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Drug–polyvinylpyrrolidone (PVP) dispersions. A differential scanning calorimetric study

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Numerous workers have shown that dispersing a drug in polyvinylpyrrolidone will markedly enhance the drug's dissolution rate (e.g. Chiou and Riegelman, 1971; Resetarits et al., 1979; Simonelli et al., 1969; Corrigan and Timoney, 1975). A maximum enhancement of drug dissolution is found when the ratio of drug to polymer in these systems is low. It has been proposed that the increased drug dissolution rate is a result of its presence as a high energy form when the ratio is low, possibly in a non-crystalline state (Simonelli et al., 1976). To date, investigations of these dispersions have not provided definitive information regarding the state of the drug in them. In an effort to shed more light on the nature of the drug in PVP dispersions, studies have been initiated to examine these systems by differential scanning calorimetry (DSC) and X-ray powder diffractometry (XRD). This is a preliminary report on some of our observations.

Dispersions were prepared by the solvent method (Chiou and Riegelman, 1971) using PVP with an average molecular weight of 40,000 (Plasdone K-29-32, GAF, N.Y.). Appropriate amounts of the organic compound to be dispersed – cholesterol (mp. 144°C), methyl-*p*-hydroxybenzoate (mp. 130°C), methyl-*p*-aminobenzoate (mp. 113°C), ethyl-*p*-aminobenzoate (mp. 88°C), 4-amino antipyrene (mp. 104°C) and griseofulvin (mp. 218°C) – and PVP were dissolved in absolute alcohol (amount of alcohol varied according to solubility of drug). The solvent was removed under vacuum at room temperature. Physical mixtures were prepared by grinding the ingredients with a mortar and pestle. Thermal gravimetric analyses (Perkin Elmer TGS-2) of the samples was carried out to ensure that the amount of solvent present was minimized during preparation and storage. All samples were stored in dessicators at room temperature. No significant changes, in the parameters measured for the systems were observed on storage.

The endothermic heats associated with the melting of the crystalline compound were determined by DSC (Perkin Elmer DSC-2). Samples weighing between 5 and 10 mg were placed in aluminum pans and analyzed at scanning speeds ranging from 10 to 40°K/min. The instrument was calibrated with an Indium standard. The endothermic energy was derived by gravimetrically measuring the peak areas. Duplicate measurements were carried out on each sample and many dispersions were prepared more than once for examination.

TABLE 1

MEASURED ENDOTHERMIC HEATS FOR PVP DISPERSIONS (ESTIMATED STANDARD DEVIATIONS IN PARENTHESES)

Mass fraction of drug (f_T)	$q_0(d)$ (mcal/mg)	f_s
Cholesterol		
0.2	1.0 (0.1)	
0.4	3.6 (0.1)	
0.6	6.8 (0.1)	
0.8	9.9 (0.1)	
1.0	17.4 (0.2)	0.13
Methyl-p-hydroxybenzoate		
0.2	_ [a]	
0.4	_ [a]	
0.6	3.5 (0.4)	
0.8	16.1 (1.2)	
1.0	43.9 (0.4)	0.54
Methyl-p-aminobenzoate		
0.2	_ [a]	
0.4	1.7 (0.2)	
0.6	11.0 (0.6)	
0.8	21.0 (0.1)	
1.0	37.2 (0.3)	0.37
Methyl-p-aminobenzoate (PVP of 10,000 molecular weight)		
0.2	_ [a]	
0.4	1.9 (0.1)	
0.6	10.8 (0.3)	
0.8	22.2 (0.14)	0.37
Ethyl-p-aminobenzoate		
0.2	_ [a]	
0.4	1.0 (0.7)	
0.6	8.1 (0.9)	
0.8	18.4 (0.6)	
1.0	32.9 (0.5)	0.42
4-amino antipyrine		
0.2	_ [a]	
0.4	_ [a]	
0.6	7.2 (0.1)	
0.8	14.3 (0.4)	
1.0	23.8 (0.3)	0.43
Griseofulvin		
0.2	_ [a]	
0.4	7.5 (0.2)	
0.6	13.5 (0.3)	
0.8	19.8 (0.9)	
1.0	28.6 (0.8)	0.12

[a] Unable to discern endotherm of significant value.

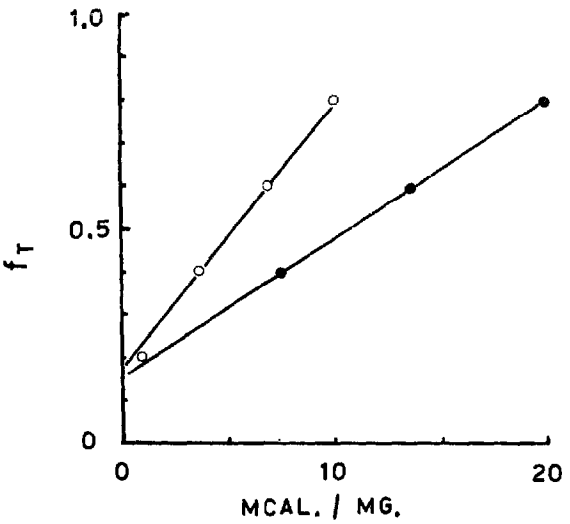

Fig. 1. Plot of mass fraction of drug in dispersion (f_T) vs measured endothermic energy ($q_0(d)$). Filled in circles are griseofulvin and open circles are cholesterol.

The measured values for the endothermic energy of the dispersions ($q_0(d)$) in millicalories per milligram of sample are listed in Table 1. It was not possible to discern an endotherm for the dispersions prepared with the lowest mass fraction of the compound (f_T). Cholesterol was an exception to this. XRD examinations (Toshiba ADG-301 diffractometer) of the dispersions showed that where no endotherm was found, the sample lacked crystallinity. On the other hand, physical mixtures made with the same proportions of materials exhibited characteristic crystalline diffraction patterns.

The apparent solubility of the various compounds in the polymer at their respective melting points can be estimated from plots of $q_0(d)$ versus f_T (Theeuwes et al., 1974). In these plots the intercept at $q_0(d)$ equal to zero is the apparent mass fraction solubility (f_s). Fig. 1 is such a plot for the cholesterol and griseofulvin dispersion data. The apparent solubilities of the various compounds obtained in this manner are presented in Table 1.

The data indicate that all the compounds examined are capable of dissolving to a certain degree in the polymer. Those compounds which are capable of participating in a hydrogen bond interaction as a proton donor gave the larger apparent solubilities in PVP. The compound with the most acidic hydrogen exhibited the greatest solubility. In this regard, it is interesting to note that the apparent solubility for methyl-*p*-hydroxybenzoate represents approximately a 1 : 1 interaction between the compound and the PVP subunit. The solubilities of the amine compounds are to a first approximation 1 : 2 interactions (drug: PVP subunit).

The influence of the polymer's molecular weight on the termal characteristics of the dispersion was examined. The apparent solubility of methyl-*p*-aminobenzoate in dispersions prepared with PVP of molecular weight 10,000 and 40,000 was similar (see Table 1).

The data indicate that PVP is able to molecularly disperse a variety of compounds in its matrix. Higher dispersibility (solubility) resides with those compounds capable of

interacting through hydrogen bonding with the pyrrolidone moiety of the polymer. It is this molecularly dispersed form of the drug in the polymer that is probably the reason for the observed higher intrinsic dissolution rate of dispersions over physical mixtures.

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