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The solubility parameter and fractional polarity of microcrystalline cellulose as determined by mechanical measurement

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Summary

The solubility parameter, δ, and fractional polarity, X_p, of microcrystalline cellulose have been successfully determined by mechanical measurement. Values determined by measurement of Young's modulus of elasticity and critical stress intensity factor are 24.9 and 24.4 $MPa^{1/2}$, respectively, with a fractional polarity of 0.61. The values compare favourably with those calculated from surface free energy measurements but are significantly lower than those calculated from group molar attraction constants and inverse gas chromatography. It is suggested that a value of 25.7 ± 1.4 $MPa^{1/2}$ with a fractional polarity of 0.55 ± 0.05 be taken as indicative of the typical material used in processing.

Introduction

The solubility parameter (δ) cohesive energy density (CED or δ^2) and fractional polarity (X_p) are important parameters describing solid-solid, solid-liquid and liquid-liquid interactions. Solubility parameters and polarity have been used to describe lubricant interactions in binary. (Rowe, 1988a) and ternary powder mixtures (Rowe, 1988b) and interaction of colourants with excipients (Rowe, 1989a). Similarly δ and X_p have been used to predict optimum binders in wet granulation (Rowe, 1988c, 1989b). It is therefore important that values for these parameters are known and that they are representative of the material as used in pharmaceutical processing.

For pharmaceutical materials the methods used for the determination of these parameters vary from calculation using group molar attraction constants (Martin et al., 1983), to solubility measurements in solvents of known properties (Martin and Miralles, 1982), to calculation from known relationships with surface free energies (Samaha and Naggar, 1990), to direct measurement using inverse gas chromatography (Huu Phuoc et al.,

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1986, 1987a,b). Unfortunately, the values determined do not always represent the typical material used in processing. This is especially true of inverse gas chromatography where the test materials need to be preconditioned at a temperature of 80°C for 48 h before measurement (Huu Phuoc et al., 1986, 1987a,b).

An indirect method, but one which has no such disadvantage, relies on the known interrelationships between these parameters and known mechanical properties especially tensile modulus and stress cracking (see Barton, 1983 for references). Of specific interest in this work is a recent study with a number of organic molecular solids (Roberts et al., 1991) which showed that there was a direct relationship between the Young's modulus of elasticity, E_0 (calculated by extrapolation to zero porosity of measurements made on compacted specimens of varying porosity) and the cohesive energy density (CED) of the form:

$$E_0 = 0.01699\mathrm{CED} - 2.7465 \qquad (1)$$

It is interesting to note that the gradient found by regression analysis (0.01699) is very close to that predicted by theory (0.016; Tobolsky, 1961). The intercept value was found necessary to correct for the fact that measurements were performed at room temperature.

For relationships with stress cracking the reader is referred to the work of Mai and Atkins (1976) who found that if the critical stress intensity factors (K_{IC}) of both plain and glass filled polystyrene were measured in various organic solvents a minimum occurred when the solubility parameter of the solvent equalled that of the polymer thus enabling the solubility parameter of unknown specimens to be determined.

Since such measurements as Young's modulus of elasticity and critical stress intensity factor can now be made with relative ease on pharmaceutical materials using flexure testing (Mashadi and Newton, 1987; Bassam et al., 1990; York et al., 1990; Robert et.al., 1991, 1993), it would appear logical to investigate the applicability of the above concepts to a material used extensively in pharmaceutical processing, viz. microcrystalline cellulose.

Materials and Methods

Microcrystalline cellulose (Avicel PH101, FMC Corp.) with a moisture content of 5.21% w/w (determined by thermogravimetry) was used to validate the technique since it is a well characterised material in terms of its Youngs modulus, E, and critical stress intensity factor, K_{IC}.

All solvents used (Table 1) were Analytical grade. Solubility parameters were taken from Barton (1983) and polarities were calculated from the dispersion, δ_d, component using the following equation:

$$X_p = 1 - \left[\frac{\delta_d}{\delta}\right]^2 \qquad (2)$$

Calculation of solubility parameter and polarity of cellulose

Calculations for the solubility parameter and polarity of cellulose were undertaken using the Hansen (1967) approach from tables of group molar attraction contributions (Barton, 1983) and the Fedors (1974) method for the calculation of molar volume. The partial solubility parameters are related to the total solubility parameter, δ, by Eqn 3:

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \qquad (3)$$

where δ_d is the component due to dispersion

TABLE 1

Solubility parameters and polarities of the solvents used (data taken from Barton, 1983)

No.	Solvent	Solubility parameter (MPa$^{1/2}$)	Polarity (X_p)
1	*n*-hexane	14.9	0
2	toluene	18.2	0.02
3	dichloromethane	20.3	0.20
4	butan-1-ol	23.1	0.52
5	propan-2-ol	23.5	0.55
6	acetonitrile	24.4	0.61
7	*N*,*N*-dimethylformamide	24.8	0.51
8	ethanol	26.5	0.64
9	methanol	29.6	0.74

forces, δ_p the component due to dipole interactions, and δ_h the component due to hydrogen bonding.

Young's modulus measurement

The Young's modulus of microcrystalline cellulose was measured by three point flexure using beams of various porosities as described by Roberts et al. (1991). The Young's modulus was determined using Eqn 4:

$$E = \frac{Fl^3}{4(s-d)t^3w} \tag{4}$$

where E is Young's modulus, F the applied dynamic load, l the distance between the supports (17 mm), t the thickness of the beam, w the width of the beam, s the flexure of the beam at the mid-point, and d the distortion of the rig (predetermined using a blank measurement).

The Young's modulus of the beam at zero porosity, E_0 was determined by extrapolating the measured modulus E of the beam specimens compacted to porosity P using an exponential relationship (Eqn 5), proposed by Spriggs (1961):

$$E = E_0 \exp(-bP) \tag{5}$$

where b is a constant.

Critical stress intensity factor measurement

Beams of dimensions (20 mm × 7 mm × 3.5 mm) of a porosity of approx. 3% with a sawn straight through notch were prepared and tested as described by Roberts et al. (1993), with the exception that the breaking stress of the beams was measured with both the three point bend rig and beam immersed in the various solvents in Table 1. The measurement was performed immediately after immersion to eliminate any effects of the solvent on the integrity of the beam (e.g., due to dissolution of the beam).

The critical stress intensity of the porous beams was calculated using the following equation:

$$K_{IC} = Y\frac{3Flc^{1/2}}{2wt^2} \tag{6}$$

where F is the load that caused the beam to fracture, c the crack length, l the distance between rollers (17 mm), w the width, t the thickness; Y is a function of the geometry of the specimen expressed as a polynomial of the parameter c/t (Brown and Srawley, 1966) given by Eqn 7:

$$Y = 1.93 - 3.07\left(\frac{c}{t}\right) + 14.53\left(\frac{c}{t}\right)^2 - 25.11\left(\frac{c}{t}\right)^3 + 25.8\left(\frac{c}{t}\right)^4 \tag{7}$$

Results and Discussion

Young's modulus measurement

Extrapolation of the data from measurements on beams of known porosity (Fig. 1) to zero porosity using Eqn 5 gave a value of 7.80 GPa. Substitution of this value in Eqn 1 leads to an estimation of the cohesive energy density for microcrystalline cellulose of 620.7 MPa, i.e., a solubility parameter of 24.9 MPa$^{1/2}$. This value compares favourably with that calculated with data from other workers (Table 2) using four point beam bending techniques as opposed to the three point used in this study. It is likely that the differences seen are as a result of either the variable moisture content of the material used to prepare the beam specimens or the equilibrium moisture content of the beams themselves after storage. Bassam et al. (1990), for instance, reported that their beams were stored at 20°C and 40% RH for 1 week before testing. This would mean that they would attain a moisture content of approx. 4% (calculated from standard equilibrium moisture content/humidity curves for microcrystalline cellulose). As might be expected, their measured modulus, E_0, is higher and hence the calculated solubility parameter is higher (Table 2). Using the calculated solubility parameter from group molar attraction constants (Table 3) the measured Young's modulus (using Eqn 1) would be 12.7 GPa, a value that would be ex-

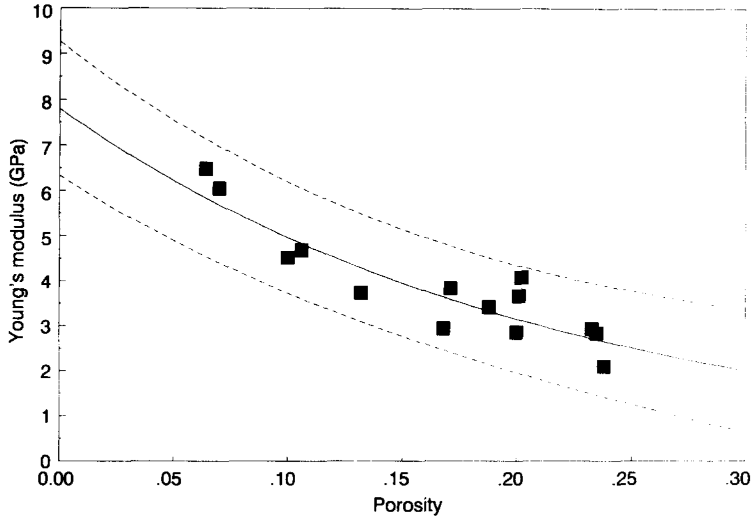


Fig. 1. The Young's modulus vs porosity for microcrystalline cellulose. Dashed line indicates 95% confidence limits and continuous line indicates best fit for the data according to Eqn 5.

pected for a dry beam of microcrystalline cellulose. This value is not unreasonable in view of the reported values of microcrystalline cellulose (Table 2).

Finally, it is interesting to note that all the values in Table 2 are significantly lower than that reported by Huu Phuoc et al. (1987a) using inverse gas chromatography. The value of 39.3 $\mathrm{MPa}^{1/2}$ measured using this technique would mean that the measured Young's modulus of elasticity would have to be of the order of 23.5 MPa comparable to that for α-lactose monohydrate (Roberts et al., 1991) but unlikely to be the case for such a soft ductile material as microcrystalline cellulose.

Critical stress intensity measurement

Figs. 2 and 3 show the measured critical stress intensity factor of microcrystalline cellulose immersed in the test solvents (Table 1). In both cases, a value of the critical stress intensity factor measured in air is included for comparison. Both sets of data show distinct minima for acetonitrile indicating that microcrystalline cellulose has a solubility parameter and polarity equivalent to that of acetonitrile, i.e., 24.4 $\mathrm{MPa}^{1/2}$ and 0.61, respectively.

It is interesting to note that with the exception of *N*,*N*-dimethylformamide in which the beam showed some slight signs of cracking, splitting and dissolution of the beam after the testing, all other solvents showed no signs of swelling or dissolution contrary to the findings of Karehill and Nystrom (1990). These workers suggested that penetration of a microcrystalline cellulose tablet by such a solvent as methanol with a high dielectric constant would cause swelling and increased incidence of capping. In this work the critical stress intensity factor measured in methanol was insignificantly different from that measured in air indicating little or no bulk interaction on the short time scale of the experiment.

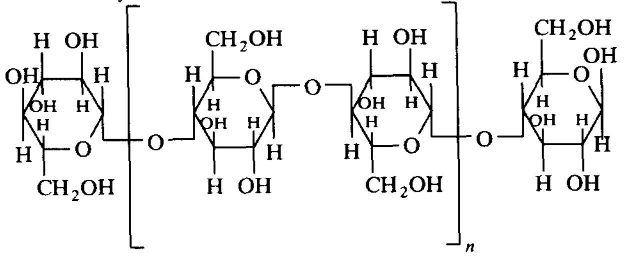
TABLE 2

The Young's modulus of Avicel PH101 from various workers and the corresponding calculated values of CED and solubility parameter using Eqn 1

Young's modulus (GPa)	CED (MPa)	δ ($\mathrm{MPa}^{1/2}$)	Reference
7.8	620.7	24.9	This work
9.2	703.1	26.5	Bassam et al. (1990)
9.7	732.6	27.1	Roberts and Rowe (1987)
10.3	787.9	27.7	Mashadi and Newton (1987)

TABLE 3

Calculation of the solubility parameters for cellulose



$n = 220$

Molecular weight of repeating unit, 324.28 g mol^{-1}; true density, 1.514 g cm^{-3}; molar volume, 214. 19 cm^3 mol^{-1}.

Group	No.	^zF_d ($J^{1/2}$ cm$^{3/2}$ mol^{-1})	$^zF_p^2$ (J cm^3 mol^{-2})	^zE_h (J mol^{-1})
$>$CH–	10	800	0	0
–CH_2–	2	540	0	0
OH	6	1260	1500000	120000
–O–	4	400	640000	12000
Ring closure	2	380	–	–
Σ		3380	2140000	132000
δ (MPa$^{1/2}$)		δ_d (MPa$^{1/2}$)	δ_p (MPa$^{1/2}$)	δ_h (MPa$^{1/2}$)
30.19		15.78	6.83	24.82
$X_p = 1 - \left[\frac{\delta_d}{\delta}\right]^2 = 0.73$				

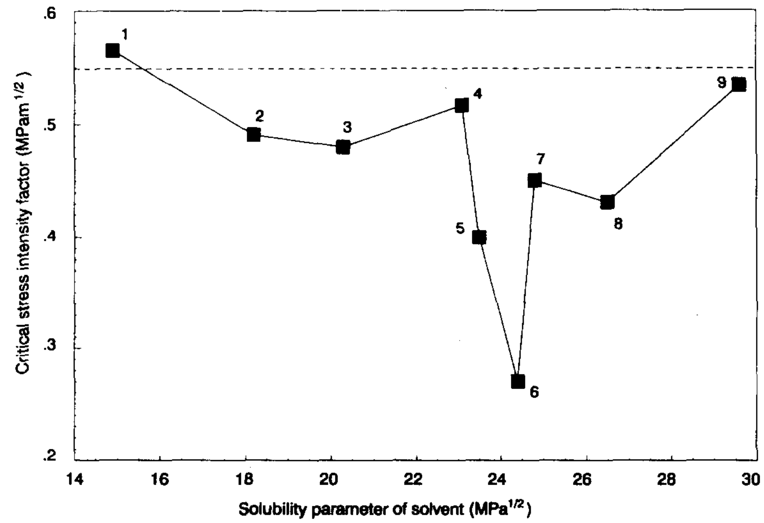


Fig. 2. The critical stress intensity factor of microcrystalline cellulose vs the solubility parameter of the solvent. Numbers refer to solvent used and are listed in Table 1.

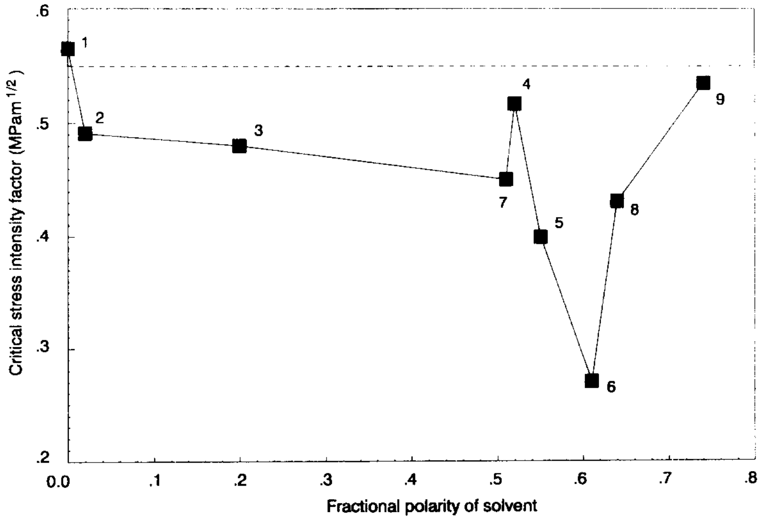


Fig. 3. The critical stress intensity factor of microcrystalline cellulose versus the fractional polarity of the solvent. Numbers refer to solvent used and are listed in Table 1.

A mechanism often quoted in grinding literature which can be applied to this system is that attributed to Rehbinder (Rehbinder effect – for the effect of chemical additives on wet grinding (Rehbinder and Kalinkovskaya, 1932)), who suggested that the adsorption of an additive on the surface of a solid lowers the cohesive force of the material. Evidence for such a mechanism has been provided by Shchukin and Yushchenko (1981), who performed molecular dynamics simulations on the role of foreign molecules on cracking. The interaction of additive molecules at the crack tip creates a force which is able to 'spread' the walls of the crack, resulting in a decrease in the surface free energy of the solid in contact with the added molecules. Similarly, the mechanism for the lowering of critical stress intensity factor (e.g., for acetonitrile) is probably due to a surface interaction with the solvent adhering to the fresh surface created during cracking thus providing an additional driving force for crack extension.

TABLE 4

Surface free energies and polarities from a number of workers and the calculated solubility parameters using Eqn 8

Surface free energy (mN m^{-1})	X_p	Reference	δ (MPa$^{1/2}$)
71.4	0.50	Zajic and Buckton (1990)	26.4
63.9	0.54	Lee and Luner (1972)	25.0
57.2	0.55	Hancock (1991)	23.6

Calculation

Calculation of the solubility parameter and fractional polarity of microcrystalline cellulose from group molar attraction constants (Table 3) results in values of 30.2 MPa$^{1/2}$ and 0.73, respectively. These are higher than determined from mechanical measurements but still lower than measured by inverse gas chromatography.

It is also possible to calculate the solubility parameter of microcrystalline cellulose from a knowledge of its surface free energy using the relationship derived by Beerbower (1971) recently shown to be applicable to a wide range of pharmaceutical solids (Samaha and Naggar, 1990):

$$\delta = \left(58.5 \frac{\lambda}{V^{1/3}}\right)^{1/2} \tag{8}$$

where λ is the surface free energy (mN m^{-1}) and V the molar volume (cm^3), giving the solubility parameter in units of MPa$^{1/2}$.

Using data on surface free energy from a number of literature sources, values for the solubility parameter of microcrystalline cellulose can be calculated (Table 4). Although the values are in good agreement with those determined from mechanical measurements, the polarities are somewhat lower.

Conclusion

A comparison of all the values of the solubility parameter of microcrystalline cellulose indicate that there is an overwhelming body of evidence to suggest that the value from inverse gas chromatography is too high. This is probably due to the nature of the available surface of the material when water is removed on conditioning the column before measurement. The mean value determined from mechanical measurement (26.1 $MPa^{1/2}$) compares favourably with that calculated from surface free energy measurements (25.0 $MPa^{1/2}$). It is suggested that a value of 25.7 ± 1.4 $MPa^{1/2}$ with a fractional polarity of 0.55 ± 0.05 be taken as indicative of the typical, material used in processing.

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