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Short Communications

Amorphous forms of thiazide diuretics prepared by spray-drying

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The differences in physicochemical properties between amorphous and crystalline forms of a drug may be sufficient to significantly alter biological activity, e.g. insulin, novobiocin (Haleblian, 1975). Amorphous forms of the cardiac glycosides digoxin (Florence and Salole, 1976) and digitoxin (Chiou and Kyle, 1979) have been produced by grinding and the presence of amorphous drug has been implicated in solubility differences observed between batches of such cardiac glycosides. Amorphous phases of fluprednisolone (Haleblian et al., 1971) and a number of β-lactam antibiotics (Pikal et al., 1978) have been prepared by lyophilization. Rapid quenching of the drug melt was used to produce amorphous phases of sulphathiazole (Simonelli et al., 1976) and of a number of barbiturates (Summers, 1978). Precipitation methods were used to prepare amorphous iopanoic acid (Stagner and Guillory, 1979), while spherical amorphous drug microparticles were prepared by spray drying (Nurnburg, 1976; Sato et al., 1981; Corrigan et al., 1983). The relative enhancements in solubility of amorphous phases varies from less than 2-fold for indomethacin (Imaizumi et al., 1980) and hydroflumethiazide (Corrigan et al., 1983) to greater than 20-fold for 9,3''-diacetylmidecamycin (Sato et al., 1981). In this report the properties of spray-dried chlorothiazide, hydrochlorothiazide, bendrofluazide, cyclothiazide, cyclopenthiazide and polythiazide are presented.

Each drug was spray-dried from an ethanolic solution using a Buchi Minispray 190 spray-drier, as outlined previously for hydroflumethiazide (Corrigan et al., 1983). Samples were analyzed by powder X-ray diffraction (Philips PW 1050/25), Differential Scanning Calorimetry (DSC) (Perkin Elmer Model DSC-1B) and Scanning Electron Microscopy (Jeol J S M—T200) as previously described (Corrigan et al., 1983). Apparent solubilities (Chiou and Kyle, 1979) were determined at 37°C in 0.1 N HCl, containing 1% PVP to inhibit crystallization in metastable systems

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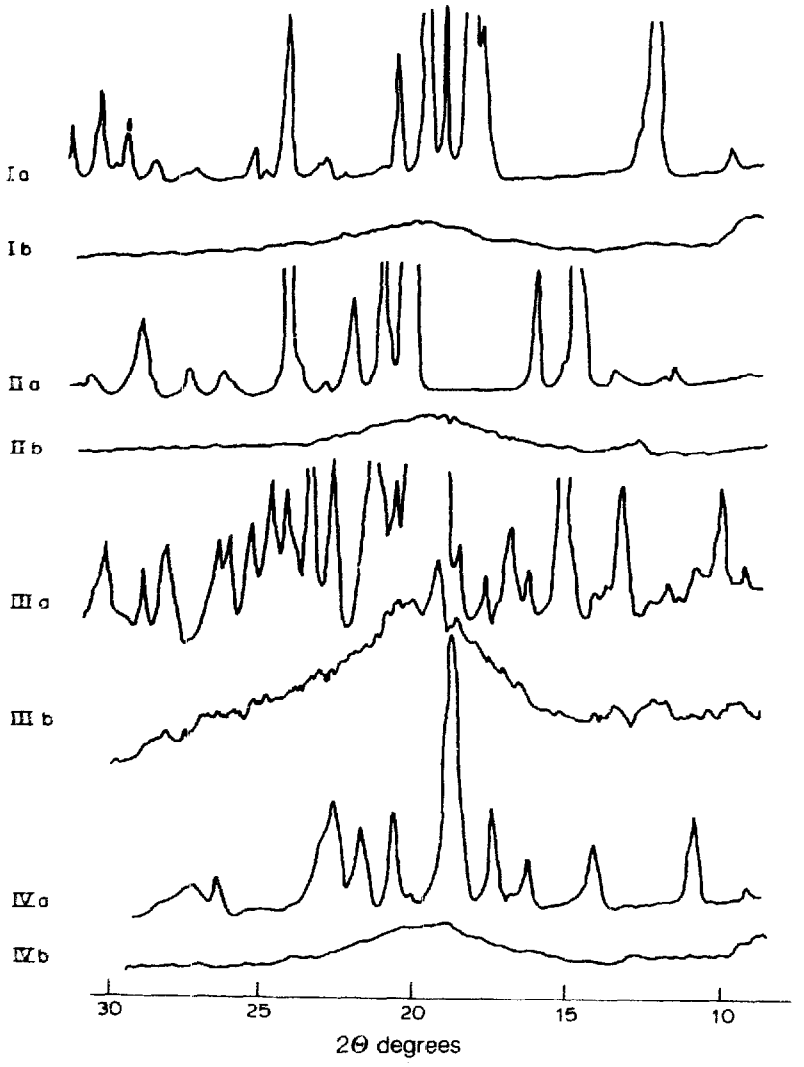

Fig. 1. Powder X-ray diffraction scans of: (a) crystalline; and (b) spray-dried samples of cyclopenthiazide (I), polythiazide (II), bendrofluazide (III) and cyclothiazide (IV).

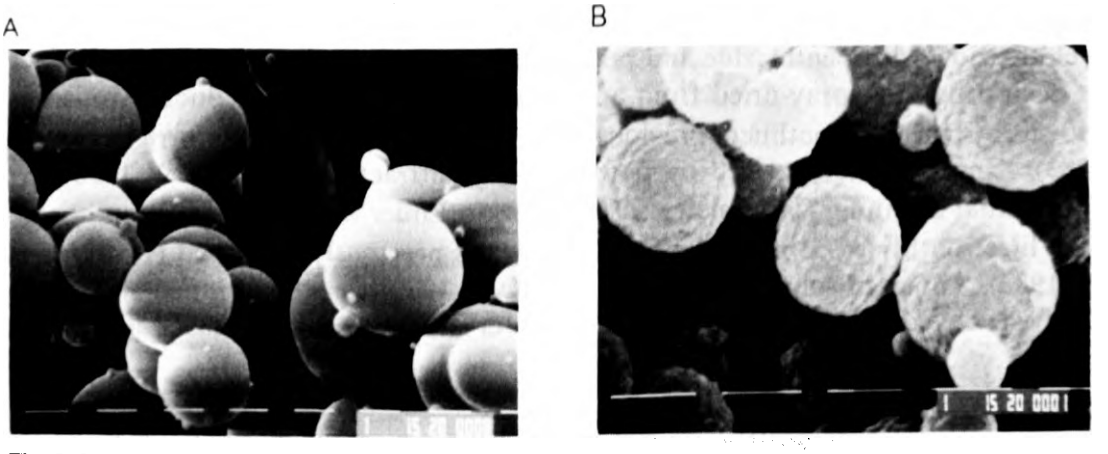

Fig. 2. Photomicrographs of spray-dried polythiazide (A) and chlorothiazide (B).

(Corrigan and Timoney, 1974). The filtered (Millipore 0.22 μm) diluted samples were assayed by UV spectroscopy.

X-Ray diffraction scans of samples of cyclopenthiazide, polythiazide, bendrofluazide and cyclothiazide before and after spray-drying are shown in Fig. 1. The absence of crystallinity in the spray-dried systems is evident. Chlorothiazide and hydrochlorothiazide gave similar patterns before and after spray-drying. Scanning electron microscopy of spray-dried systems revealed microfine spherical particles in each case. The surfaces of spray-dried chlorothiazide and hydrochlorothiazide particles were not smooth, in contrast to the other 4 spray-dried thiazides. Typical photomicrographs of chlorothiazide and polythiazide are shown in Fig. 2. Each of the 6 crystalline thiazides gave a single endothermic peak on DSC analysis which corresponded to the melting transition. In contrast, the freshly spray-dried forms, with the exception of chlorothiazide, all contained an additional exothermic peak corresponding to the temperature at which spontaneous crystallization occurred (Fig. 3). Samples of spray-dried hydrochlorothiazide lost this exotherm in less than

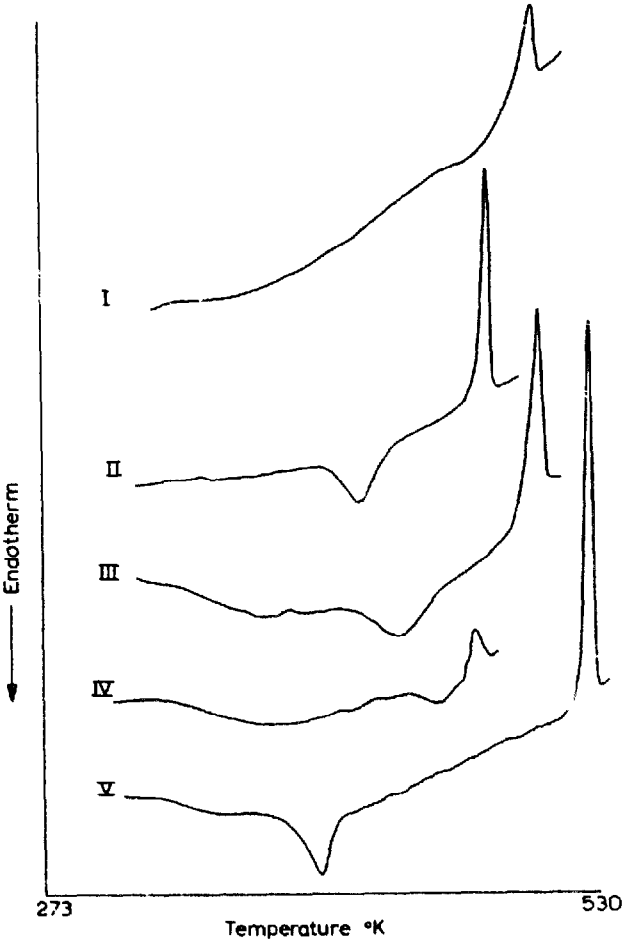

Fig. 3. DSC scans of spray-dried samples of cyclopenthiazide (I), polythiazide (II), bendrofluazide (III), cyclothiazide (IV) and hydrochlorothiazide (V).

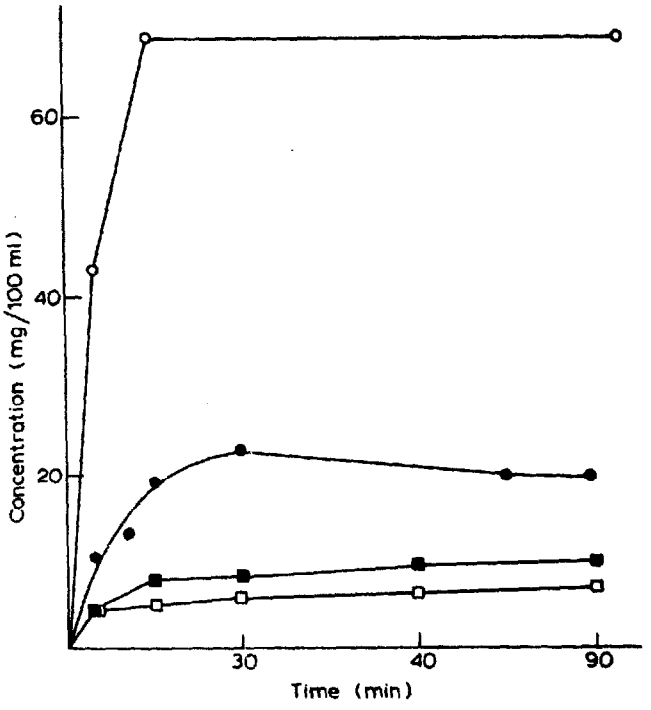

Fig. 4. Solubility profiles for polythiazide: crystalline (□), and spray-dried (○); and bendrofluazide: crystalline (■), spray-dried (●).

24 h indicating that an amorphous, but highly unstable, phase had also been produced on spray-drying this drug. The other amorphous phases were still physically stable after 12 months. A relatively small endothermic peak preceding the exotherm was observed in spray-dried bendrofluazide and polythiazide. A similar peak was noted with amorphous iopanoic acid and was attributed to an endothermic glass transition (Stagner and Guillory, 1979).

Chlorothiazide was therefore the only thiazide which failed to form an amorphous phase by direct spray-drying from alcohol. An amorphous product was, however, produced on spray-drying from alcoholic solutions containing PVP, sufficient to give a final product containing 5% PVP. The presence of chlorothiazide in an amorphous

TABLE 1

APPARENT SOLUBILITIES OF CRYSTALLINE AND AMORPHOUS THIAZIDE DIURETICS

Drug	Apparent solubility ($mg \cdot ml^{-1}$)			
	Molecular weight	Crystalline	Amorphous	Ratio
Hydrochlorothiazide	297.7	1.17	1.30	1.1
Bendrofluazide	421.4	0.108	0.303	2.8
Cyclothiazide	389.9	0.0588	0.363	6.2
Cyclopenthiazide	379.9	0.0430	0.355	8.3
Polythiazide	439.9	0.0705	0.688	9.8

phase has also been suggested in chlorothiazide–PVP coprecipitates containing larger proportions of PVP (O'Driscoll and Corrigan, 1982). The amorphous spray-dried drug forms gave higher apparent solubilities than the corresponding crystalline phases. Profiles obtained for polythiazide and bendrofluazide are illustrated in Fig. 4. The apparent solubility results are summarized in Table 1. The increase in apparent solubility of the amorphous phases ranged from nearly 10-fold in the case of polythiazide to 1.1-fold for hydrochlorothiazide. It appears therefore that the lower molecular weight thiazides, i.e. chlorothiazide, hydrochlorothiazide and hydroflumethiazide, form amorphous phases less readily and when such phases are produced by spray-drying they have poor physical stability and give moderate enhancement in relative apparent solubility (less than 2-fold). In contrast, the larger molecular weight compounds, which tend to be less compact, having substituents in the 3-position of the benzothiazine ring, give amorphous phases on spray-drying which are physically more stable and have greater enhancements in relative apparent solubility (3–10-fold).

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References

Chiou, W.L. and Kyle, L.E., Differential thermal, solubility and aging studies on various sources of digoxin and digitoxin powder: biopharmaceutical implications J. Pharm. Sci., 68 (1979) 1224–1229.

Corrigan, O.I., Sabra, K. and Holohan, E.M., Physicochemical properties of spray-dried drugs: phenobarbitone and hydroflumethiazide. Drug Dev. Ind. Pharm., 9 (1983) 1–20.

Corrigan, O.I. and Timoney, R.F., Anomalous behaviour of some hydroflumethiazide crystal samples. J. Pharm. Pharmacol., 26 (1974) 838–840.

Florence, A.T. and Salole, E.G., Changes in crystallinity and solubility on comminution of digoxin and observations on spironolactone and oestradiol. J. Pharm. Pharmacol., 28 (1976) 637–642.

Haleblian, J.K., Characterization of habits and crystalline modification of solids and their pharmaceutical applications. J. Pharm. Sci., 64 (1975) 1269–1288.

Haleblian, J.K., Koda, R.T. and Biles, J.A., Isolation and characterization of some solid phases of fluprednisolone. J. Pharm. Sci., 60 (1971) 1485–1491.

Imaizumi, H., Nambu, N. and Nagai, T., Stability and several physical properties of amorphous and crystalline forms of indomethacin. Chem. Pharm. Bull., 28 (1980) 2565–2569.

Nurnberg, Von E., Neuere Untersuchungsergebnisse von pharmazeutischen Sprühtrocknungsprodukten. Pharm. Ind., 38 (1976) 74–82, 228–232.

O'Driscoll, K.M. and Corrigan, O.I., Chlorothiazide–polyvinylpyrrolidone (PVP) interactions: influence on membrane permeation (everted rat intestine) and dissolution. Drug. Dev. Ind. Pharm., 8 (1982) 547–564.

Pikal, M.J., Lukes, A.L., Lang, J.E. and Gaines, K., Quantitative crystallinity determinations for β-lactam antibiotics by solution calorimetry: correlation with stability. J. Pharm. Sci., 67 (1978) 767–773.

Sato, T., Okada, A., Sekiguchi, K. and Tsuda, Y., Difference in physicopharmaceutical properties between crystalline and non crystalline 9,3″-diacetylmidecamycin. Chem. Pharm. Bull., 29 (1981) 2675–2682.

Simonelli, A.P., Mehta, S.C. and Higuchi, W.I., Dissolution rates of high energy sulfathiazole–povidone coprecipitates II: Characterization of form of drug controlling its dissolution rate via solubility studies. J. Pharm. Sci., 65 (1976) 355–361.

Stagner, M.C. and Guillory, J.K., Physical characterization of solid iopanoic acid forms. J. Pharm. Sci., 68 (1979) 1005–1009.

Summers, M.P., Glass formation in barbiturates and solid dispersion systems of barbiturates with citric acid. J. Pharm. Sci., 67 (1978) 1606–1610.