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SPIRONOLACTONE CRYSTAL FORMS

E.G. Salole and F.A. Al-Sarraj,
Department of Pharmacy,
University of Strathclyde,
Glasgow, Scotland.

ABSTRACT

Spironolactone was obtained in three polymorphic and five solvated crystalline forms which differed in initial dissolution rate in water by about a factor of 12, the most rapidly dissolving form achieving concentrations about twice the equilibrium solubility; on prolonged contact with water transformation to an hydrated phase occurred. It is suggested that the facility with which spironolactone adopts different crystal forms may be utilised to enhance its dissolution-related oral bioavailability.

That spironolactone, a useful diuretic, is poorly soluble and highly dependent on a fine particle size for adequate dissolution and oral bioavailability is well recognised.[1] In view of its apparent inclination towards polymorphism,[2,3] its sensitivity to grinding,[4] and the differences in tablet dissolution and bioavailability reported for identical formulations of drug batches from different sources,[5] spironolactone presented itself as a candidate for an examination of the effects of the process of solvent-deposition on drug form;[6] to which end it was screened for appropriate crystalline modifications.

MATERIALS AND METHODS

Crystallisation of spironolactone (batch 338M, Searle Laboratories, UK; batch 78C-0449, Sigma London Chemical Co., UK) from organic

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solvents ('AnalaR' grade) was achieved by: (i) forced-convection evaporation-solutions on a watch glass were subjected to the ambient-temperature stream from an air-blower; (ii) natural-convection cooling of warm saturated solutions to room temperature in closed flasks; (iii) solvent evaporation at 30°C under reduced pressure in a rotary evaporator; (iv) natural-convection evaporation - solutions on a watch glass were allowed to evaporate under ambient conditions. Residues were further dried for 48h at 30°C/6.7 kPa in a vacuum oven.

Infrared Spectra were obtained with a Pye Unicam SP200 spectrometer, using the liquid paraffin-mull technique.

Particle Sizes determined as weight distributions with a Coulter Counter model TAII, using pre-saturated 0.9% $^{w}/_{v}$ sodium chloride as electrolyte.

Powder Dissolution rates were determined by suspending 14mg samples in 2dl water in a conical flask fitted with a magnetic follower and filter-stick assembly,[4] equilibrated in a bath at 37.0 $\pm$ 0.2°C. At intervals, 8ml samples were removed, filtered through a 0.7μm glass-fibre pad (Whatman Ltd., UK) and, discarding the first 3ml of filtrate, assayed spectrophotometrically at 238 nm.

Scanning Electron Microscope (SEM) photographs were taken with a Phillips P SEM 500 instrument (specimens sputter-coated with gold).

Solubility was determined by suspending 20mg samples in 0.2dl water in stoppered flasks in a shaking water-bath at 37.0 $\pm$ 0.2°C for 14d. Filtrates were obtained and assayed as previously described.

Thermal Analyses were carried out by Kofler hot-stage microscopy (HSM) of samples mounted in silicone oil, thermogravimetry (TG) with a Perkin-Elmer TGS-2 thermobalance and differential thermal analysis (DTA) with a Stanton Redcroft 671B analyser (5mg specimens heated in open cups at 10°C min^{-1} in static ambient atmosphere, alumina reference).

X-Ray Powder Diffraction patterns were obtained with a Phillips XDL-700 Guinier camera, aligned for the $K_{\alpha 1}$ line of a copper

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Polymorphic and Solvated Spironolactone Crystal Forms.

Form	Source (cryst.meth.)	Habit	Diam./μm[1]	IR[2]	M.p./°C[3]	Soly./mg dl^{-1}
I	ethanol (i)	bladed	52	(a)	212	2.3
II	Searle	amorphous	12	(b)	209	2.9
III	acetone (i-iv)	tabular	85	(c)	209	2.6
A	Sigma	amorphous	13	(d)	209	2.8
B	propanol (iv)	amorphous	87	(b)	207	2.7
C	methanol (ii)	platy	84	(a)	207	2.4
D	methanol (i)	acicular	87	(a)	202	2.7
E	methanol (iv)	prismatic	117	(d)	201	2.6

1. Cumulative oversize weight distribution median. 2. Fig. 1. 3. DTA peak temp.

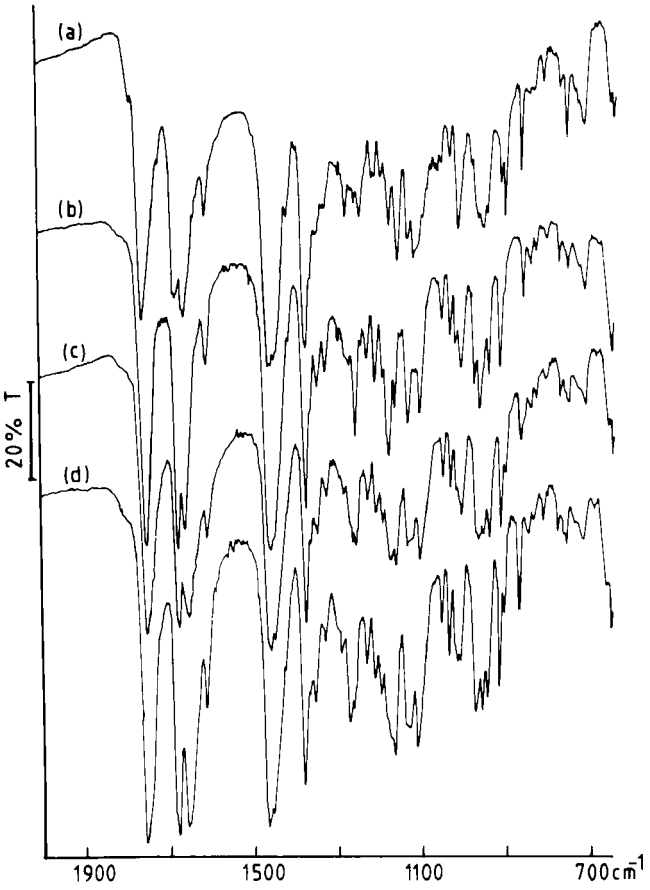

FIGURE 1

Infrared (mull) spectra of spironolactone crystal forms: (a) I, C, D; (b) II, B; (c) III; (d) A,E.

target (specimens mounted on adhesive cellulose tape and irradiated for 5h). Relative line-intensities ($^{I}/_{I_o}$) were estimated microdensitometrically.

RESULTS AND DISCUSSION

Spironolactone was obtained in three polymorphic and five solvated crystalline forms (Table 1). The two finely divided commercial samples exhibited different IR spectra (Fig. 1b,d) and, although apparently amorphous, powder diffraction patterns (Table 2); the DTA curve of Form A exhibited a wide, shallow

TABLE 2

Interplanar Spaces (d) and Relative Line-Intensities of Spironolactone Crystal Forms.

Form II		Form A		Form III		Form D	
d/Å	I/I_o	d/Å	I/I_o	d/Å	I/I_o	d/Å	I/I_o
9.60	10	10.56	8	9.60	10	9.72	8
7.77	8	8.75	10	8.68	8	8.88	7
7.13	9	8.67	9	7.77	9	7.67	8
5.57	10	7.13	2	7.13	9	6.67	9
5.32	10	6.48	4	6.34	9	6.14	10
5.11	10	6.36	4	5.57	10	5.89	9
4.77	10	6.27	2	5.32	10	5.51	8
4.63	9	5.50	10	5.11	10	5.28	10
4.37	8	5.35	9	4.77	9	5.07	10
4.05	8	5.25	2	4.63	8	4.85	9
3.84	7	4.69	6	4.37	9	4.60	8
3.61	6	4.60	5	4.05	7	4.28	8

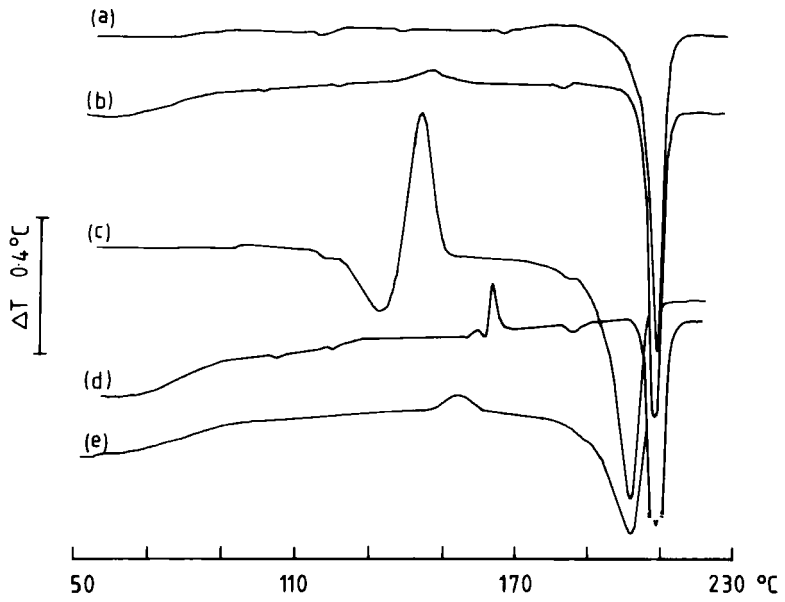

FIGURE 2
DTA curves of spironolactone crystal forms: (a) II; (b) A; (c) D (C, E pre-melting peaks are at 139/157°C, 154/162°C); (d) A-residue in solubility flask; (e) C-residue after 3d in aqueous suspension.

endotherm below 110°C and a small pre-melting exotherm at 150°C (Fig. 2b), indicating desolvation (1.2% mass loss by TG) and some lattice rearrangement. Whereas spironolactone consistently crystallised from acetone as Form III (Fig. 3a), methanol provided acicular Form D (Fig. 3b) and Forms C and E, which characteristically exhibited DTA curves with a pronounced pre-melting endotherm-exotherm doublet (Fig. 2c), corresponding to simultaneous desolvation (0.4% and 1.5% TG mass loss for D and E, respectively), melting and crystal growth, as observed under HSM.

The eight forms of spironolactone were found to dissolve at different rates, which did not correlate with particle size, initial concentrations varying by about a factor of 12 (Fig. 4). Form D dissolved most rapidly, achieving concentrations well above the reported solubility of 2.2 - 2.8 mg dl^{-1}, [3,7] as also did Form II, in contrast to Forms A and III (Fig. 4). However, all

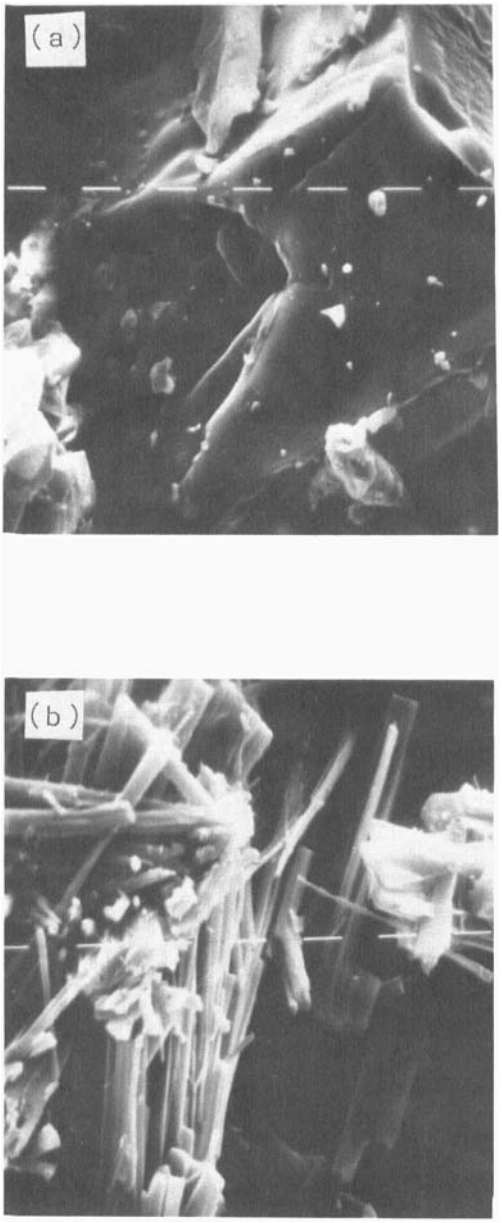

FIGURE 3
SEM micrographs of spironolactone crystal forms: (a) III; (b) D (scale marker 10 μm).

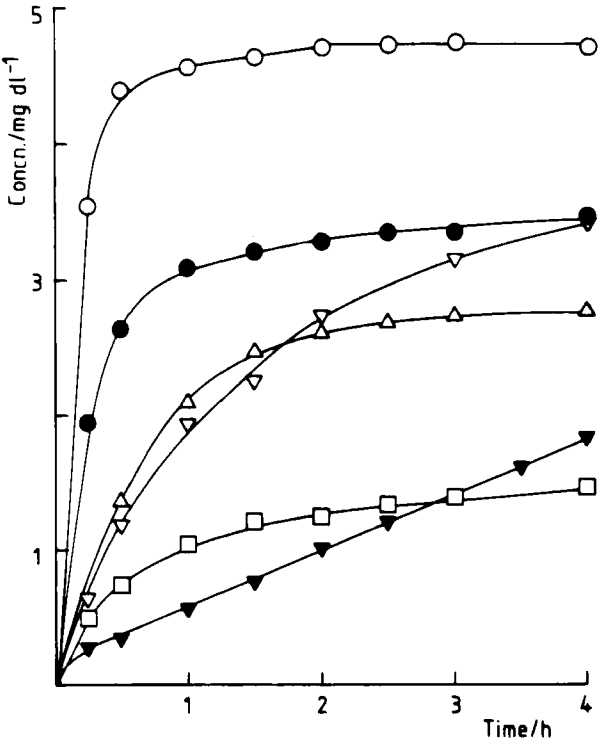

FIGURE 4
Dissolution curves of spironolactone crystal forms in water at 37°C: ○ D; ● II; △ A; ▽ C; □ E; ▼ III; curve I matches A to 1.5h, rising to 3.1 mg dl^{-1} at 4h; curve B intersects A at 3h, rising to 3.0 mg dl^{-1} at 4h.

forms of spironolactone were found to have apparent equilibrium solubilities within the literature range (Table 1); examination of the dried crystalline residues from solubility flasks found that, with the exception of Form II, all exhibited an IR spectrum and DTA curve similar to Form A, with a pronounced exotherm at about 160°C (Fig. 2d, e). It appeared that spironolactone crystals underwent transformation to a relatively poorly soluble hydrated phase, similar to Form A, on prolonged suspension in water; the apparent resistance of Form II to transformation, despite its lowered solubility, may have been a

reflection of its relative lattice stability and success at seeding for excess solute.

The crystal properties of spironolactone are clearly complex: as with other steroidal drugs[8,9] it can adopt polymorphic, nonstoichiometrically solvated or amorphous glass forms from the same solvents, and undergo solvent-mediated and other solid-state transformations[2,3,10,11] (in this study the use of compressed discs for IR spectroscopy was abandoned because some samples transformed under pressure). The facility with which spironolactone does this may be due to a flexible lattice (being bound only by relatively weak van der Waals forces[11]) allowing the molecule to adopt subtly distorted conformations,[2,11] and must have implications for the performance of oral formulations.

It has long been recognised that the bioavailability of spironolactone from tablet formulations is closely related to dissolution rate. This study and the recent report by El-dalsh et al[10] indicate in turn that dissolution is not simply a matter of drug particle size. That the solid-state properties of spironolactone may play an important role may be inferred from Clarke et al[5] who reported significant correlations between tablet dissolution at 40 min and bioavailability, and found substantial differences between identically formulated and processed tablets of drug batches from different sources; in this study commercial batches were found to differ and different crystal forms shown, after 1h in water, to achieve concentrations varying from half to twice the accepted drug solubility. Although its shallow dose-response relationship, high therapeutic ratio[12] and incompletely characterised pharmacokinetics[13] make it difficult to assess the clinical relevance of variations in spironolactone bioavailability, improvement in the latter and consistent product performance by the judicious selection of crystal form would appear to be worthy of consideration.

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