

FATTY ACID SOLVATES OF GRISEOFULVIN

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The ability of a drug to form solvates can greatly increase the number of available possibilities for modifying and controlling bioavailability, dissolution rate, stability and processing (see Haleblan, 1975). The present communication reports the preparation and properties of some fatty acid solvates of the valuable antifungal agent, griseofulvin.

Griseofulvin was crystallised slowly from each liquid *n*-alkanoic acid from C₁ to C₉, by dissolving the solid in hot acid and allowing the mixture to cool slowly to 20°C. The properties of the solid phases obtained are summarised in Table 1. For all solids except that from propanoic acid hot stage microscopy (HSM) of the solid dispersed in silicone oil showed desolvation at temperatures below both the boiling point of the solvent and the melting point of the original griseofulvin. Thus, only propanoic acid does not form a solvate. Spontaneous desolvation of each solvate took place slowly on standing in a vessel open to the atmosphere but was prevented by the presence of a little excess acid in a closed container. On heating, desolvation occurred with decreasing rapidity on ascending the homologous series. The solid obtained in each case was the original unsolvated form of griseofulvin (X-ray data) melting at 220-224°C (HSM, DTA). X-ray powder diffraction indicated that the solvates were new solid phases different from pure griseofulvin. The diffraction patterns of the solvates of the acids C₁, C₂, C₄-C₆ appeared crystalline and those of the acids C₇-C₉ appeared amorphous.

Table 1 strongly suggests that each solvate belongs to one of two types. The solvates of type I closely resemble the griseofulvin, chloroform (1:1) solvate in their physico-chemical properties. (Sekiguchi & others, 1964; Shefter & Srikrishnan, 1979) whereas those of type II resemble the griseofulvin, benzene (1:2) and the griseofulvin, dioxane (2:1) solvates (Sekiguchi & others, 1976). For the type I solvates, the initial desolvation step and DTA peak corresponded to loss of free solvent, whereas the second corresponded to the stoichiometric loss of 1 mole of solvent from the crystal lattice. Attempts to determine the mole ratio of the type II solvates led to variable or uncertain results and it is tentatively proposed that they are inclusion compounds. It is suggested that hydrogen bonding governs the properties of the type I solvates whereas van der Waals forces are mainly involved in the type II solvates. If griseofulvin is required in the form of a solvate or inclusion compound, it is proposed that the fatty acid solvates be scrutinized on account of the low-toxicity of the solvents. Table 1. General properties of the *n*-alkanoic acid solvates of griseofulvin.

Fatty acid	C ₁ , C ₂	C ₃	C ₄ -C ₉
thermogravimetric analysis steps	2	0	1
differential thermal analysis peaks	3	1	2
	(final one due to melting 220-224°C)		
transparency on standing	lost	retained	retained
<u>moles acid</u>	1	0	variable
<u>moles griseofulvin</u>			0.2 to 1.5
solvate type	Type I	None	Type II

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