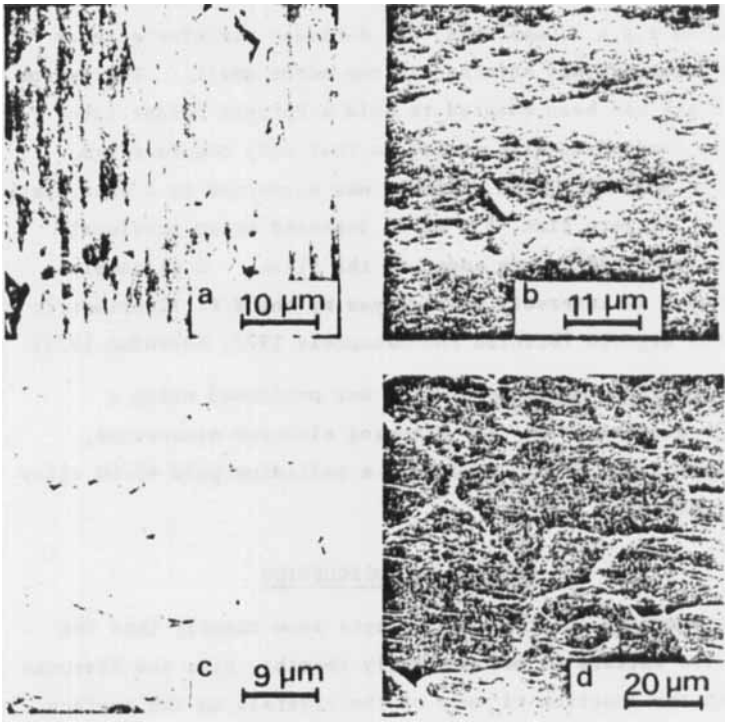

FIGURE 1

Pre-dissolution surfaces of discs of:

a. Swiss Micronized digoxin; b. Swiss Micronized digoxin ball-milled ("amorphous"); c. B.C.R.S. digoxin; d. sodium chloride.

the knowledge of the random crystal packing and uneven stresses that are seen in a cleaved section of disc (Fig. 2b). As comminution leads to amorphous, highly soluble layers[11] and in view of reports of polymorphic transitions under pressure[4] it may be that the outermost layers of the digoxin discs are compressed layers of an amorphous phase. While in sodium chloride discs the edges of discrete crystals can be seen (Fig 1d), BCRS digoxin does not display this characteristic

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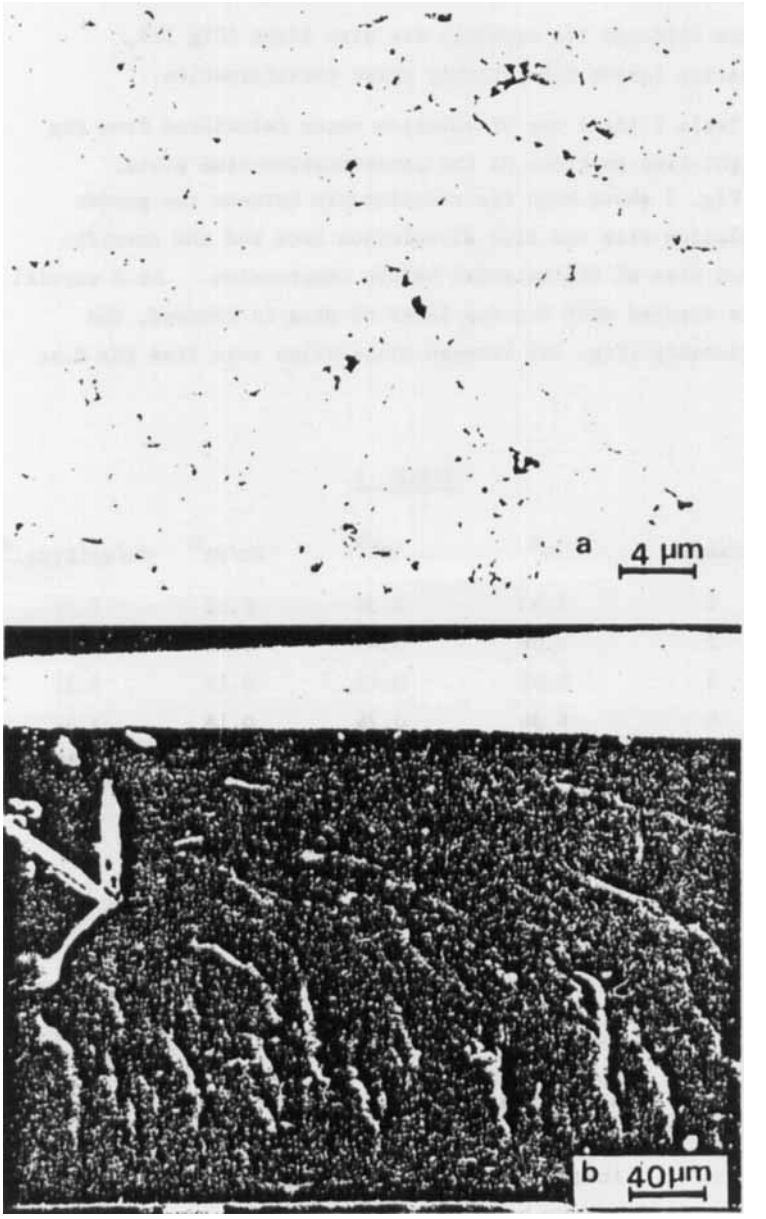

FIGURE 2

a. Post-dissolution surface of a disc of Swiss Micronized digoxin; b. Fractured vertical section through a disc of Swiss Micronized digoxin ball-milled ("amorphous").

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pattern although its crystals are also large (Fig 1c), suggesting fusion and possibly phase transformation.

Table 1 lists the dissolution rates calculated from the straight-line portions of the concentration-time plots.

Fig. 3 shows both the relationship between the powder dissolution rate and disc dissolution rate and the specific surface area of the material before compression. As a crystal bed is exposed when the top layer of drug is removed, the relationship (Fig. 3b) between dissolution rate from the disc

TABLE 1

Sample	S[a]	σ[b]	dc/dt[c]	dc/dt(Disc)[d]
1	2.43	0.30	0.02	2.32
2	4.06	0.43	0.08	2.55
3	6.02	0.63	0.11	3.31
4	6.36	0.76	0.18	3.52
5	6.48	4.00	0.20	7.48

Notes:

Sample 1 BCRS
2 Swiss Standard
3 British Standard
4 Swiss Micronized
5 British Standard ball-milled ("amorphous")

a. S = solubility in mg dl^{-1}

b. σ = specific surface area in $m^2 g^{-1}$

c. Initial dissolution rates in $mgdl^{-1}$ min^{-1} were extrapolated from powder dissolution rate curves between t = 0 and t = 10 min. (Florence & Salole, 1974 and 1976).

d. dissolution rate from disc $mgdl^{-1}$ min^{-1} x 10^4

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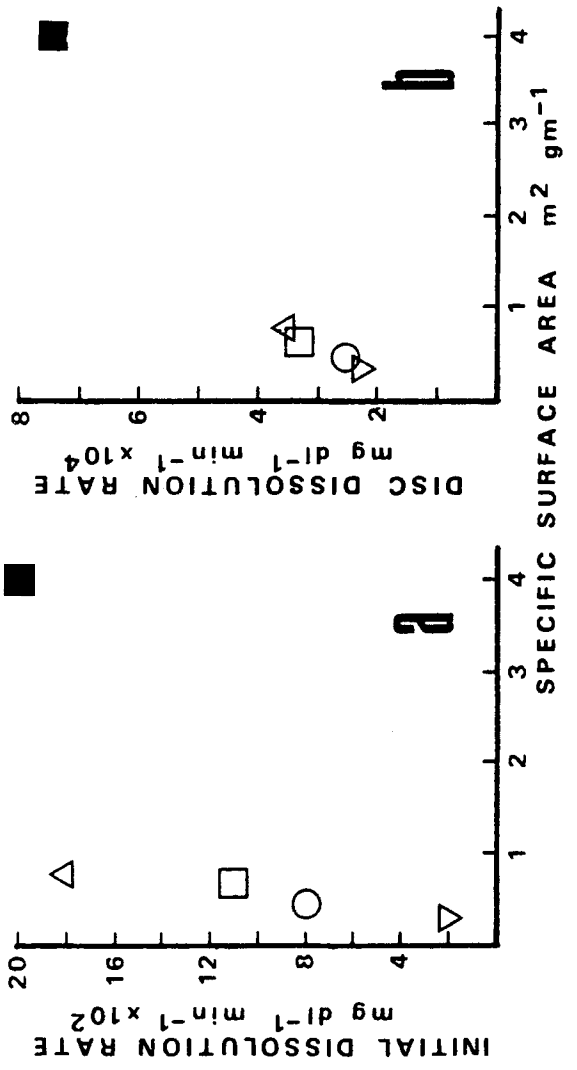

FIGURE 3

Plots of initial powder dissolution rate and disc dissolution rate against powder specific surface area for digoxin samples: ▽ B.C.R.S.; ○ Swiss Standard; □ ■ British Standard, crystalline and amorphous respectively; △ Swiss Micronized.

and constituent particle surface area is not unexpected. The correlation between disc dissolution rate and powder dissolution rate is also expected as there is a linear relationship between specific surface areas below 3 m^2 g^{-1} and dissolution from their powders[12]. The unusual nature of digoxin shows in the differing apparent equilibrium solubilities derived from different crystalline samples of digoxin. A rank order correlation exists between disc dissolution rate and sample solubility (Table 1): compression does not therefore destroy the characteristics of the particles. There is a clear difference in the disc dissolution rates of crystalline and amorphous samples (crystalline BCRS 2.32 x 10^4 $mgdl^{-1}$ min^{-1}; amorphous British Standard 7.48 x 10^4 $mgdl^{-1}$ min^{-1}), but as crystalline fractions show a 2.6 fold range in dissolution values, intrinsic dissolution rates cannot be abstracted from the data.

ACKNOWLEDGEMENTS

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