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EFFECT OF SOLVENT-DEPOSITION ON SPIRONOLACTONE CRYSTAL FORM

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ABSTRACT

Spironolactone deposited from acetone and methanol onto glass particles in the forms obtained on recrystallisation, but adopted different forms on lactose due to the effects of solvent on the matrix.

Solvent-deposition, the precipitation of solute onto a matrix surface by evaporation, is an established process in the manufacture of solid dosage forms, and is commonly used as a mixing technique. As reports of comprehensive studies on the effects of deposition systems on drug particle size, dissolution rate and stability had noted the occurrence of polymorphic behaviour,[1,2] it was considered of interest to examine whether forms with particular characteristics could be developed on solvent-dsposition. Spironolactone, a steroidal diuretic with variable and dissolution-dependent bioavailability,[3] was selected for study as it had been found to crystallise from volatile solvents in different forms exhibiting substantially different dissolution rates;[4] powdered glass was employed as a model matrix.[5]

MATERIALS AND METHODS

Infrared Spectra in liquid paraffin mulls were obtained with a Pye Unicam SP200 spectrometer, using a compensating sample of

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excipient in the reference beam when necessary to clearly distinguish the strong and characteristic 3-ketone/7-thioester carbonyl peaks around 1680 cm^{-1}.

Powder Dissolution rates were determined by suspending the equivalent of 14mg spironolactone in 2dl water in a conical flask, fitted with a magnetic follower and filter-stick assembly, equilibrated in a bath at 37.0 ± 0.2°C.[6] At intervals, 8ml samples were withdrawn, filtered through a 0.7μm glass fibre pad (Whatman Ltd.,UK) and, discarding the first 3ml of filtrate, assayed spectrophotometrically at 238nm.

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

Solvent-Deposition of spironolactone (batch 338M, Searle Laboratories, UK) onto matrices of glass (crushed 'Pyrex', >60<120μm sieve fraction) or lactose monohydrate B.P. ('Regular Grade', Whey Products Ltd., UK; sieve analysis : < 53μm 29%, > 53μm < 75μm 22%, > 75<105μm 21%, > 105<125μm 11%, > 125μm < 150μm 6%, >150 < 210μm 8%) in 1:3 ratio was carried out by intermittently wetting 0.75g of matrix on a watch glass with a concentrated drug solution in either acetone or methanol ('AnalaR' grade, used as received), and drying by gently tumbling under the ambient-temperature stream from an air-blower.

Thermal Analyses were carried out by Kofler hot-stage microscopy (HSM) of samples mounted in silicone oil, and by differential thermal analysis (DTA) with a Stanton Redcroft 671B analyser (samples equivalent to about 5mg of spironolactone were heated at 10°C min^{-1} in open cups in a static, ambient atmosphere, with an equal mass of alumina as reference; samples of spironolactone deposited on lactose were analysed using an "active reference", consisting of an equivalent mass of lactose, to compensate for baseline shifts due to the matrix).

X-Ray Powder Diffraction patterns were obtained for spironolactone deposited on glass with a Phillips XDL-700 Guinier camera aligned for $K_{\alpha 1}$ copper radiation, the specimens mounted on adhesive cellulose tape and irradiated for 5h. Relative line-intensities ($^{I}/Io$) were estimated microdensitometrically.

RESULTS AND DISCUSSION

Spironolactone deposited on glass from acetone exhibited IR peaks around 1680 cm^{-1} and DTA curve (Fig. 1a) similar to those of form III, the phase previously obtained by crystallisation from acetone.[4] X-ray diffraction revealed a spacing pattern identical to Form III, except that the strong line at 8.68 Å was absent (Table 1), perhaps due to lattice strain imposed on the relatively small crystals (Fig. 2a) by the rapidity of precipitation.
It appeared therefore that spironolactone deposited from acetone onto glass adopted the form obtained by crystallisation.[4] Similarly, the IR carbonyl peaks, DTA curve (with characteristic pre-melting endotherm-exotherm doublet (Fig. 1b), corresponding to simultaneous desolvation, melting and crystal growth under HSM) and X-ray diffraction pattern (Table I) of the acicular crystals of spironolactone deposited from methanol on glass (Fig. 2b) confirmed them as Form D, the solvated phase also obtained previously by crystallisation.

When examined for dissolution rate, the product from methanol exhibited rapid dissolution, as anticipated, achieving concentrations not only in excess of the apparent equilibrium value (about 2.6mg dl^{-1}) but also higher than recrystallised Form D (Fig. 3),[4] perhaps due to a smaller particle size and apparently tenuous attachment to glass (Fig. 2b). However, after peaking at about 5.5mg dl^{-1} the curve exhibited a steep decline in concentration, characteristic of the precipitation of a less soluble phase; indeed the IR and thermal characteristics of the

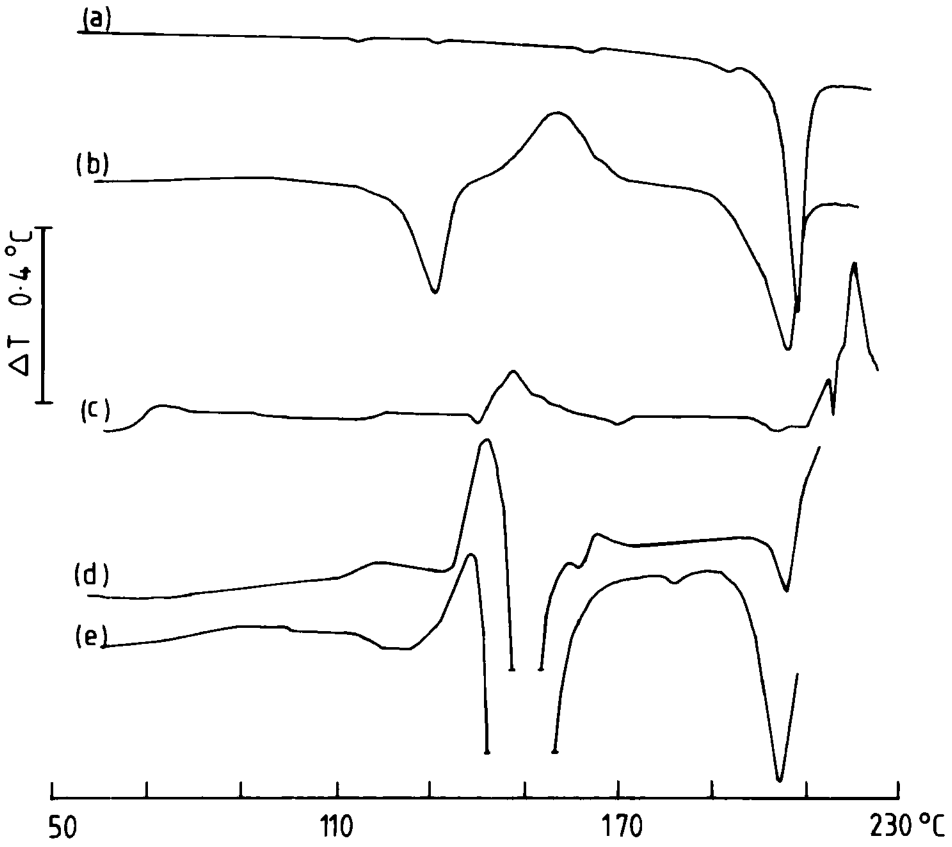


FIGURE 1

DTA curves of spironolactone deposited on glass from (a) acetone and (b) methanol, and on lactose from (d) acetone and (e) methanol; (c) DTA curve of lactose using an "active reference".

residue in suspension after 4h were similar to those of Form A, the poorly soluble hydrated form of spironolactone to which others were found to transform on prolonged contact with water.[4] Since Form D obtained by crystallisation had previously been found to retain its maximal solubility of 4.75mg dl^{-1} for at least 48h, it appeared that the rate of transformation to Form A was sensitive to the degree of supersaturation and that metastable

TABLE I

Interplanar Spaces (d) and Relative Line-Intensities of Spironolactone Deposited on Glass.

from Acetone		from Methanol	
d/Å	$^{I}/Io$	d/Å	$^{I}/Io$
9.60	9	9.72	7
7.77	6	8.88	5
7.13	7	7.67	6
6.34	9	6.67	8
5.57	9	6.14	9
5.32	10	5.89	9
5.11	10	5.51	8
4.77	9	5.28	7
4.63	9	5.07	10
4.37	10	4.85	10

concentrations of spironolactone (i.e.$<$5.5mg dl^{-1}) could be maintained for considerable periods.

Following the results with the model glass matrix, the dissolution rates of spironolactone deposited on lactose were found to be disappointingly low (Fig. 3). Relative intensities of the IR peaks around 1680cm^{-1} clearly indicated that the still acicular crystals from methanol (Fig. 2c) were of Form D but that the acetone sample now consisted of Form A. On DTA, using an "active reference" to negate the large lactose endotherms at 147 and 219°C due to desolvation and melting, respectively (Fig. 1c), the acetone sample's endotherm-exotherm around 160°C (Fig. 1d) suggested Form A, but any signs of Form D in the methanol sample were masked by lactose dehydration (Fig. 1e). Apparently the

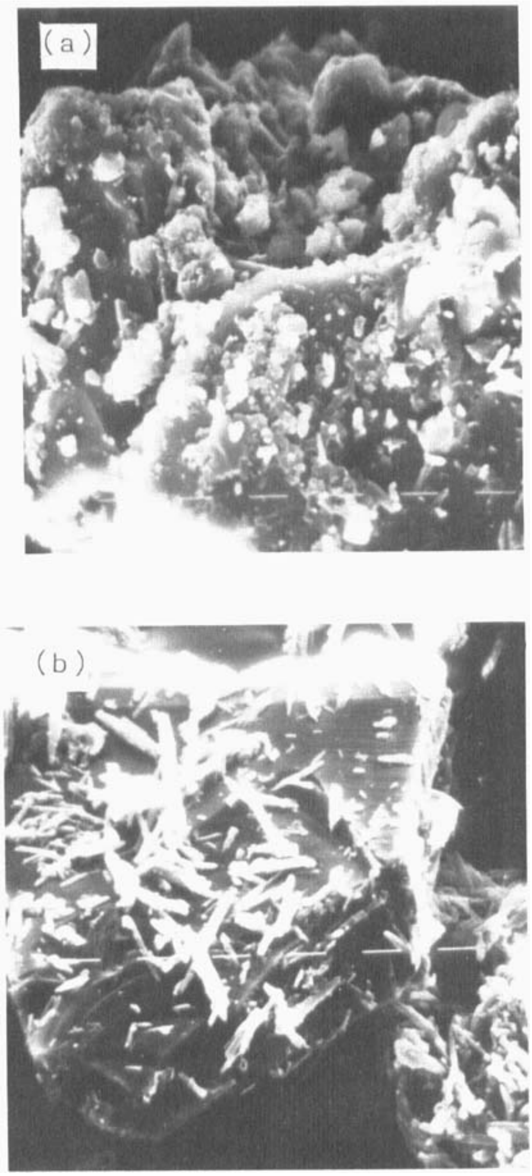
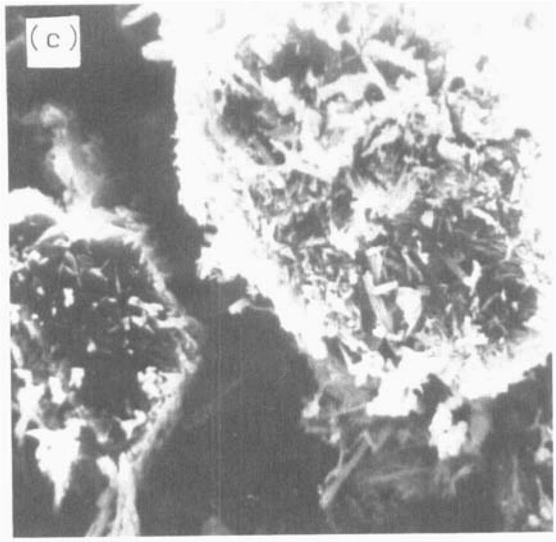


FIGURE 2

SEM micrographs of spironolactone deposited on glass from (a) acetone and (b) methanol, and on lactose from (c) methanol (scale marker = 10μm).



(Figure 2 Continued)

deposition of spironolactone on lactose did not parallel that on glass; the development of Form A from acetone may have been due to surface moisture (present at about 0.3% $^{w}/_{w}$), but to investigate the unexpectedly poor solubility of the methanol sample deposits were made on >150<210μm and <53μm lactose fractions and tested for dissolution.

The <53μm fraction exhibited a lower dissolution rate than found previously (Fig. 3), but in contrast, although of similar granule size, the larger fraction dissolved as rapidly as the glass system, the curve also peaking at about 5.5mg dl^{-1} before falling away (Fig. 3). DTA was uninformative, the curves being similar to those of unfractionated material, but IR spectra suggested that spironolactone deposited as Form D on the large matrix but developed as Form A on the small lactose fraction. DTA and HSM of lactose treated with plain solvents revealed that it was rapidly dehydrated by methanol (a conclusion since

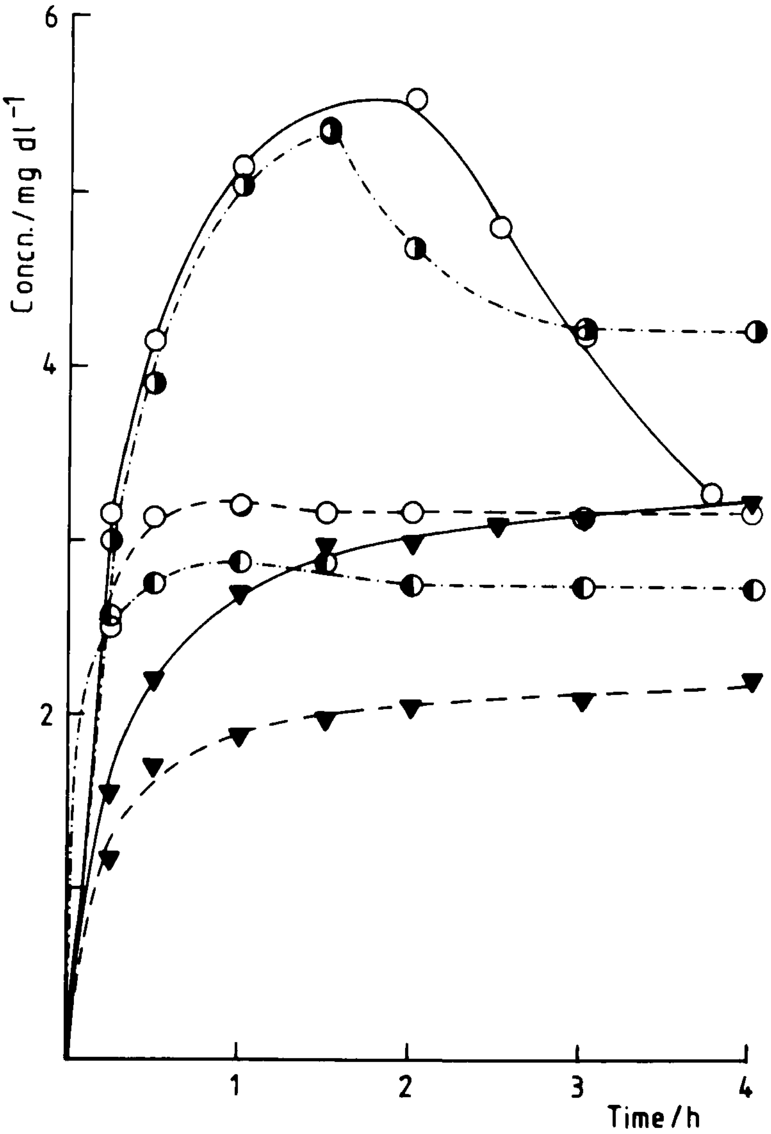


FIGURE 3

Dissolution in water at 37°C of spironolactone deposited on (———) glass and (- - -) lactose from (▼) acetone and (○) methanol; deposited on (◐) <53µm and (◑) >150<210µm lactose fractions from methanol.

corroborated in detail by Lerk[7]); therefore the difference between spironolactone forms deposited on large and small fractions may have been due to the greater degree of dehydration experienced by the latter, and the relatively poor dissolution of unfractionated matrix a reflection of its particle size distribution.

It appears that the polymorphic characteristics of spironolactone are maintained on solvent-deposition, the development of particular forms depending less on the properties of the matrix than on those of the solvent, in terms of its interactions with both drug and the base. The latter aspect has implications for wet-granulation and the other manufacturing processes involving lactose, solvents and drugs susceptible to subtle crystallographic transformations, and may indeed have contributed to the reported differences between tablet formulations of spironolactone.[8,9]

Considering that the bioavailability of spironolactone is highly dissolution-dependent, it would appear that, within limits, particle size of raw material is perhaps not the major consideration and that the crystal form present at the end of the manufacturing process is of greater relevance to product performance.

Solvent-excipient interactions notwithstanding, glass particles would appear to serve well as a model matrix in pre-formulation assessment, having the outstanding advantage of not interfering with the key analytical methods of thermal analysis and X-ray diffraction.

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