

Measuring Surface Energy, Surface Heterogeneity, and Vapor Permeability of Pharmaceutical Powders using Chromatographic, Microbalance, and Microcalorimetric Methods.

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A drug powder available as a crystalline and amorphous form were studied using Inverse Gas Chromatography (*iGC* 2000, SMS, London) to characterize their surface energies by measuring retention times at 303K using different probes at infinite dilution. Helium was the carrier gas and methane used to measure dead volume. The amorphous form shows a dispersive energy of 47.10 mJ/m² (+/- 3%) and the crystalline form 35.13 mJ/m². The result was unexpected but substantiated in heterogeneity studies where probe and flow rate are held constant and concentration is varied. All the probes indicated a homogeneous distribution of energy sites. Nonpolar probes (nonane, octane, hexane) interact more strongly with the crystalline form i.e. peak energy values are higher than those of the amorphous form. However, using polar probes (1,4-dioxane, ethanol, and ethyl acetate) the peak energy of interaction was always higher for the amorphous form. A different drug substance was used to study vapor permeability. It was amorphous. Permeability at infinite dilution in the *iGC* was studied with octane and ethanol vapor at 4 temperatures by measuring the effect of flow rate on peak height. The diffusion coefficient using the nonpolar probe was significantly higher than that using the polar probe; e.g. at 303K, D (cm²/sec) was 4.12E-5 for octane and 8.48E-6 for ethanol. The polar probe permeates more slowly probably due to greater interaction. The activation energy of permeability using octane was 25.36 kJ/mol. and 14.46 kJ/mol using ethanol. The bulk permeability of water into the amorphous powder was studied using a microbalance (DVS 1000, SMS, London) and an isothermal microcalorimeter (TAM 2277, Thermometric, Sweden). In each instrument about 10 mg of sample are allowed to equilibrate under a flowing stream of dry nitrogen. The sample is then exposed to an atmosphere of controlled water partial pressure and the change in mass is monitored in the DVS and the heat followed in the TAM. After the system equilibrates at a given relative humidity, the sample is again exposed to dry nitrogen and the rate of water removal is followed. There is a rapid increase in initial mass and in initial heat flow assumed to be a result of surface interaction. Following this there is a slow increase in mass (DVS) and a decreasing heat flow in the TAM. It can be assumed that this latter phase is a diffusion-controlled process. Fick's Law results in

$$M_t / M_a = A_t / A_a = \frac{6}{r_p} \left(\frac{Dt}{\rho} \right)^{0.5} - \frac{3Dt}{r_p^2} \text{ where } M_t \text{ and } M_a \text{ are mass at time } t \text{ and } \alpha \text{ in the DVS}$$

and A_t and A_a are the areas under the heat flow vs. time relationship at corresponding times in the TAM. r_p is the radius of the particle (9.1E-4 cm) and D is the diffusion coefficient. The equation can be least squares fit to generate a value for D. As an example, the DVS result at 298K is 1.34E-11 cm²/sec. Alternatively, the data may possibly be treated via Netzsch Thermokinetics^R.