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True density and thermal expansivity of pharmaceutical solids: comparison of methods and assessment of crystallinity

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Summary

Three methods for determining the density of solids, namely displacement of a liquid, displacement of a gas and flotation in a liquid, have been compared using adipic acid doped with various concentrations of oleic acid. The liquid displacement method is tedious and tends to underestimate the true density. Gas pycnometry is rapid, non-destructive and relatively simple to use, but requires expensive instrumentation and a large sample size, while its accuracy is limited by the relatively low precision of the volume measurements. The flotation method is much simpler in operation, is inexpensive and demonstrates the probabilistic nature of density distribution within a powder sample. Although it is more time consuming than gas pycnometry, the final density values can be accurate to four significant figures using the simplest apparatus. More elaborate set-ups increase the accuracy. The use of two or more suspending liquids in the flotation method enables the density of a given crystal to be determined at two or more temperatures and therefore provides the thermal expansivity. The crystal density at ambient temperature may be interpolated from a plot of density against temperature. The presence of traces of oleic acid in adipic acid crystals marginally lowers the density. Application of the flotation method to acetaminophen crystals shows that the presence of traces of *p*-acetoxyacetanilide increases the mean density by shifting the density distribution closer to its upper limit. Trace additives in the crystals of both adipic acid and acetaminophen change the thermal expansivity of the most dense crystals in each sample. The use of a single liquid in the flotation method, together with the assumption that the densities of crystals are independent of temperature, may hide significant effects. The results suggest that the thermal expansivity is a more reliable indicator of crystallinity than density measurements at a fixed temperature.

Introduction

Solid density is a physical property the value of which is frequently required in both fundamental and applied pharmaceutics. Thus, some common methods of evaluating solid formulations in pharmaceutics require prior knowledge of the true density of the materials being tested, for example, in the determination of tablet strength (Hiestand and Peot, 1974) and in the investigation of tablet consolidation behaviour employing the Heckel relationship (Krycer et al., 1982). Density measurements have also been used to investigate crystallinity, which expresses the degree of order present in the lattice of a solid (Hüttenrauch, 1978).

Since similar materials are often compared in pharmaceutical tests (Paronen and Juslin, 1983), and since the differences in their properties may

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be quite small, accuracy in measurements of density becomes critical. The investigation of a fundamental property, such as crystallinity, always calls for the greatest possible precision. Recently, the effects of impurities or trace additives on the physical properties of some pharmaceutical crystals have been investigated (Chow, K.Y. et al., 1984, 1985). Based on these and other findings, a novel approach to the investigation of crystalline disorder caused by foreign substances in the crystal lattice of a host, termed the disruption index, has been derived from the measurement of the entropy of fusion (York and Grant, 1985) or entropy of solution of a solid material (Grant and York, 1985). Since the approach based on entropy is proposed as an alternative to crystallinity scales based on density, it would be useful to compare the sensitivities of the two approaches to the minute changes which sometimes occur.

In theory, solid density determination should be relatively simple. The expansion coefficients of solids are usually much smaller than those of liquids or gases (Weast and Astle, 1982) and losses due to sample volatility can usually be neglected. However, although a pharmaceutical powder can be easily weighed, the determination of its volume is the critical procedure in the derivation of an accurate value for density. Many difficulties arise because of this. Using adipic acid doped with various concentrations of oleic acid, three methods of density determination have been compared, namely displacement of a liquid, displacement of a gas and flotation in a liquid. The flotation method was also applied to the study of the effect of varying amounts of *p*-acetoxyacetanilide (PAA) on the density of acetaminophen crystals.

Materials and Methods

Reagents and materials

Adipic acid (lot 732570) was supplied by Fisher Scientific, Don Mills, Ont.. Acetaminophen was supplied by Frank W. Horner, Montréal, Qué., and by McNeil Consumer Products, Guelph, Ont. PAA was prepared as described by Chow, A.H.-L. et al. (1985).

The liquid used in the displacement method of density determination was isooctane (99 mole %, Fisher, Don Mills, Ont.). The liquids used in the flotation method were 1,1,1-trichloroethane (Fisher, lot 743356, d_4^{25} 1.309 $g \cdot cm^{-3}$), 1-bromopropane (Fisher, lot 721179, d_4^{25} 1.346 $g \cdot cm^{-3}$), 1-bromobutane (Fisher, lot 734145, d_4^{25} 1.269 $g \cdot cm^{-3}$), dichloromethane (Fisher, lot 775007, d_4^{25} 1.316 $g \cdot cm^{-3}$), a mixture (d_4^{25} 1.372), of 1,1,2-trichloroethane (Fisher lot 743993, d_4^{25} 1.435 approx. 47% w/w) and dichloromethane (as above, approx. 53% w/w), a mixture (d_4^{25} 1.352) of trichloroethylene (Fisher, lot 418603, d_4^{25} 1.456 $g \cdot cm^{-3}$, approx. 26% w/w) and dichloromethane (as above, approx. 74% w/w), and a mixture (d_4^{25} 1.291 $g \cdot cm^{-3}$) of dichloromethane (as above, approx. 47% w/w) and 1-bromobutane (as above, approx. 53% w/w). The pycnometers were calibrated with water which had been double-distilled in glass.

Sample preparation

According to the method described by Chow, K.Y. et al. (1984), adipic acid was crystallized containing a trace additive, oleic acid, at various mole fractions (0, 3.86×10^{-4} and 16.3×10^{-4}, designated as O-0, O-4, and O-16, respectively). It has been shown that a higher proportion of the oleic acid is concentrated on the crystal surfaces than in the crystal bulk (Chow, K.Y. et al., 1985). Since oleic acid is quite soluble in the liquids employed in the flotation and displacement methods, the crystals used in these tests were previously washed with chloroform to remove the surface layer. Had it been allowed to remain on the crystal surfaces, its subsequent dissolution might produce error. The same particle sieve fraction (425–850 μm, 35–20 mesh) was employed for each series of tests. A range of particle sizes was always present in each sample.

Acetaminophen was crystallized from water containing various concentrations of PAA and dried, as described by Chow, A.H.-L. et al. (1985). The initial concentrations of PAA in the crystallization solutions were 0, 50 and 500 $mg \cdot dm^{-3}$ and a constant particle sieve fraction (335–500 μm, 40–32 mesh) was employed.

Liquid displacement method

A 50 cm^3 Pyrex pycnometer was equipped with a thermometer which was calibrated against a

thermometer that fulfilled NBS specifications (Ertco 49223). The volume of the pycnometer was calibrated with water for which very accurate values of the density are known (Weast and Astle, 1982), and this enables the absolute densities of the solids to be calculated. The displacement liquid, iso-octane, was chosen since it dissolves adipic acid to a very limited extent (24.2 $mg \cdot dm^{-3}$ at 25°C). The isooctane was saturated with adipic acid at 25°C to avoid error due to dissolution of the crystals after immersion. The following successive weighings were performed on a Mettler balance (model number 1-911): pycnometer + air, pycnometer + sample + air, pycnometer + sample + immersion liquid, and pycnometer + immersion liquid. Sample density was calculated from these values according to established procedures (Bauer and Lewin, 1972). After about half of the immersion liquid had been added to the solid sample in the pycnometer, the mixture was evacuated for varying periods of time under a bell jar at 8 kPa (60 mm Hg) to remove trapped air from the system. The sample was intermittently agitated to help dislodge the bubbles of air.

Gas displacement pycnometry

The simple relationship between volume, pressure and temperature for an ideal gas, which is displaced by the solid, provides a quick, non-destructive means of measuring powder density. An accurately weighed sample (ca. 5 g) of either pure or doped adipic acid crystals was placed in the sample cell of a Quantachrome Stereopycnometer (Quantachrome Corp., Syosset, NY). The cell was then evacuated to remove any physically-adsorbed gases. The displacing gas, either nitrogen or helium, was then admitted into the sample cell under pressure, P_1, which was recorded. By opening a valve the gas was allowed to expand into a chamber, of known volume, V_a, and after thermal equilibration, the new pressure, P_2, was recorded. The procedure was repeated with each sample until the ratio, P_1/P_2, did not vary by more than 0.1% for three consecutive pressurizations.

The density of the solid sample may be calculated using Eqn. 1

$$V_s = V_c - \frac{V_a}{(P_1/P_2 - 1)} \qquad (1)$$

where V_s = volume of the sample, V_c = volume of the sample cell, V_a = additional volume for expansion, P_1 = initial pressure, P_2 = final pressure. This equation assumes that the temperature remains constant. Since the gas expands from P_1 to P_2 in an almost adiabatic manner, temperature equilibration is necessary before and after the measurement of these pressures.

Properties of the flotation liquids and operation of the flotation method

The choice of the flotation liquid is critical. The solid and liquid should have similar densities but will generally possess different thermal expansivities (expansion coefficients), so that a small variation in temperature will cause them to exhibit the same density at a specific temperature. The liquid should dissolve very little of the solid and should exhibit a low surface free energy so that it may easily wet the solid. Suitable liquids are restricted almost entirely to the paraffins or halogenated paraffins. Bromoparaffins were sometimes found to promote recrystallization if the temperature was allowed to vary more than 40°C due to their greater solvency; however, this effect was negligible using 1-bromopropane or 1-bromobutane with the solids under investigation and the temperature ranges employed in the present work. Iodoparaffins were not used owing to their even greater polarizability and hence greater solvency and greater sensitivity to photolysis. Chloroparaffins were preferred because they suffered minimally from the above disadvantages. Fluoroparaffins, fluorochloroparaffins and perfluorocarbons may also be suitable but were not used in the present work owing to their lesser availability. Compounds or mixtures of suitable density were chosen with the help of Beilstein (1941). When possible, pure liquids were used in preference to defined mixtures, since the components of a mixture of two or more liquids may evaporate at different rates, resulting in a change of density of the mixture.

A calibration curve of density against temperature for each liquid or mixture was prepared using the pycnometer described above. For this purpose each liquid was saturated at progressively increasing temperatures with the solid under study, placed in the pycnometer, equilibrated at the final tem-

TABLE 1

PARAMETERS FOR THE LINEAR APPROXIMATION OF THE RELATIONSHIP BETWEEN DENSITY AND TEMPERATURE FOR THE LIQUIDS EMPLOYED IN THE FLOTATION METHOD OF SOLID DENSITY DETERMINATION

Flotation liquid	Correlation coefficient	Residual standard deviation ($g \cdot cm^{-3}$)	Intercept (density, $g \cdot cm^{-3}$ at 273.15 K)	Density ($g \cdot cm^{-3}$ at 298.15 K)	Slope $\times 10^3$ ($g \cdot cm^{-3} \cdot K^{-1}$)	Thermal expansivity (kK^{-1}) at 298.15 K
1-Bromobutane	0.9982	0.0005	1.3051	1.2686	−1.4528	1.1452
1,1,1-Trichloroethane	0.9984	0.0002	1.3495	1.3092	−1.6040	1.2252
Dichloromethane	0.9989	0.0002	1.3632	1.3162	−1.8662	1.4179
1-Bromopropane	0.9991	0.0001	1.3842	1.3463	−1.5077	1.1199
Dichloromethane + 1,1,2-Trichloroethane	0.9981	0.0002	1.4141	1.3722	−1.6667	1.2146
Trichloroethylene + Dichloromethane	0.9995	0.0001	1.3984	1.3517	−1.8573	1.3740
Dichloromethane + 1-Bromobutane	0.9999	0.0001	1.3320	1.2908	−1.6380	1.2690

perature of interest and weighed. Three runs were performed for each liquid and the procedure was repeated with water. Equations describing the relationship between density and temperature for the saturated liquids were calculated (Table 1) with the use of linear regression. The density–temperature relationships of the flotation liquids (Fig. 1) were found to be virtually linear, an approximation which was found to be statistically acceptable within the range of error and temperatures employed. Evaluation of the residuals indicated that the curves were indistinguishable from straight lines. In one case extrapolation by 8°C was necessary and the maximum error was ± 0.0007 g · cm $^{-3}$ (> 95% confidence). The reliability of this extrapolation was checked by comparison with literature values (Beilstein, 1941). In every other case interpolation was possible and the largest confidence interval was ± 0.0004 g · cm $^{-3}$ (> 95% confidence). Although varying the concentration of additives in the adipic acid and acetaminophen crystals may change the solubility of the crystals in the flotation liquids, it was found that this was not significant in the calculation of the density versus temperature curves for the flotation liquids.

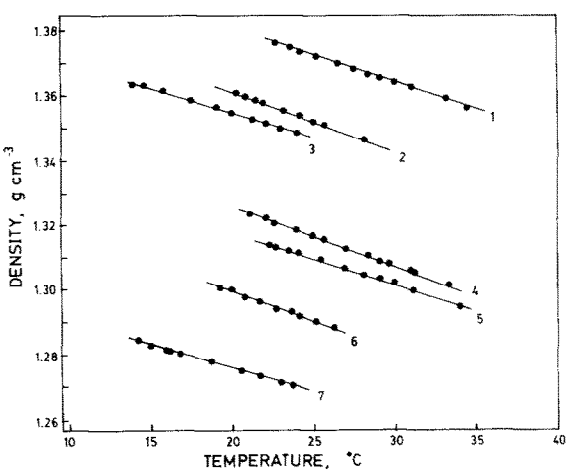

Fig. 1. Calibration curves of density against temperature for the following flotation liquids and mixtures saturated with adipic acid (*) or acetaminophen (†): 1,1,2-trichloroethane plus dichloromethane * (1); trichloroethylene plus dichloromethane * (2); 1-bromopropane * (3); dichloromethane † (4); 1,1,1-trichloroethane † (5); dichloromethane plus 1-bromobutane † (6); and 1-bromobutane † (7).

Approximately 20–40 crystals of a given sample were placed in an appropriate saturated liquid whose density was close to that of the crystals. The temperature was chosen so that all, or most, of the crystals sank in the liquid. The samples were initially evacuated for 30 min, but it was found that evacuation had no significant effect on the derived density values. The temperature of this suspension was then increased by at most 5°C in a water bath until no more than 1 crystal remained floating. The density of the liquid at this temperature was the same as that determined during the calibration procedure. Subsequently, the temperature was al-

lowed to fall at a maximum rate of 0.3°C/min. This was sufficiently slow to minimize movement of the crystals by convection within the liquid. The temperature at which the solid became suspended in the liquid was taken to be that at which the solid and liquid had the same density (Andrae, 1889). The temperature was also varied in the opposite direction over the restricted range of maximum crystal density. This value was found to be independent of the direction of temperature variation. Repeated heating and cooling had no significant effect on the apparent densities of the crystals. The temperature was measured with a thermometer which was graduated in 0.1°C and which was immersed in the flotation liquid.

Results and Discussion

Liquid displacement method

Initially, the time of evacuation was held constant to ensure similar treatment of all the samples. Without agitation during evacuation, the density values obtained by this method (O-0, 1.319 $g \cdot cm^{-3}$; O-4, 1.339 $g \cdot cm^{-3}$; O-16, 1.348 g cm^{-3}) were much lower than the literature value of 1.360 $g \cdot cm^{-3}$ (Buckingham, 1982). Although no further spontaneous evolution of bubbles was apparent after this initial evacuation time, tapping of the bell jar caused a sudden evolution of bubbles in some of the samples. Accordingly, evacuation was repeated with intermittent agitation until no further increase in the apparent density of the samples was observed. The final densities of the samples (Table 2) were much closer to the literature value. The air was probably physically trapped by the crystal heap, and not simply adsorbed onto the crystal surfaces, since the problem was not observed with the flotation method. This phenomenon may be related to crystal habit, a property which is also affected by additive concentration (Chow, K.Y. et al., 1985). The length of time necessary to reach stability in the density determinations was different for each run. The densities cited above are still lower than expected, probably because complete removal of trapped air was not achieved, a confounding problem which is well recognized (Taylor, 1967).

A relatively large sample is required for each determination and the sample may suffer contamination in the process. To obtain accurate results requires great care and is very time consuming. Whether or not the evacuation process is successful depends on the material, and this uncertainty is reflected by decreased confidence in the density values obtained.

TABLE 2

COMPARISON OF THE DENSITY VALUES OF ADIPIC ACID CRYSTALS, MEASURED AT 25°C BY LIQUID DISPLACEMENT, GAS PYCNOMETRY AND FLOTATION, AND THEIR 95% CONFIDENCE INTERVALS

Method	Sample	Mole fraction of oleic acid	Density ($g \cdot cm^{-3}$)	Confidence interval (95%)
Liquid displacement	O-0	0	1.351	±0.001
	O-4	3.86×10^{-4}	1.352	±0.004
	O-16	16.3×10^{-4}	1.354	±0.001
Gas pycnometry using helium	O-0	0	1.355	+0.002
	O-4	3.86×10^{-4}	1.353	±0.002
	O-16	16.3×10^{-4}	1.350	±0.002
Gas pycnometry using nitrogen	O-0	0	1.354	±0.002
	O-4	3.86×10^{-4}	1.360	±0.007
	O-16	16.3×10^{-4}	1.362	±0.003
Flotation in a liquid	O-0	0	1.3599 [a]	±0.0004
	O-4	3.86×10^{-4}	1.3594 [a]	±0.0004
	O-16	16.3×10^{-4}	1.3595 [a]	±0.0004

[a] Maximum density, which is the density of the most dense crystals and is not representative of the whole sample.

Gas displacement pycnometry

The displacing gas of choice is helium. Its behaviour is close to ideal and its minimal interaction with other materials, as a result of its minimal polarizability, reduces any error resulting from the surface adsorption of the gas. Furthermore, its smaller molecular size facilitates pore penetration, which, if incomplete, would cause underestimation of the true density of the material. To test the influence of the displacing gas, the densities of unwashed adipic acid crystals doped with various mole fractions of oleic acid were determined using either nitrogen or helium (Table 2). The densities of pure adipic acid (O-0) determined using either gas were not significantly different statistically. However, with increasing uptake of oleic acid two different patterns emerged. With helium, there was an apparent decrease in crystal density with increasing additive concentration, although the statistical significance is marginal. With nitrogen, a significant increase in apparent crystal density was observed. This may reflect a change in the surface energy of the crystals as the surface concentration of oleic acid increases progressively.

The precision of repeated pressurizations on the same sample was high ($s = 0.0007$ g · cm^{-3} for three pressurizations). However, the variation between samples was greater (Table 2). The nominal precision of the instrument is 0.2% with a large sample size (ca. 10 g), but, realistically, 0.3% precision is expected, since powder samples may have a relatively low bulk density (ca. 0.6 g · cm^{-3}). The third decimal place is of questionable significance and, if it is stated, the error should be reported.

Flotation method and its use in evaluating thermal expansivity

The density of the crystals which began to float at the lowest temperature ('maximum' or 'terminal' density) was taken to be the closest approximation to the true crystal density at that temperature (Andrae, 1889). This assumption was supported by the fact that the distribution of crystal densities was skewed in that direction with a definite lower temperature limit, while the high temperature limit (minimum density) extends into the tail of an asymptote as shown in Fig. 4. Since the number of crystals is finite, at least one of them must exhibit a minimum density.

In the flotation method only a single liquid is commonly utilized and the thermal expansivity (i.e. coefficient of thermal expansion) of the solid is generally assumed to be insignificant in comparison with that of the liquid (Hüttenrauch, 1978). Thus, the density of the solid particle at ambient

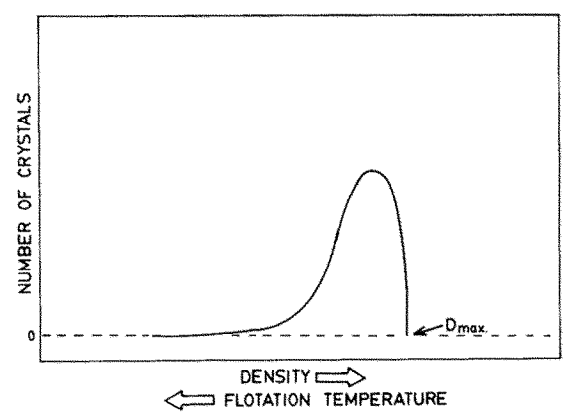

Fig. 2. Typical flotation density–distribution for crystals in a powder sample. D_{max} signifies the 'maximum' or 'terminal' density.

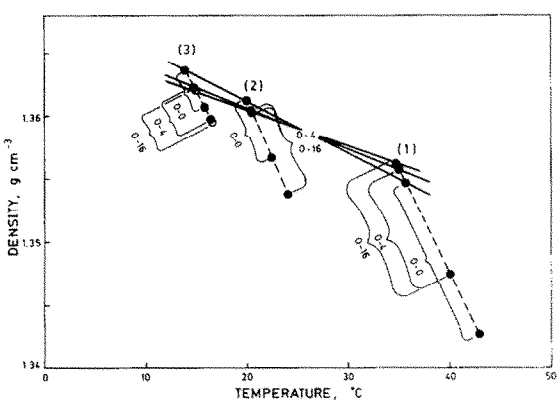

Fig. 3. Plots of the flotation density against temperature for adipic acid crystals doped with the following mole fractions of oleic acid: 0 (sample O-0), 3.86×10^{-4} (sample O-4), and 16.3×10^{-4} (sample O-16). For each sample the bracketed circles indicate the observed limits of density and temperature determined by flotation in the following liquids and mixtures (Fig. 1): 1-bromopropane (3); trichloroethylene plus dichloromethane (2); 1,1,2-trichloroethane plus dichloromethane (1). Each broken line plots the range of densities (Fig. 2) in each sample. Each full diagonal line plots the maximum density in each sample against the temperature of flotation in each of the above liquids.

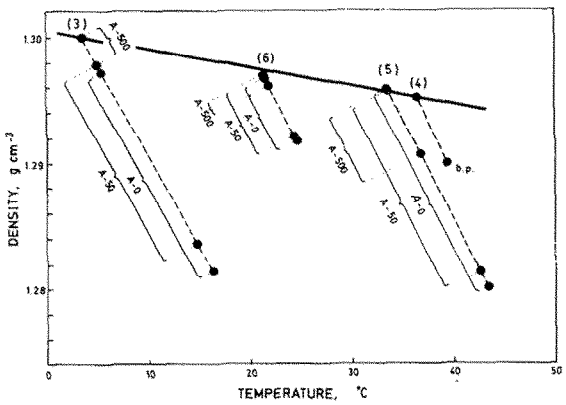

Fig. 4. Plots of the flotation density against temperature for acetaminophen crystals grown in the presence of the following concentrations of *p*-acetoxyacetanilide: 0 (sample A-0), 50 mg·dm^{-3} (sample A-50), 500 mg·dm^{-3} (sample A-500). For each sample the bracketed circles indicate the observed limits of density and temperature determined by flotation in the following liquids and mixtures (Fig. 1): 1-bromobutane (3); dichloromethane plus 1-bromobutane (6); 1,1,1-trichloroethane (5); dichloromethane (4). Each broken line plots the range of densities (Fig. 2) in each sample. In dichloromethane (4) lower density measurements were limited by its boiling point (b.p.) and all three samples gave identical results. The full diagonal line plots the maximum density in sample A-500 against the temperature of flotation in each of the above liquids.

temperature is assumed to be equal to that of the suspending liquid at the temperature of flotation. In the present work, however, we recognize that the density of a solid may change with temperature and we therefore determined the densities of the crystals in several liquids of slightly different density. Since the temperature of flotation (i.e. of equidensity) is generally different in each liquid, the thermal expansivity of the crystals may be evaluated.

Plots of the 'maximum' densities of adipic acid and acetaminophen against temperature were found to be linear (full lines in Figs. 3 and 4) and the densities at 25°C were interpolated. The values of 1.360 g·cm^{-3} and 1.296 g·cm^{-3} for pure adipic acid and acetaminophen, respectively, agree with recent values stated in the literature (1.360 g·cm^{-3}, Buckingham, 1982; 1.296 g·cm^{-3}, Haisa et al., 1974).

The broken lines in Figs. 3 and 4 show the range of densities observed in each liquid. Each of these lines has a steep slope since it corresponds to the relationship between density and temperature for the saturated flotation liquid. The results derived from Fig. 3 and 4 are recorded in Tables 3 and 4.

The (isobaric) thermal expansivity, α, is defined (McGlashan, 1971) as follows:

$$\alpha = \frac{1}{V}\left(\frac{dV}{dT}\right)_p \qquad (2)$$

where V is the (molar or specific) volume, T is the absolute temperature and the subscript p denotes that the pressure is constant (e.g. atmospheric). In

TABLE 3

EXTREME FLOTATION DENSITIES OF ADIPIC ACID CRYSTALS DOPED WITH VARIOUS MOLE FRACTIONS OF OLEIC ACID

Flotation liquid	Sample	Mole fraction of oleic acid	Upper temp. limit (°C)	Minimum density (g·cm^{-3})	Lower temp. limit (°C)	Maximum density (g·cm^{-3})
1-Bromopropane	O-0	0	15.9	1.361	14.0	1.3631
	O-4	3.86×10^{-4}	16.6	1.360	14.8	1.3619
	O-16	16.3×10^{-4}	16.4	1.360	15.0	1.3616
Trichloroethylene plus dichloromethane	O-0	0	22.5	1.356	20.5	1.3603
	O-4	3.86×10^{-4}	24.0	1.354	20.4	1.3605
	O-16	16.3×10^{-4}	24.0	1.354	20.4	1.3605
1,1,2-Trichloroethane plus dichloromethane	O-0	0	42.9	1.343	35.6	1.3548
	O-4	3.86×10^{-4}	40.0	1.347	35.0	1.3558
	O-16	16.3×10^{-4}	40.0	1.347	34.7	1.3563

TABLE 4

EXTREME FLOTATION DENSITIES OF ACETAMINOPHEN CRYSTALS DOPED WITH VARIOUS MOLE FRACTIONS OF *p*-ACETOXYACETANILIDE (PAA)

Flotation liquid	Sample	Concentration of PAA in aqueous crystallization solution ($mg \cdot dm^{-3}$)	Upper temp. limit (°C)	Minimum density ($g \cdot cm^{-3}$)	Lower temp. limit (°C)	Maximum density ($g \cdot cm^{-3}$)
1-Bromobutane	A-0	0	16.2	1.282	5.5	1.2971
	A-50	50	14.8	1.284	4.9	1.2980
	A-500	500	5.5	1.297	3.5	1.3000
1,1,1-Trichloroethane	A-0	0	43.3	1.280	33.5	1.2958
	A-50	50	42.5	1.281	33.6	1.2956
	A-500	500	36.7	1.292	33.5	1.2958
Dichloromethane	A-0	0	–	–	36.5	1.2951
	A-50	50	–	–	36.5	1.2951
	A-500	500	–	–	36.5	1.2951
Dichloromethane plus 1-bromobutane	A-0	0	24.5	1.291	21.6	1.2966
	A-50	50	24.3	1.291	21.4	1.2969
	A-500	500	21.9	1.296	21.4	1.2969

terms of density, D, Eqn. 2 becomes

$$\alpha = -\frac{1}{D}\left(\frac{dD}{dT}\right)_p \qquad (3)$$

The thermal expansivity, α, may be calculated from the slope of the plot of D against T (or T − 273.15, i.e. in °C) and from D at the temperature of interest in the appropriate liquid. For example, using plots of the data in Fig. 3, we find at 25°C that α is 2.9×10^{-4} K^{-1} for pure adipic acid, but progressively decreases with increasing mole fraction of oleic acid in the crystals, thus α is 2.4×10^{-4} K^{-1} for O-4 and α is 2.1×10^{-4} K^{-1} for O-16.

Within the temperature range studied the relationship between the maximum density and the temperature was curvilinear for pure acetaminophen, but became more linear with increasing concentration of PAA and was essentially linear for acetaminophen grown with 500 $mg \cdot dm^{-3}$ PAA. The thermal expansivity was 1.0×10^{-4} K^{-1} for the latter sample. In general, the linear relationship between density and temperature is a good approximation over moderate temperature ranges. The values of α obtained in the present work are of the same order of magnitude as those of other materials determined by other methods (e.g. Andrae, 1889; Hodgman et al., 1961).

In the samples of adipic acid crystals (Table 3) increasing concentration of additive tended to skew the distribution to a lower density but did not significantly alter the range of densities observed. For acetaminophen the effect of increasing additive concentration on the distribution of crystal densities was more pronounced (Table 4). The range of densities observed became much smaller and was shifted to higher values. The effect of PAA on the range and terminal densities of acetaminophen may arise from a decreased crystallization rate and a greater degree of perfection of the crystals. The fact that the water content of the crystals decreases with increasing additive concentration supports this idea (Chow, A.H.-L. et al., 1985). PAA may actually alter the expansion coefficient of acetaminophen crystals in a manner similar to oleic acid in adipic acid crystals, but the effect may be hidden by the greater changes in crystallization rate and water content of the crystals.

Comparison of the relative merits of various methods of density determination

Table 2 provides a quantitative comparison.

The liquid displacement method is tedious and persistent uncertainties render it problematic for routine use. If the mean density of the particles of a solid sample is required, gas pycnometry, employing helium, seems to be the method of choice, provided that the precision of the method is found to be acceptable. It is rapid and non-destructive. The requirement of relatively large samples may be a drawback in the study of materials which are expensive or difficult to produce.

The flotation method is simple, accurate and inexpensive. Five significant figures may be obtained by the use of more extensive instrumentation (Bauer and Lewin, 1972) but are seldom called for in pharmaceutical applications. Although this method seems better suited to the study of density distribution, the median densities of several samples appear to approximate fairly well to their mean densities. If a large spread is observed, or if a more accurate estimation of the mean is required, the crystals can be separated into density fractions, weighed and a weighted mean calculated. In general, the flotation method has the added advantage of enabling crystals of different densities to be separated for further studies, and this is currently being explored and exploited.

Density and thermal expansivity as measures of crystallinity

It is usually assumed that crystal density decreases with increasing lattice imperfection. This may not be true if the defects involve the addition of molecules at interstitial sites. Nevertheless, based on this assumption, density measurements have formed the basis of a frequently used crystallinity scale in which the crystallinity is assumed to increase with increasing density in a linear fashion (Hüttenrauch, 1978).

The expected changes in the fractional volume however, are highly dependent on the type of material in question, and the type of defect. For example, the volume change caused by numerous line defects (dislocations) is small, since the only net volume change is at the dislocation core. Severe plastic deformation of copper, a process which greatly increases the density of dislocations, causes a fractional volume change of only 0.02% (Argon and McClintock, 1966). However, transition from the crystalline to the glassy state may cause relatively pronounced changes in density, especially with polymers. Thus, cellulose crystals possess a density of 1.588 $g \cdot cm^{-3}$, while the amorphous form possesses a density of 1.482 $g \cdot cm^{-3}$ (Hüttenrauch, 1978). In the case of impurities, the manner in which a guest molecule fits into the host lattice will affect the expected change in lattice volume. This has been explored by Chow, K.Y. et al. (1984).

Two models of crystallinity have been proposed. In the two-phase model, individual crystals are considered to be either totally amorphous or totally crystalline (USP XX/NF XV, 1980). In the single-phase model no phase differences are evident; rather, a gradual increment of crystallinity is assumed. The continuous range of densities observed in the flotation method would seem to support the second model and the conclusions of Suryanarayanan and Mitchell (1984). However, pockets of amorphous material or inclusions in a crystalline substance might also explain the findings.

With increasing uptake of oleic acid by crystals of adipic acid or of PAA by crystals of acetaminophen, the thermal expansivity decreases (Fig. 3 and 4). On the other hand, the density of the crystals may increase or decrease with increased doping depending on the temperature and may actually be unaffected by doping at a certain temperature. Therefore, thermal expensivity may be a more reliable indicator of crystallinity than density measurements at an arbitrary temperature. For example, if the density at 26°C were to be the criterion for crystallinity of adipic acid (Fig. 3), it would be incorrectly concluded that additives in solid solution exert no effect on crystallinity.

Density and thermal data as measures of crystal imperfection

The heat of fusion, heat of solution, melting point and density of a substance are useful probes, each of which provides its own restricted aspect of the changes in crystal structure caused by trace additives. When devising a crystallinity scale, it is intuitively assumed that parallel changes in a given physical property occur with increasing lattice dis-

turbance, in this case, with increasing additive concentration. Although the direction of the change in crystallinity caused by some perturbation or stress is usually the same, regardless of the crystallinity scale employed, an exact or even an approximately quantitative parallelism is usually not evident (Nakai et al., 1977; Pikal et al., 1978), nor should it be expected. Material characteristics, such as density or calorimetric data, reflect different aspects of the energy and entropy of a crystal lattice.

Thermodynamic approaches to crystallinity would seem to be simpler quantitatively than approaches based on density since interpretation of density data must take into account the mean, standard deviation, skew and perhaps even the kurtosis of the distribution of densities in a powder sample. If one type of measurement were to be used in isolation, a thermodynamic approach might be preferable. However, it would be more predictive and meaningful if that approach could be supplemented by measurements of density and thermal expansivity.

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