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The fatty acid solvates of griseofulvin-desolvation data

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The solubility, dissolution rate and bioavailability of a drug can be influenced by its physical form, of which solvates are an example. The ability of a drug to form solvates can increase the possibilities for modifying, controlling and improving the stability, processing and formulation of the drug as well as its dissolution rate and bioavailability (Haleblian 1975).

Griseofulvin is a valuable systemic antifungal agent which forms solvates with chloroform (Sekiguchi et al 1964, 1968; Cheng et al 1979) and with benzene and dioxane (Sekiguchi et al 1976), when the drug is crystallized from the respective solvent. The griseofulvin-chloroform solvate illustrates the pharmaceutical application of solvates in crystal size reduction by repeated desolvation and solvation (Sekiguchi et al 1964, 1968) and in increasing the solubility, dissolution rate and bioavailability (Bates et al 1975, 1977). However, solvates containing chloroform, benzene or dioxane may have limited applicability in view of the toxicity of the solvents.

We previously reported (Abougela & Grant 1979) that griseofulvin forms a number of solvates with fatty acids which, with the exception of formic acid, are not toxic. Additional data on the desolvation properties (Tables 1, 2) and preparation of these solvates is now provided.

The materials used, griseofulvin and various n-alkanoic acids from C_1 to C_9, contained not less than 99% of the pure substances. Griseofulvin gave a single sharp peak in differential thermal analysis (DTA) at the melting point (220–224 °C). In the original form, after a variety of treatments (Hansford et al 1980) and after desolvation of the solvates, griseofulvin showed no evidence of polymorphism by DTA, hot stage microscopy (HSM), X-ray diffraction and infrared spectrophotometry. The great stability of the only known crystalline lattice of pure griseofulvin is indicated by its very high melting point (218–224 °C; Martindale 1977). DTA and HSM were as described by Kaur et al (1980). Thermogravimetry was carried out by heating 5 to 10 mg of sample from 18 to 360 °C at 5 or 10 °C min^{-1} in a Stanton Redcroft TG-750 Thermobalance.

The solvates were prepared by dissolving griseofulvin crystals (0·5 g) in the fatty acid (7 cm^3) by gradual heating (1 to 2 °C min^{-1}) with stirring until the solution was homogeneous. On slow cooling (1 to 3 °C min^{-1}) to 20 °C crystals were obtained which were kept in a closed sample tube in the presence of a few drops of solvent to prevent desolvation. The relative stability of the filter-dried solvates are shown in Tables 1 and 2.

Table 1 shows the temperature at which bubbles of solvent formed when solvate crystals were suspended in silicone oil (Dow Corning 200/30000 CS) were gradually heated under HSM. The boiling points of the fatty acids from C_1 to C_6 are sufficiently low for these substances to have evaporated below the melting point of pure griseofulvin. Although the boiling points of the fatty acids from C_7 to C_9 are comparable with or higher than the melting point of pure griseofulvin, these acids have evidently also evaporated, since the melting point of griseofulvin was not depressed. The difference (boiling point of the solvent—temperature at which bubbling begins) generally increased with increasing chain length of the solvent. This probably reflects a greater dispersion interaction between the hydrocarbon chains in the liquid solvent than between the hydrocarbon chains of the included solvent and the griseofulvin molecule in the crystal.

Griseofulvin forms two types of solvate, I and II (Abougela & Grant 1979). In the Type I solvates, which are formed with formic or acetic acid, the most important intermolecular interaction between griseofulvin and the carboxylic acid appears to be hydrogen bonding. The resemblance between the Type I solvates and the chloroform solvate of Sekiguchi et al (1964) probably arises from the ability of these solvents to act as hydrogen bond donors and griseofulvin to act as a hydrogen bond acceptor.

Table 2 provides detailed desolvation data of the Type I solvates. Freshly prepared griseofulvin–formic acid solvate showed two desolvation steps, each corresponding to about 0·5 mol of solvent per mol of griseo-

Table 1. Hot stage microscopic data of griseofulvin after crystallization from n-alkanoic acids.

Acid	m.p.* °C	b.p.* °C	Bubbling temp/°C start(s)	finish	Diff., (b.p.)-s °C	Bubbling quantity
Formic	8·4	101	70	102	41	++++
Acetic	16·6	118	50	95	68	++++
Propanoic	−20·8	141	—	—	—	—
Butanoic	−4·3	163	70	120	93	++
Pentanoic	−33·8	186	80	140	106	++
Hexanoic	−1·5	205	102	165	103	++
Heptanoic	−7·5	223	109	180	114	++
Octanoic	16·5	239	105	195	134	++
Nonanoic	12·2	255	98	170	157	++

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fulvin. Prolonged contact (e.g. 20 days) with formic acid led to decomposition of griseofulvin. Freshly prepared griseofulvin–acetic acid solvate also exhibited two desolvation steps but the low temperature step showed variable loss of solvent roughly increasing with the time of contact with the solvent (from 0 to 38 days) and indicative of solvent loosely bound in the crystals. Loss of more strongly bound acetic acid (about 1 mol) occurred at temperatures (78–103 °C) similar to those for formic acid from its solvate (78–120 °C), but thermogravimetry did not further resolve this desolvation of acetic acid.

In the Type II solvates, which are inclusion compounds formed with the longer chain n-alkanoic acids (from C_4 to C_9), the most important intermolecular interactions between griseofulvin and the fatty acid appear to be non-specific van der Waals interactions such as London and Debye forces (Abougela & Grant 1979). The resemblance between the Type II solvates and the solvates with benzene or dioxane (Sekiguchi et al 1976) probably arises from the fact that hydrogen bonding is impossible between griseofulvin and benzene or dioxane and is less significant in the Type II solvates on account of the longer hydrocarbon chain of the fatty acids C_4–C_9.

Table 2 provides detailed desolvation data of the Type II solvates which exhibited one DTA endotherm corresponding to a TG desolvation step during heating and one DTA endotherm which was without a counterpart in TG and corresponded to the melting of desolvated griseofulvin close to 220 °C. The results correspond to the behaviour expected of non-stoichiometric adducts. In general, increasing time of contact with the solvent (a) increased the molar ratio, included solvent/griseofulvin, (b) increased the temperature range of the endotherms and desolvations and (c) decreased the temperature at which desolvation commenced in TG. The main exceptions to this were the solvates with octanoic and nonanoic acids which have a relatively low volatility. In general, the temperature marking the end of desolvation in TG increased with increasing boiling point and chain length of the included fatty acid. Increasing strength of the dispersion interaction, which is responsible for increasing boiling point on ascending the homologous series, is probably also responsible for increasing strength of the intermolecular interaction in the inclusion compounds between griseofulvin and fatty acids of increasing chain length.

The inability of propanoic acid to form a solvate with griseofulvin is probably linked with its intermediate position between Types I and II. It is possible that the orientations of the propanoic acid molecules with respect to the griseofulvin molecules are so different for Type I and Type II solvates that either behaviour is impossible with this solvent.

Table 2. Endotherms from differential thermal analysis and desolvation steps from thermogravimetry of crystalline solvates of griseofulvin with formic, acetic and propanoic acids, and the n-alkanoic acids C_4–C_9.

Solvent and time of contact	Endotherm °C	Desolvation °C	Mols acid lost mol^{-1} griseofulvin	
Formic acid	78	78	0·43	Total = 0·86
	118–122 (m.p. 219)	118·5	0·43	
Acetic acid	—	37	Variable	
	78, 103 (m.p. 223)	95	0·86	
Propanoic acid	None (m.p. 219)	None	0	
Butanoic acid freshly prepared	60–76 (m.p. 219)	62–78	0·18	
Butanoic acid 33 days	62–124 (m.p. 219)	39–89	1·25	
Pentanoic acid freshly prepared	50–103 (m.p. 217)	54–94	0·22	
Pentanoic acid 14 days	48–162 (m.p. 219)	39–104	0·86	
Hexanoic acid freshly prepared	100–144 (m.p. 219)	100–145	0·39	
Hexanoic acid 18 days	99–159 (m.p. 219)	70–118	1·50	
Heptanoic acid freshly prepared	78–134 (m.p. 219)	81–125	0·30	
Heptanoic acid 14 days	37–162 (m.p. 219)	35–147	0·81	
Octanoic acid freshly prepared	66–162 (m.p. 219)	76–164	0·57	
Octanoic acid 9 days	78–144 (m.p. 219)	83–147	0·30	
Nonanoic acid freshly prepared	71–164 (m.p. 219)	105–181	0·20	
Nonanoic acid 7 days	70–170 (m.p. 219)	104–180	0·22	

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