Research Article

Surface Energy of Microcrystalline Cellulose Determined by Capillary Intrusion and Inverse Gas Chromatography

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Abstract. Surface energy data for samples of microcrystalline cellulose have been obtained using two techniques: capillary intrusion and inverse gas chromatography. Ten microcrystalline cellulose materials, studied using capillary intrusion, showed significant differences in the measured surface energetics (in terms of total surface energy and the acid–base characteristics of the cellulose surface), with variations noted between the seven different manufacturers who produced the microcrystalline cellulose samples. The surface energy data from capillary intrusion was similar to data obtained using inverse gas chromatography with the column maintained at 44% relative humidity for the three samples of microcrystalline cellulose studied. This suggests that capillary intrusion may be a suitable method to study the surface energy of pharmaceutical samples.

KEY WORDS: capillary intrusion; dynamic contact angle; excipient; inverse gas chromatography; microcrystalline cellulose; surface energy.

INTRODUCTION

Surface energy measurements are frequently used in polymer sciences to investigate wettability and adhesion characteristics (1). In pharmaceutical science, and in particular pharmaceutical dosage forms, surface energy measurements have been employed, in part, to describe specific interactions such as drug adsorption, cohesion, adhesion, mucoadhesion (2,3), dispersion stability, coating performance (4) and lubricant sensitivity (5–9).

In terms of pharmaceutical formulation, it has been reported that the mixing properties of binary and ternary blends can be predicted *via* surface energy calculations (10). Such predictions are clearly of importance when preparing complex blends/granules used in tablet and capsule production. For example, during the granulation process there is evidence that the ‘spreading’ of binding agents (which occurs as a function of the surface energy of the solid and binding medium), has a significant influence on the strength of the granules, with stronger granules (more efficient intragranular binding) resulting from systems with higher spreading coefficients (11,12). Water–solid interactions, including absorp-

tion, adsorption and hydration may also be of interest for excipients designed to facilitate tablet disintegration, such as, for example, microcrystalline cellulose (MCC) and sodium starch glycolate (13–15).

Fundamentally, the surface energy of a solid can be defined as the reversible work required to form a unit area of new surface under constant temperature, pressure, mass and volume (16). This can be measured directly using techniques such as the brittle fracture method (17), however, the particulate nature of most pharmaceutical materials precludes them from such direct surface energy measurement. As an alternative, the definition that the surface energy is equal to the sum of the energy of all adsorption sites over a unit area may be exploited (18). Clearly, such a definition may be more useful than the previously described classic definition, particularly where surface energy measurements are to be used for absorption-related studies.

Historically, the interactions of solids with liquids have been investigated using contact angle goniometry. However, such a technique usually requires the solid under investigation to be a flat non-porous surface with contact angles obtained using non-reactive liquids. In general, contact angles between the extremes of non-wetting and perfect wetting ($0^\circ < \theta < 90^\circ$) are used for the indirect measurement of solid surface energies. In this region of non-spontaneous wetting, Young’s equation (Equation 1) may be used to explain the relationship between the contact angle and the three interfacial tensions:

$$\gamma_L \cos \theta = \gamma_S - \gamma_{SL} \quad (1)$$

where γ_L is the air–liquid interfacial tension (liquid surface tension), γ_S is the air–solid interfacial tension (solid surface tension) and γ_{SL} is the solid–liquid interfacial tension. There-

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fore, the contact angle is a function of the surface energies of the solid and the liquid and, importantly, the nature of the surrounding medium.

Several methods for calculating the total surface energy and the respective contributions of polar and disperse components to the total surface energy of a solid have been published (19,20). However, the generally preferred method, also used in this study, is based on the acid–base approach (1), since it has been shown to produce results with improved internal consistency compared with equation of state methods (21).

The specific surface energy of a solid may be calculated from contact angle measurements using liquids which exhibit different and known polar and disperse components. The dynamics between the specific interactions produce a stable surface contact angle between the surface and the liquid which can be attributed to a composite of the dispersive (Lifschitz-van der Waals, γ_L^{LW}), acid–base (γ_L^{AB}) and individual positive and negative polar (γ_L^+ , γ_L^-) components of the solid's surface energy and the surface tension of the liquid.

As previously stated, contact angle goniometry usually requires the solid under investigation to be a flat non-porous surface. Although compacts of powders have been used for contact angle measurements (22), the general utility of compacts for surface contact angle measurements is questionable since a certain level of surface roughness must be expected, complicating angle measurement. Furthermore, for many powder compacts, the contact angle measurements may be complicated by the action of surface-accessible pores, thereby decreasing the droplet volume by capillary action during measurement. In addition, the compaction of powder particulates may affect the material solid state, for example *via* pressure-induced crystallography changes (23) or inducing material anisotropy, for example in compacted MCC (24), leading to orientation-specific results after compaction. In part, such observations have been confirmed *via* variation in the surface energy properties as a function of compaction force (25,26).

To address the potential 'pitfalls' that exist in measuring surface energy values from compacted particulates, alternative methods of measuring the surface energy of uncompacted systems must be developed. Two of the most common methods are capillary intrusion of liquid analytes into the powder sample and analyte adsorption onto a powder bed at infinite dilution using inverse gas chromatography (IGC). Each approach will be discussed in more detail below.

Capillary Intrusion

The mathematical calculations of surface energies from contact angle data can be applied to the capillary intrusion (CI) method, where a powder column is assumed to be analogous to a packed column of capillaries, and may be used as an alternative to the direct measurement of contact angles of powders (27). The spontaneous filling of a void by a liquid is due to capillary forces. Consequently, contact angles may be determined *via* the rate of liquid uptake through such capillary action in porous monolithic samples. In simple terms, the measurement of the liquid uptake rate relates to

contact angle *via* the Washburn equation for the spontaneous uptake of liquid due to capillary action:

$$t = Am^2 \quad (2)$$

where t is time, m is the mass of liquid adsorbed and A is a constant:

$$A = \frac{\eta}{c\rho^2\gamma\cos\theta} \quad (3)$$

where h is the viscosity of the liquid, c is the material constant, ρ is the density of the liquid, γ is the surface tension and θ is the contact angle. The material constant, c , is dependent on the porous architecture of the sample. The two equations above may be combined and rearranged to give:

$$\cos\theta = \frac{m^2}{t} \frac{\eta}{\rho^2\gamma c} \quad (4)$$

Therefore, by experimentally monitoring m^2/t for liquid uptake, the sample contact angle for a liquid can be obtained. The value of c , however, remains unknown and may be determined for a reproducible sample using a liquid with a contact angle of 0° ($\cos\theta=1$). For materials with surface energies $> 30 \text{ mJ/m}^2$, n -hexane ($\sigma=18.4 \text{ mJ/m}^2$) may be used to determine the value of c . For free-flowing powders suitable powder columns may be achieved by controlled tapping of the loaded sample holder, provided that the initial loading is carried out reproducibly (28).

Several liquids are suitable for this type of study, but four liquids are commonly used. Water, ethylene glycol and n -hexane are readily available liquids with known acid–base and dispersive surface tension components while diiodomethane may be used to determine the dispersive contribution of the solid surface energy, since it possesses negligible acid–base character and a high surface energy (50.8 mJ/m^2) (29). The procedure by which contact angle data are used to obtain the individual components of the surface free energy using the acid/base approach have been described in detail elsewhere and will not be repeated here (1,30,31).

Inverse Gas Chromatography

Solid surface energetics may be investigated by the measurement of the retention volumes of non-polar (n -alkanes) and polar probes (*e.g.* ethanol, acetone) after passing through a packed column of the material under investigation. For a minimum amount of probe vapour (infinite dilution), the apparent retention time in the column is a function not only of carrier gas flow rate, but also of the degree of interaction between the probe vapour and the powder column. Therefore, the surface energy of a solid can be linked to the retention volume of a probe by (32):

$$RT\ln V_R = 2N_A(\gamma_s^d)^{1/2}a(\gamma_L^d)^{1/2} + C \quad (5)$$

where R and T are the gas constant and absolute temperature respectively, V_R is the retention volume, a is surface area of the probe molecule in the adsorbed state and γ_s^d and γ_L^d are the dispersive components of the surface energies of the solid and liquid, respectively. Consequently, the slope of a linear plot of a

Fig. 1. Example of raw data obtained from IGC experiments using Emcocel HD90 as stationary phase. The alkane series (filled) are used to calculate the dispersive component of the solid surface energy. The energies of specific interactions of polar probes (unfilled) are calculated with reference to the alkane baseline

$(\gamma_L^d)^{1/2}$ against $RT\ln V_R$, obtained using *n*-alkanes may be used to obtain the non-polar contribution of the solid surface energy (γ_s^d), an example of which is shown in Fig. 1.

Specific interactions (e.g. acid–base) can be examined using suitable probes, with the deviation of the measured $RT\ln V_R$ from the alkane baseline giving the Gibb's free energy of the acid–base contribution to the total surface energy. An example of this is given in Fig. 1 for 1, 4-dioxane. The abscissa of 1, 4-dioxane is positioned on the basis of the molecular area of the probe, so that the 'drop-down' to the alkane baseline from the γ_L^d value can be made. The Gibb's free energy of the acid–base contribution to the surface energy of the probe is the difference between the total surface energy and the projected γ_L^d from the alkane baseline.

The standard method used to determine surface energy properties from IGC measurements is based on the concept of donor and acceptor numbers (33). Liquids are characterised as Lewis bases (electron donors) or Lewis acids (electron acceptors) and the donor number and 'corrected acceptor number' (DN and AN*, respectively) are used to calculate the acid and basic parameters of the solid by referencing published values of DN and AN* of the probe solvents:

$$\Delta G_{abs}^{AB} = K_A \cdot DN + K_D \cdot AN^* \quad (6)$$

where K_A and K_D are the acceptor and donor parameters, respectively, measurements of the acidic and basic characteristics of the solid. Equation 6 can be rearranged to give:

$$\frac{\Delta G_{abs}^{AB}}{AN^*} = \left(\frac{DN}{AN^*} \right) \cdot K_A + K_D \quad (7)$$

Hence, a linear plot of ΔG_{abs}^{AB} against DN/AN* will yield values for K_A and K_D .

The DN value is the energy of a co-ordinate bond between a donor atom and the antimony atom of $SbCl_3$ (33), while the values of AN* (34) are derived from the relative chemical shift of the in the ^{31}P nuclear magnetic resonance spectrum of Et_3PO when dissolved in the acid species of

interest. Although AN* is normally a dimensionless quantity, it may be converted to an energy per mole value using the DN number for Et_3PO of 167.4 kJ/mol.

The values for the specific interactions (DN and AN*) are expressed in J/mol, whereas surface energy data are normally expressed in J/m² (or the equivalent N/m). In order to harmonise the surface energy data units, the specific surface area of the probe molecules used in IGC measurements of surface area must be known (35).

MATERIALS AND METHODS

Materials

Microcrystalline cellulose samples used throughout the study and are detailed in Table 1. All samples were used as supplied. For the CI experiments, water was purified by reverse osmosis and ultrafiltration (MilliQ grade, Millipore, Watford, UK). Diiodomethane and ethylene glycol was supplied by Aldrich (Gillingham, UK), while *n*-hexane was supplied by Fisher (Loughborough, UK). All physical and surface tension data, except those determined here, were from the literature (36–38) and are summarised in Table 2. Solvents used for IGC measurements were: *n*-hexane, *n*-heptane, *n*-octane, *n*-nonane, *n*-decane, acetone, 1,4-dioxane, dichloromethane and ethanol (Fisher, Loughborough, UK). Surface areas, surface tension and donor/acceptor data required were obtained from the literature and are shown in Table 3 (33,34,39). All solvents used throughout the investigation were of at least analytical grade.

Methods

Physico-chemical characteristics of the MCC samples

The surface area of each MCC was determined by 5-point BET N₂ adsorption (Gemini 2360, Micromeritics, Dunstable, UK) in triplicate at 77 K. Samples were dried at 40°C to constant mass (typically 16 hours) under a stream of dry nitrogen prior to analysis. This drying regime was confirmed by monitoring the sample mass over drying periods of 1 to 24 hours.

Table 1. Summary of the Microcrystalline Cellulose (MCC) Samples Used in this Study for the Determination of Surface Energy by Capillary Intrusion

MCC	Batch	Supplier	Country
Ankit	n/a	Ankit	India
Avicel PH101	6902C	FMC Inc.	USA
Ceolus KG-802	H0134	Asahi Kasei Corp.	Japan
Emcocel 50M	E5D8C17X	Penwest Co.	USA
Emcocel HD90	HD9B5K3X	Penwest Co.	USA
Emcocel SP15	SPD7C01X	Penwest Co.	USA
Pharmacel 101	90971	DMV International	The Netherlands
Prosolv 50 ⁱ	P5B7D26X	Penwest Co.	USA
Tabulose 101	113/99	Blanver Ltda.	Brazil
Vivapur 101	5610193529	J. Rettenmeier GmbH	Germany

ⁱ Silicified MCC, silicon dioxide co-spray dried with MCC.

Table 2. Summary of Relevant Physical Data and Surface Tension Parameters for the Five Liquids Used in the Determination of Microcrystalline Cellulose Surface Energy by Capillary Intrusion

Liquid	Density (kg/m ³)	Viscosity (mPas)	γ_L (mJ/m ²)	γ_L^{LW} (mJ/m ²)	γ_L^+ (mJ/m ²)	γ_L^- (mJ/m ²)	γ_L^{AB} (mJ/m ²)
<i>n</i> -hexane	659	0.31	18.4	18.4	0	0	0
Ethylene glycol	1113	15.4	48.0	29.0	1.9	47.0	19.0
Diiodomethane	3325	2.6	50.8	50.8	0	0	0
Water	1000	1.00	72.3	21.8	25.5	25.5	51.0

All data reported at 20°C. Density and viscosity measured independently. Surface tension parameters from references (53–55).

Capillary intrusion

Prior to CI surface energy measurement, the physical properties of the analyte probes were determined in terms of density and viscosity. Liquid densities were determined in triplicate using individually calibrated 25 ml density bottles (Grade A, Fisher, Loughborough) at 20°C. Viscosity was determined using cone and plate geometry with a controlled stress rheometer (CSL, TA Instruments, Leatherhead, UK) at 20°C. Newtonian behaviour is normally assumed for the liquids used in CI measurements, since the variable solvent front velocity for non-Newtonian liquids cannot readily be incorporated into the model used to link solvent front velocity to contact angles. The assumption of Newtonian behaviour was shown to be valid for all solvents over the strain rate range 1 to 200 /s, approximately the strain rate range under which the intrusion occurs.

Although liquid surface tension data (total, Lifschitz-van der Waals, positive and negative components), used during the CI experiments, were obtained from the literature, the total surface tension was monitored during experiments to ensure that no surface-active materials were introduced into the solvent either by atmospheric contamination or by leaching of soluble components from the test solids. Surface tension was determined using the rod method, whereby the maximum force required to break the contact between the liquid surface and a flat-faced rod in contact with the surface should vary by <10% throughout the series of experiments.

The rate of uptake of liquid by a packed powder column was determined gravimetrically. Powders and solvents were

stored in an air-conditioned room maintained at 20°C and 45% RH. All measurements were performed in the same room. Pyrex tubes with a porous frit (in-house designed, external diameter 13.0 mm, internal diameter 10.7 mm, length approximately 78 mm) were packed by pouring 1000±10 mg of powder into the tube and tapping using a jolting volumeter (J. Engelsmann, Ludwigshaven, Germany: 3 mm movement, 240/min) for 50 taps. Each tube was then suspended under an analytical balance (HM-120 4-figure balance, A & D Instruments, Abingdon, UK) over a bath of the liquid being used. A wide bath with a diameter of 10 cm was used to ensure the liquid level was not significantly affected by uptake of the liquid into the sample.

The bath was then raised using a laboratory jack until the bottom of the tube just contacted the liquid surface and capillary rise could be seen to have begun. The reproducibility of the *n*-hexane blank indicated that there was no error induced due to the buoyancy of the loaded tube. Raw data were collected automatically at a rate of one point per second over no more than 30 seconds of the intrusion since swelling of the MCC samples by water or ethylene glycol affects the intrusion rate higher up the powder column by restricting the capillaries at the base of the column.

Each MCC was analysed in the same tube which was used to determine the ‘*c*’ constant (Equation 4). Small variations in the diameter of the tubes were shown to affect the calculated ‘*c*’ constant, since it was found that the porous architecture of the sample was affected by the tube profile; each of the tubes yielded a different, but reproducible, ‘*c*’ constant when the rate of uptake of *n*-hexane was measured for any one batch of MCC.

Table 3. Characteristics of Probe Molecule Used for IGC Experiments

Probe	a (Å ²) ⁱ	γ_L^d (mJ/m ²) ⁱⁱ	a (γ_L^d) ^{0.5} (Jm ^{0.5} x 10 ⁻²⁰)	DN ⁱⁱⁱ	AN ⁱⁱ	Lewis characteristics
<i>n</i> -hexane	51.5	18.4	6.99	–	–	Neutral
<i>n</i> -heptane	57.0	20.3	8.12	–	–	Neutral
<i>n</i> -octane	62.8	21.3	9.17	–	–	Neutral
<i>n</i> -nonane	68.9	22.7	10.4	–	–	Neutral
<i>n</i> -decane	75.0	23.4	11.5	–	–	Neutral
acetone	34.0	16.5	4.37	17.0	2.5	Amphoteric
CH ₂ Cl ₂	24.5	24.5	3.83	0.0	3.9	Acidic
Ethanol	21.1	35.3	5.13	20.0	10.3	Amphoteric
1,4-dioxane	31.4	33.2	5.72	14.8	0.0	Basic

ⁱ Probe molecular surface area in the adsorbed state.

ⁱⁱ Liquid surface tension of probe

ⁱⁱⁱ Donor number (DN) and acceptor number (AN) of probe.

Data from literature (33,34,56).

Blank experiments ($n=5$) were conducted using each intrusion tube in order to determine the contribution of the solvent adsorbed in the frit and surface tension to the recorded mass. This value, which remains constant throughout the experiment, was subtracted from the raw data prior to plotting the curve of mass^2 against time.

Least squares linear regression analysis was used to obtain the slope for the straight part of the mass^2 against time curve. Equation 4 was used to obtain either the material constant (with *n*-hexane) or the contact angle. Equation 5 was used to obtain the Lifschitz-van der Waals component of the surface energy of the solid (γ_s^{LW}) from the contact angle of diiodomethane and the positive and negative components of the surface energy of the solid (γ_s^+ and γ_s^-) were obtained *via* acid–base theory from the contact angles of water and ethylene glycol.

Inverse gas chromatography

Inverse gas chromatography experiments were conducted at infinite dilution using a SMS IGC 2000 (SMS, London, UK), column oven maintained at a constant temperature of 303 K. All MCC samples were used as supplied. Samples were equilibrated for 12 hours at the required experimental relative humidity. Approximately 2000 mg of each MCC was loaded into glass columns (nominal internal diameter 3 mm), previously treated with dimethyldichlorosilane (BDH, Poole, UK) to passivate the glass surface. Experiments were conducted at 44% or 0% relative humidity (RH), peak detection was by flame ionisation detection. A flow rate of 10 ml/min was used throughout. The same loaded sample column was used for both the 44% RH and the 0% RH determinations, with the 44% RH experiment being completed before drying the loaded column for the study at 0% RH.

RESULTS

Capillary Intrusion

The measuring of contact angles, and subsequent determination of surface energies, using the CI method is dependent on the reproducible determination of the material constant ‘*c*’ (in Equation 4) (Table 4). The relative standard

deviation of the calculated material constant ($n=5$) was less than 6% for all MCCs, indicating good reproducibility. Reproducible material constants resulted only if the same tube was used each time for a MCC sample.

Contact angle data for the ten MCC samples investigated using the CI method are summarised in Table 4. As previously stated, the acid–base method was used to calculate the values for the components of the surface energy from the contact angle measurements.

Values for the specific components of the surface energy of the ten MCCs studied are summarised in Table 5. Analysis of the data suggests that the MCC samples have a predominantly negatively charged surface. This confirms the generally acidic nature of the MCC surface ($\text{pK}_a=4.0\text{--}4.3$), as demonstrated by the presence of titratable carboxyl groups in the surface (40). Silyl groups in the surface of the silicified MCC (Prosolv 50) would not be expected to contribute significantly to the negative part of the surface energy, because hydrophilic colloidal silicon dioxide exhibits a similar pK_a to MCC (4.4 product data sheet).

Significant positive contributions to the total surface energy were indicated from the results obtained for Emcocel HD90 and Pharmacel 101. These may be artefacts resulting from the low contact angle determined for ethylene glycol. However, previous surface energy measurements of wood suggested an amphoteric nature (31,41). Species absent in most forms of purified cellulose (e.g. lignin), but still apparent in these two products, may be responsible for the minor positive surface energy component.

ANOVA of the surface energy values calculated from the CI data for the ten MCC samples followed by Fisher’s post hoc pairwise test suggests that there is no significant difference between the dispersive components or the total surface energies of nine of the MCC samples ($p<0.05$) and that surface energy of Emcocel SP15 is significantly different to the calculated surface energies of the other nine MCCs. Furthermore, the data obtained using Emcocel SP15 as substrate and ethylene glycol (and, to a lesser extent, water) as probe were highly variable, likely a result of rapid swelling of the small particle size of this MCC grade resulting in partial closure of the pores between the particles.

In comparison, for the acid–base contributions, significant differences were observed using Fisher’s pairwise comparison

Table 4. Summary of Calculated Material Constants and Contact Angles for Diiodomethane, Ethylene Glycol and Water on Ten MCC Samples, Derived from Capillary Intrusion Experiments

MCC	Material constant ($\times 10^{-15} \text{ m}^5$)		Diiodomethane		Ethylene Glycol		Water	
	Value	SD	Angle	SD	Angle	SD	Angle	SD
Ankit	2.624	0.053	47.7°	2.0	41.3°	6.9	55.4°	3.1
Avicel PH101	4.246	0.215	46.1°	0.7	48.7°	11.9	64.3°	1.1
Ceolus KG802	4.289	0.234	46.7°	3.3	59.2°	10.8	57.5°	1.8
Emcocel 50 M	4.267	0.245	38.3°	1.4	39.1°	4.7	56.5°	1.4
Emcocel HD90	2.722	0.085	50.5°	2.4	28.4°	4.2	68.7°	5.7
Emcocel SP15	1.033	0.025	54.5°	4.6	28.6°	32.8	7.3°	5.2
Prosolv 50	2.616	0.047	36.3°	1.7	34.3°	3.8	51.4°	3.7
Pharmacel 101	3.938	0.088	50.2°	1.4	26.4°	0.9	65.7°	0.2
Tabulose 101	4.065	0.014	42.9°	0.9	38.7°	5.0	55.7°	6.5
Vivapur 101	4.239	0.165	51.1°	3.8	47.5°	2.9	65.5°	1.1

Standard deviations (SD) values calculated by error propagation for contact angles.

Table 5. Summary of Solid Surface Energy (γ_s) (mJ/m²) Determined from the Capillary Intrusion Data in Table 4 via the Acid–Base Method

MCC	Dispersive (γ_s^d)	Positive (γ_s^+)	Negative (γ_s^-)	Acid–base (γ_s^{AB})	Total (γ_s)
Ankit	35.6 (2.3)	0.1 (0.0)	29.5 (4.0)	3.8 (1.2)	39.4 (2.5)
Avicel PH101	36.4 (0.8)	0.0 (0.0)	21.3 (4.9)	1.3 (0.4)	37.7 (0.9)
Ceolus KG-802	36.1 (3.7)	0.5 (0.0)	38.4 (4.4)	8.3 (1.2)	44.4 (3.9)
Emcocel 50 M	40.5 (1.9)	0.0 (0.0)	26.1 (2.6)	2.0 (0.5)	42.4 (1.9)
Emcocel HD90	34.0 (2.5)	1.9 (0.1)	9.3 (1.7)	8.5 (1.6)	42.5 (3.0)
Emcocel SP15	31.7 (4.3)	0.2 (0.1)	76.8 (37.1)	6.9 (6.6)	38.6 (7.9)
Pharmacel 101	34.2 (1.5)	1.9 (0.0)	11.7 (0.4)	9.3 (0.3)	43.4 (1.5)
Prosolv 50	41.4 (2.2)	0.1 (0.0)	30.6 (2.5)	2.5 (1.4)	43.9 (2.7)
Tabulose 101	38.1 (1.1)	0.1 (0.1)	27.4 (2.9)	3.4 (2.1)	41.6 (2.4)
Vivapur 101	33.7 (3.9)	0.2 (0.0)	19.4 (1.2)	3.7 (0.3)	37.4 (3.9)

Errors (standard deviation) in brackets.

($p < 0.05$), with two groupings being identified: Ceolus KG-802, Emcocel HD90 and Pharmacel 101 all possess ‘high’ acid–base (> 8.3 mJ/m²) components when compared to the other six MCCs (< 3.8 mJ/m²).

It has been suggested (42) that the ‘C’ parameter (affinity of adsorbed gas for the substrate) determined from N₂ BET adsorption data may be related to the dispersive component of the surface energy of a material. However, no correlation ($R^2 = 0.001$) was found between the ‘C’ values listed in Table 6 and the γ_d values calculated here (Table 4). This may be a result of the modification of the cellulose surface during freezing in liquid N₂, indicating that, for these samples at least, the ‘C’ parameter measured for samples frozen at 77 K do not relate to γ_d values determined at 20°C using CI methods.

The lower surface energy of the high density MCC may also contribute to the generally lower strength of compacts made from these materials, since the cohesive energy density within a compact is, in part, related to the surface energy of the material (43). There was no significant difference (ANOVA, Fisher’s test, $p < 0.05$) between either the dispersive, positive or negative components of the surface energies of the standard MCC Emcocel 50M and the silicified MCC Prosolv 50. The generally improved compactibility and reduced lubricant sensitivity of the silicified MCC (44) cannot be explained simply in terms of surface energetics. The improved compactibility of the silicified MCC (SMCC) is likely a result of a physical keying effect, due to the presence of the colloidal silicon dioxide (45,46).

From the surface energy data presented here (Table 5), together with surface area data (Table 6), it is possible to

determine the surface energy per gram of a material. In Table 6, the product of the surface energy (J/m²) and the specific surface area determined by BET N₂ adsorption (m²/kg) yields a specific surface energy (SSE, J/kg). This may be related to the potential bonding energy between the MCC particles, with a higher SSE indicative of potentially stronger compacts. A cursory review suggests that, at comparable density, Prosolv 50 should produce stronger compacts than the unmodified grades, and Emcocel HD90 should produce weaker compacts than standard MCCs. This has been shown to be generally true for SMCC (45) and high-density MCCs (47). It is important to note, no linear correlation between compact strength and specific surface energy can be expected using such a simple relationship and other factors, especially particle size, plasticity and surface roughness, must be considered when attempting to predict the relative compactibility of materials.

The high specific surface energy value calculated for Emcocel SP15 would suggest that Emcocel SP15 would produce strong compacts although practical experience argues against strong compacts being made of the small particle size grades of MCC. However, the relatively weaker compacts produced from Emcocel SP15 in direct compression are a function of the physical processes involved in tablet compaction. Inefficient and highly variable die filling, a result of the poor flowability of the material, can leave voids in the powder column and lead to capping of the tablets. Slow die filling, or tableting under vacuum, can overcome the inherent limitations of small particle size materials (such as SP15) as direct compression excipients, however the use of such techniques are rarely practical.

Table 6. Specific Surface Energy for Ten MCC Samples, Determined from N₂ BET Surface Area Data and Surface Energy Data in Table 5

MCC	Surface energy (γ_s) (mJ/m ²)	N ₂ BET surface area (m ² /kg)	C coefficient	Specific surface energy (J/kg)
Ankit	39.4 (2.5)	1120	83.0	44.1
Avicel PH101	37.7 (0.9)	1220	86.0	46.0
Ceolus KG-802	44.4 (3.9)	1250	115	55.5
Emcocel 50 M	42.4 (1.9)	1270	85.9	53.8
Emcocel HD90	42.5 (3.0)	690	79.8	29.3
Emcocel SP15	38.6 (7.9)	3320	108	128
Pharmacel 101	43.4 (1.5)	1300	87.9	56.4
Prosolv 50	43.9 (2.7)	4910	101	216
Tabulose 101	41.6 (2.4)	1340	93.3	55.7
Vivapur 101	37.4 (3.9)	1450	90.4	54.2

Table 7. Summary of Dispersive Component Value (γ_s^d) Parameters Calculated for Three MCC Samples by IGC at 0% and 44% RH; Calculated Errors Are in Brackets

MCC	γ_s^d at 0% RH (mJ/m ²)	γ_s^d at 44% RH (mJ/m ²)
Emcocel 50 M	55.5 (0.6)	44.9 (0.5)
Emcocel HD90	45.6 (0.4)	40.5 (0.4)
Prosolv 50	70.2 (0.5)	45.6 (0.4)

Inverse Gas Chromatography

Inverse gas chromatography was used to determine the surface energy of three MCC samples; Emcocel 50 M, Emcocel HD90 and Prosolv 50. Emcocel 50 M is a standard grade of MCC, Emcocel HD90 was used to represent hardwood derived MCCs and Prosolv 50 was used to investigate the effect of silicification on the surface energy of MCC.

Dispersive contributions at 0% and 44% RH are presented in Table 7. Dispersive, electron donor and electron acceptor values determined at 44% RH are summarised in Table 8. Errors are based on the standard deviations calculated for the data by the linear regression software (Minitab 12, Minitab Inc., State College, PA, USA). Emcocel 50 M was used as the control material.

The values of the dispersive components of the surface energies determined here are in general agreement with previously reported values obtained using IGC; γ_s^d of 52.3 mJ/m² for an Avicel sample (48) and γ_s^d of 45.9 mJ/m² for an unspecified MCC sample (18). As mentioned previously, both these studies employed MCC samples which were dried at elevated temperatures prior to analysis.

In general, the dispersive components of the surface energies of the three MCCs determined at 44% RH are similar to the results obtained in the CI experiments. However, at 0% RH a discrepancy between the surface energies determined using the IGC data and the surface energies determined using the CI data is observed, with the IGC-derived results being 5 to 6 mJ/m² higher than those determined using CI. Interestingly, the same rank order is observed: Prosolv 50 > Emcocel 50 M > Emcocel HD90.

The generally higher total surface energy values determined using IGC at 0% RH may be attributed to the availability of higher energy adsorption sites, which, at 44% RH, are preferentially occupied by water molecules. This may not be the case here, since, from water adsorption studies conducted using dynamic vapour sorption, it is known that the monolayer coverage of MCC is exceeded at 44% RH (13). Therefore, the observed variation at 0% RH may be a result of the retention of polar probes, which are not completely eluted from the previous experiment. This suggests that caution must be exercised when re-using columns for IGC experiments.

From Table 8, it is clear that large errors are associated with the IGC data used to determine the acid and base parameters (electron donor and acceptor numbers) of the surface energy. Previous work using acid/base probes (e.g. (48)) attributed these errors to retention of the probes, which were eluted after the injection of water. In the current study, the use of moist carrier gas (RH 44%) did not appear to improve the accuracy of this technique, previously used

successfully for synthetic polymers and inorganic materials. It appears that more useful, readily interpretable data are obtained from CI experiments for MCC materials.

Comparison of the data obtained for the high-density MCC, Emcocel HD90, and the standard grade product, Emcocel 50 M (Table 7), indicates that the high-density grade exhibits a lower dispersive surface energy (4.4 ± 0.6 mJ/m² lower). This may have consequences for lubricant sensitivity and mixing, since lower surface energy materials would be expected to have a lower degree of interaction with components in a blend (5,10,25). Calculated acid and base parameters for the three MCCs from IGC experiments are summarised in Table 8. The very large errors associated with these results limits the quantitative value of these data, but general conclusions may be drawn. Of particular interest is the general positively charged nature of the surface of Emcocel HD90. Interestingly, the determination of the surface energy components of Emcocel HD90 using CI also suggested that there are 'positively charged' sites in the surface of Emcocel HD90. The presence of positively charged groups detected using IGC suggests that the positive groups detected using CI are a real feature, rather than being a result of an experimental error or artefact.

DISCUSSION

The Use of Surface Energy Measurements in Determining the Physico-Chemical Properties of Microcrystalline Cellulose

The fact that many pharmaceutical excipients are produced from natural sources may affect the apparent surface energy and thus physical-mechanical properties. Microcrystalline cellulose, a commonly used filler/binding/disintegrant in tablet formulation is such a material.

For example, MCC has been reported to exhibit manufacturer dependent variable characteristics in terms of compactibility (49–51) and drug adsorption (52,53). Furthermore, significant batchwise variations in MCC have been observed in terms of the crystallinity (54), drug adsorption (52), thermal properties and water sorption characteristics (55). Although, in the first instance, such variations are attributable to different manufacturing practices, pulp sources, storage times and conditions, an investigation that may link the surface physicochemical properties of the various MCCs (such as surface energy) has yet to be reported.

The specific surface energy of MCC has previously been investigated using the CI method, with an unspecified MCC yielding a total surface energy (γ_s) of 40 mJ/m² (determined

Table 8. Summary of Electron Acceptor (K_A) and Electron Donor (K_D) Parameters Calculated for Three MCC Samples by IGC at 44% RH; Calculated Errors in Brackets

MCC	γ_s^d (mJ/m ²)	K_A (J/mol)	K_D (J/mol)	K_D/K_A
Emcocel 50 M	44.9 (0.5)	67 (56)	184 (56)	2.75 (2.56)
Emcocel HD90	40.5 (0.4)	167 (56)	92 (56)	0.55 (0.40)
Prosolv 50	45.6 (0.4)	113 (134)	134 (134)	1.19 (1.84)

by Zisman's method (43)¹). This is comparable with literature values for the total surface energy of wood of 40.0 to 55.5 mJ/m², (measured by contact angle) (31). However, it is important to note, Zisman's method of analysis is generally not considered suitable for use with liquids which possess any hydrogen bonding character since a deviation from the linear relationship between $\cos\theta$ and liquid surface tension will occur (20). As a result, reliable values for the polar component of the surface energies cannot be obtained, thus limiting the usefulness of this technique.

In a different study, Dourado *et al.*, utilised a thin-layer wicking technique (thin layer of sample dried onto a glass slide) to characterise the surface energy of three MCC samples and reported a dispersive surface energy of 51.8 mJ/m² for Avicel PH101 (FMC Co., USA) and 57.2 and 59.0 mJ/m² for two MCCs supplied by Sigma Co. (UK) (7). In addition, by using four probe liquids, they were also able to determine the polar contributions to the total surface energy, calculating 42–45 mJ/m² for the negative (electron donor) contribution to the surface energy of the MCCs studied and 'practically zero' positive (electron acceptor) contribution. Planinšek and co-workers compared the dispersive component of the surface energy calculated from contact angle data (measured on compacted samples) and calculated from IGC data (22). They found that, although the underlying principles of the two techniques are different, similar values for the dispersive component of the surface energy were calculated for five pharmaceutical materials.

Using IGC, the values of the dispersive component of the surface energy determined for cellulosic samples lie in the range 32 to 52 mJ/m² (18,48,57–59). However, the results from these investigations into the surface chemistry of MCC by IGC may not be suitable for comparison with the results reported here, since many samples were heated to more than 80°C prior to analysis. It has been shown that heating to these temperatures affects the surface chemistry of cellulose with respect to, for example, adsorption from aqueous solution (52) and water–cellulose interactions relating to 'hornification' (60).

In addition to these previous studies, it is interesting to note, that the presence of a generally acidic surface was suggested by the results obtained for untreated cellulose powder from IGC (41), in comparison to the suggested amphoteric nature indicated after analysis of washed and dried wood samples. Furthermore, using immersion calorimetry measurements, Marshall *et al.*, found that the surfaces of the MCCs (Avicel brand) were energetically homogeneous (61). However, this appears to be in disagreement with some of the data presented in the investigations mentioned above, and also at odds with recent molecular modelling simulations of the hydrophilicity and lipophilicity of cellulose (62,63).

Since the previously described studies of MCC have been conducted under a series of discrete investigations, comparison between types and batches is not possible. Furthermore, as previously stated, product and batch variations may lead to significant differences in MCC performance, thus a specific comparison study of some commonly used MCCs would be of interest.

Here, both CI and IGC, are used to determine, and compare, the surface energies of a series of commonly used pharmaceutical grade MCCs, and to test the suitability of these methods for studying the surface energies of polysaccharides.

COMPARISON OF METHODS

The capillary intrusion method has been shown to be capable of measuring the surface energy characteristics of MCC samples, provided the flowability of the materials does not hinder the production of reproducible samples. Approximately equivalent values for the dispersive contribution to the surface energy of the three MCCs used for the purpose of comparing the two techniques, CI and IGC, were calculated from the data collected. A direct comparison of the magnitudes of the specific interactions is not possible, because the treatment of the IGC data yields surface energy data based on a molar energy, rather than energy per unit area. With the exception of Emcocel HD90, all MCCs are described as having predominantly negative (acidic) surfaces using IGC data. However, IGC measurements conflict with the CI data in characterising the surface of Emcocel HD90, although some positive character is in evidence for Emcocel HD90 from CI measurements. From 'work of spreading' calculations, all MCC surfaces are described as predominantly non-hydrophilic. This confirms molecular modelling investigations of the surface, where limited hydrophilic sites were identified and a predominantly lipophilic surface was computed (51). The general lipophilicity of the MCC surface may be a factor in the sensitivity of MCC to lubricants such as magnesium stearate.

The differences between the IGC and CI data are explicable in terms of the physicochemical properties as measured by the two techniques. In IGC experiments conducted at infinite dilution, there is a tendency to selectively measure the highest energy sites in the surface, which have a greater influence on the surface. Using moistened carrier gas results in a small reduction in the measured surface energy by the preferential adsorption of water at high-energy hydrophilic sites which may hinder adsorption at adjacent lipophilic sites. In contrast, CI will tend to yield an area mean value for the surface energy. Isolated high energy sites will not have as significant an effect on the measured surface energy because an excess of probe molecules is present, therefore extended retention at one site will have no measurable effect on intrusion rate.

Results obtained using CI suggest that the powder column approach used here may be applicable to powders and granules in a restricted particle size range. Smaller particle size samples may be difficult to load reproducibly and swelling of the particles will change the capillary structure more quickly than in larger particle size samples. For such materials, a thin layer wicking method may be more appropriate (7). Very large particles, such as 200 grade MCCs (not studied here) may be less suitable, since the capillary effect is restricted by the diameter of the pores in the sample and the surface energy of the probe; therefore low surface energy liquids may not be able to penetrate large pores. Either IGC or methods using microdroplets (64) may be more useful for such materials. However, in terms of pharmaceutical materials, and in particular, excipients, a more rigorous analysis of IGC data maybe required since the assumption that ΔG of adhesion is

¹ A plot of $\cos\theta$ against liquid surface tension for at least four liquids is extrapolated to $\cos\theta=1$, which is recorded as the solid surface free energy, i.e. the surface tension of a liquid which will just perfectly wet the solid.

approximately equal to ΔH may not produce data which is capable, for example identifying inter batch variations of products.

CONCLUSION

The determination of surface energy data for 10 MCC Samples from different suppliers *via* surface contact angle determination has shown significant differences between the surface energy properties of samples. The use of a hardwood rather than softwood pulp source in Emcocel HD90 appears to affect the surface energy of the MCC produced from this type of pulp source. The presence of colloidal silicon dioxide (Prosolv 50) in the surface of the MCC does not significantly affect the total surface energy of the product.

Comparison between capillary intrusion and inverse gas chromatography is problematic because the results do not fully correspond, although some correlation in terms of rank order is noted.

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