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Wettability studies of morphine sulfate powders

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Abstract

A capillary penetration technique was used to determine the wettability of morphine sulfate powders by a range of wetting and partially wetting liquids. Wetting rates were found to be dependent on both the properties of the wetting liquid and the morphine sulfate batch. A number of liquids were established as perfectly wetting, and the critical surface tension for morphine sulfate wetting was estimated to be ~ 40 mN m^{-1}. Effective capillary radii for packed beds of morphine sulfate powders were determined in the range 0.3–0.6 μm; these are compared with particle size, shape and surface area data. From the Washburn approach, the advancing water-particle contact angles for the different morphine sulfate samples were determined to be in the range 57–79°, with errors less than ± 3°. Sessile drop measurements on the same samples were unable to determine reproducible equilibrium contact angles and could not differentiate between the batches. The role of surface chemistry, crystal morphology and crystal structure in controlling morphine sulfate powder wettability was explored by X-ray photoelectron spectroscopy (XPS), scanning electron microscopy (SEM) and X-ray diffraction. Contact angles were shown to correlate with both the aspect ratio of the morphine sulfate crystals and the nitrogen-to-oxygen surface atomic concentration ratio, determined by SEM and XPS, respectively. The relative exposure of different crystal faces is considered to play an important role in controlling the wettability of morphine sulfate powders.

Keywords: Morphine sulfate powders; Contact angles; Capillary penetration techniques; Surface chemistry; X-ray photoelectron spectroscopy

1. Introduction

The physical characterisation of drug particles, both in terms of their bulk and, more importantly, their surface properties, is critically important in the search for novel or improved drug delivery systems. Drug particle wettability is one such surface property that has not been fully utilised in this regard. Since wetting is the precursor to dissolution, drug particle wettability has a controlling influence on dissolution rates and may therefore be engineered to control release characteristics in oral pharmaceutical delivery. Drug particle wettability is also influential in controlling interactions with other drug particles, and particle and polymer excipients during formulation and manufacture. Wettability therefore plays an im-

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portant role in both dry powder and suspension processing, e.g. in controlling the interfacial stability (Parsons et al., 1992), which is critical in controlling coating and granulation processes. It is also noteworthy that drug particle wettability can be significantly influenced during crystallisation, milling and compaction, although the consequences of this on subsequent processing are rarely considered. With these thoughts in mind, drug particle wettability may be directly used in controlling the quality of raw materials in formulation and in process optimisation during manufacture (Wells and Walker, 1983; Zajic and Buckton, 1990). For these to be achieved, reliable and convenient methods for the measurement of drug particle wettability are required and these should generate parameters that are representative of the drug particle behaviour during processing and/or delivery.

The contact angle is generally used to characterise the wettability of material surfaces and is commonly determined by sessile techniques, where the angle of contact of a water drop or a bubble on a surface is measured through the liquid phase. Sessile methods can be reliably used for determining the contact angle of large single crystals. They have also been widely applied to compressed discs of pharmaceutical powders (for example, Harder et al., 1970; Buckton and Newton, 1986a). It is, however, questionable whether such wettability measurements are representative of the parent drug particles. Compaction may influence both the surface energy and the surface roughness of a powder, and has been shown to decrease the contact angle of barbiturate powders (Buckton and Newton, 1986a). Sedimentation volume (Duncan-Hewitt and Nisman, 1993), vacuum microbalance (Buckton et al., 1986) and microcalorimetric (Buckton and Beezer, 1988) techniques have also been applied to characterise the wettability of pharmaceutical powders. They do not, however, directly determine the contact angle, and comparison between different techniques may not be simple.

Methods for direct contact angle measurements on powders are based on liquid penetration into particle beds. Equilibrium capillary pressure (Diggins et al., 1990) and wetting rate techniques (Washburn, 1921) have been developed for application with inorganic mineral particles (Yang et al., 1988; Diggins et al., 1990; Prestidge and Ralston, 1995; Subrahmanyam et al., 1996), but have been less frequently applied to organic drug particles (Alkan and Groves, 1982; Buckton and Newton, 1985, 1986b; Kiesvaara et al., 1993). Problems in terms of partial wetting and irreproducible wetting rates have been encountered (Buckton, 1993); however, given the simplicity and direct nature of these techniques, further studies are warranted.

The major objective of the present work was to use wetting rate measurements of particle-filled capillaries to determine the contact angles of morphine sulfate particles from different sources. Comparisons are made with sessile drop contact angles on compressed discs of the same morphine sulfate powders. Complementary characterisation studies using X-ray photoelectron spectroscopy (XPS), X-ray diffraction (XRD) and scanning electron microscopy (SEM) were undertaken in an attempt to rationalise the observed differences in particle wettability. These studies were employed to further develop the relationship between drug particle surface chemistry, wettability and processing performance.

2. Experimental

2.1. Materials

Water was purified by reverse osmosis and subsequently passed through a Millipore Super-Q system; it had a conductivity of < 0.5 μS m^{-1}. Surface tensions of the water and water saturated with morphine sulfate were determined using a Wilhelmy balance, and were found to be 72.8 and 71.5 mN m^{-1}, respectively. Other reference wetting liquids were spectroscopic grade reagents; their surface tension and viscosity data are given in Table 1. Seven different powder samples of morphine sulfate (pharmaceutical grade) were obtained and are identified as A–G. Both supplier variation and batch variation are represented in this group. Particle size distributions of the morphine sulfate samples were determined by laser

Table 1
Surface tension and viscosity data of the wetting liquids at 20°C

Wetting liquid	Surface tension, γ_{lv} (mN m^{-1})	Viscosity, η (mN m^{-2} s^{-1})
Water	72.8	1.002
89% Ethanol/water	23.86	1.166
Diethyl ether	17.01	0.233
n-Hexane	18.43	0.326
Acetone	23.70	0.327
Cyclohexane	25.5	0.973
Chloroform	26.67	0.580
Dichloromethane	28.00	0.430
Xylene	30.10	0.810
Dimethylformamide	37.30	1.804
Acetophenone	39.80	1.798
100% Methanol	22.65	0.597
80% Methanol/ water	27.26	0.678
50% Methanol/ water	35.31	0.800
25% Methanol/ water	46.38	0.900

diffraction (Malvern Mastersizer X), and details are given in Table 2. Prior to wettability measurements (at 20°C), the morphine sulfate samples were stored in a vacuum desiccator and kept in the dark.

2.2. Techniques

2.2.1. Sessile drop contact angles

Morphine sulfate powders were compacted at a pressure of 70 MPa for 10 min. A droplet ($\sim$ 50 μl) of morphine sulfate saturated water was placed on the morphine sulfate compact and imaged using a magnifying video technique (Olympus BHM-2). High-resolution droplet images were determined every 0.25 s and the time-resolved sessile contact angle determined to within $\pm 1°$ using an image analysis package (Galai Scanarray 3).

2.2.2. Liquid penetration rate measurements

This approach is based on measurement of the height of a penetrating liquid through a packed bed of particles contained in a capillary tube as a function of time. The experimental apparatus is equivalent to that originally used by Washburn (1921) and has been described elsewhere (Subrahmanyam et al., 1996). An essential requirement for reproducible measurements is uniform and reproducible packing of the capillary with the morphine sulfate particles. This was undertaken by adding a known weight of particles to the capillary, with a 1–2 mm compact layer of glass wool used to retain the particles, and then vibrating the capillary until a particle volume fraction of 0.60 was achieved. The time required to pack the capillary was controlled at 5 min. The packed capillary was then attached to a vertically graduated scale to enable accurate height determination. The wetting liquid was then introduced to the bottom of the capillary and the height of the wetting front was recorded against time. Given the finite solubility of morphine sulfate in water, wetting measurements were performed using both water and morphine sulfate saturated water.

Table 2
Particle size and specific surface area of morphine sulfate samples[a]

Sample	$d(0.1)^+$ (μm)	$d(0.5)^+$ (μm)	$d(0.9)^+$ (μm)	Sauter mean, $D[3,2]$ (μm)	Specific surface area[b] (m^2 g^{-1})
A	1.53	11.88	33.71	4.04	1.15
B	1.03	16.23	34.18	3.45	1.33
C	1.02	10.37	33.03	3.07	1.48
D	1.08	10.13	43.29	3.11	1.46
E	0.88	10.36	27.37	2.78	1.64
F	2.18	16.26	38.26	4.87	0.94
G	0.80	8.0	19.64	2.49	1.83

[a] Values $d(0.1)$, $d(0.5)$ and $d(0.9)$ correspond to diameters at 10, 50 and 90%, respectively, of the cumulative undersize curve.
[b] Based on equivalent spherical diameter.

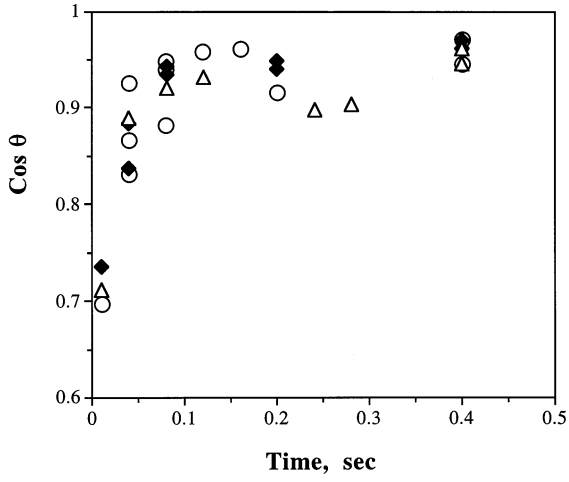


Fig. 1. Advancing water contact angles of sessile drops on compacts of morphine sulfate powders (△, A; ◆, D; ○, E), determined as a function of time after drop-surface contact.

However, this was shown to have negligible influence on the determined wetting rates and advancing water contact angle.

The wetting rate data is related to the particle contact angle through the Washburn equation, which, for steady flow conditions, relates the capillary driving force of a liquid penetrating through a compact vertical bed of particles with small pore radius and the viscous drag:

$$\frac{h^2}{t} = \frac{r_{\text{eff}}\gamma_{\text{lv}}\cos\theta_{\text{p}}}{2\eta} \quad (1)$$

where η is the viscosity of the penetrating liquid, r_{eff} the effective capillary radius, h the height of liquid penetrating the bed in time t, and θ_{p} the advancing particle contact angle, measured through the liquid phase.

For any particular fixed packing arrangement of particles in a column, a plot of h^2 versus t will be linear. If the wetting rates for two liquids, of which one is perfectly wetting (with $\cos\theta_{\text{p}} = 1$), are considered, then r_{eff} does not need direct calculation and the particle contact angle can be obtained from:

$$\cos\theta_{\text{p}} = \frac{(h^2/t)_{\text{n}}(\gamma_{\text{lv}})_{\text{w}}\eta_{\text{n}}}{(h^2/t)_{\text{w}}(\gamma_{\text{lv}})_{\text{n}}\eta_{\text{w}}} \quad (2)$$

where, $(h^2/t)_{\text{n}}$ and $(h^2/t)_{\text{w}}$ are the wetting rates for non-wetting and wetting liquids with surface tensions, $(\gamma_{\text{lv}})_{\text{n}}$ and $(\gamma_{\text{lv}})_{\text{w}}$, and viscosities η_{n} and η_{w}, respectively. θ_{p} refers to the non-wetting liquid.

2.2.3. Particle characterisation

XPS spectra of morphine sulfate powders were recorded using a Perkin Elmer PHI Model 5600 spectrometer with a Mg Kα X-ray source operating at 300 W with a pass energy of 89.450 eV. The vacuum pressure in the analyser chamber was $\sim 10^{-8}$ Torr during analysis. Surface atomic concentrations were determined from peak intensities and the corresponding sensitivity factors. SEM images of morphine sulfate powders were determined using a Cambridge instruments Cam Scan field emission microscope. Samples were carbon coated to ~ 0.5 nm prior to imaging. Powder X-ray diffraction spectra were recorded using a Philips Sietronics PW1050 diffractometer.

3. Results and discussion

3.1. Sessile drop measurements of contact angle

Sessile drops of water saturated with morphine sulfate placed on the surface of a compacted surface of morphine sulfate particles exhibited time-dependent behaviour, as exemplified for samples A, D and E in Fig. 1. For all samples, the advancing water-particle contact angles decreased from ~50 to ~20° in less than 1 min. The apparent equilibrium contact angles were less than 20°, but these were not, however, reproducible and not considered representative of the drug particle properties. Factors that contribute to this behaviour include droplet momentum, droplet penetration into the particle compact (Alkan and Groves, 1982), physical and chemical heterogeneities, and contact angle pinning due to surface roughness. Similar behaviour has been reported for water on compacted paracetamol (Stamm et al., 1984). That is, the droplet penetrates into the compact and is unable to recede to its true equilibrium value due to the effects of microroughness. In these cases, the observed contact angles are as much due to particle size and compaction variation than surface chemistry.

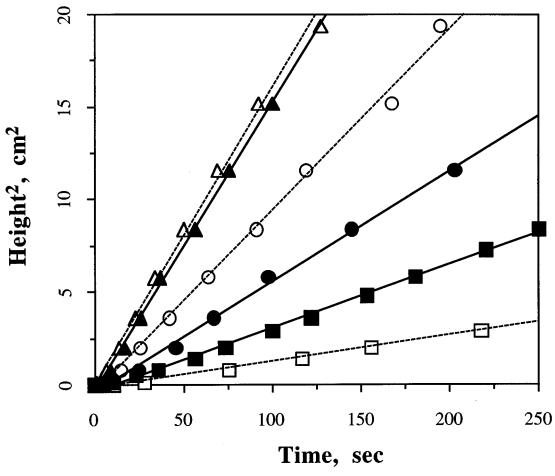


Fig. 2. Wettability data for capillaries packed with morphine sulfate particles determined using the Washburn approach. Sample E: ●, water; ▲, diethyl ether; ■, ethanol/water. Sample D: ○, water; △, diethyl ether; □, ethanol/water.

These observations clearly demonstrate the problems associated with determining advancing contact angles on morphine sulfate powders by the sessile drop technique. Alternative techniques are clearly required if a meaningful wettability measurement is made, which can reliably characterise pharmaceutical powders and be used for ascertaining differences in processing performance. Bearing this in mind, the capillary penetration technique has been applied to morphine sulfate powders and the findings are now described.

3.2. Liquid penetration measurements

3.2.1. Wetting rates and their reproducibility

Wetting rate measurements for capillaries packed with morphine sulfate particles were determined using a wide range of single-component liquids and also binary liquid (ethanol/water and methanol/water) mixtures. By way of example, wetting rate data for morphine sulfate samples D and E are given in Fig. 2. For water, diethyl ether and ethanol/water wetting, plots of h^2 (h is the height of the wetting front) against time are linear and pass through the origin, both of which are critical tests for establishing the applicability of the Washburn equation. Similar behaviour was found for the other morphine sulfate samples, using a wide range of wetting liquids, and typical h^2/t values for various wetting liquids given in Table 3.

Prior to determining contact angles of morphine sulfate particle batches, it is essential to consider the reproducibility of wetting rate measurements. The reproducibility of the measured h^2/t values depends at least on the hydrophobicity of the drug particles, the wetting liquid used and the efficiency of the column packing. The morphine sulfate particles studied here gave more reproducible wetting rates with single-component liquids of low surface tension, i.e. diethyl ether and chloroform (error, $\pm 3\%$), rather than water (error, $\pm 7\%$) or binary mixtures (error, $\pm 5\%$). With water, variations in the h^2/t values are believed to be due to localized channelling during the wetting process, i.e. non-uniform penetration

Table 3
Average wetting rates for morphine sulfate samples

Morphine sulfate sample	Average wetting rate, h^2/t (cm²/s)			
	Water	89% Ethanol/water	Chloroform	Diethyl ether
A	0.0894	0.0235	0.139	0.215
B	0.0972	0.0442	0.171	0.200
C	0.0719	0.0223	0.136	0.219
D	0.0888	0.0164	0.0919	0.145
E	0.0583	0.0321	0.0905	0.151
F	0.0280	–	0.0750	0.113
G	0.0230	–	0.0695	0.125

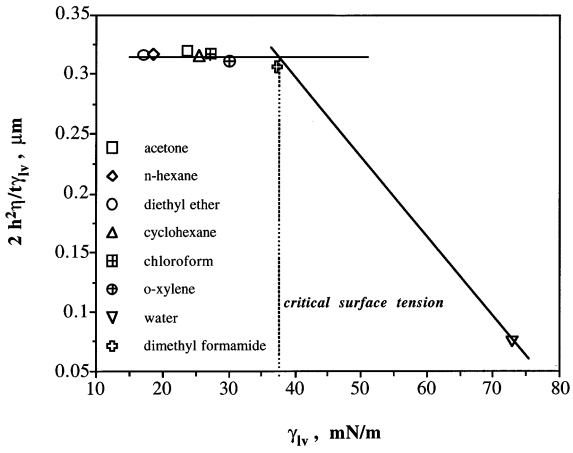


Fig. 3. Morphine sulfate wetting rates (adjusted for viscosity and surface tension) as a function of the surface tension of single-component wetting liquids.

of water through a partially hydrophobic particle bed (Yang et al., 1988; Subrahmanyam et al., 1996).

It should also be noted that it is desirable to use narrow size fractions of drug particles so as to minimise the variation in the effective capillary radii in the particle bed (Diggins et al., 1990). For capillary beds with particles of a broad size range, the largest capillary radii, i.e. those between the larger particles, will dominate the apparent wetting process. Wetting rates may be artifactually high, leading to non-representative particle contact angle values. Capillary beds with small particles, i.e. with small effective capillary radii, give relatively low wetting rates that can be measured more accurately. For relatively large particles (i.e. >75 μm), it can be difficult to precisely determine the relatively fast wetting process, hence leading to larger errors in measured h^2/t values. The capillary wetting rate technique also has the advantage that its operation is simple and quick. A measurement can be made in less than 10 min, enabling multiple measurements to be taken with a corresponding improvement in statistics, and hence reliability.

3.2.2. The role of surface tension on capillary wetting rates

For the morphine sulfate particles used in this work, r_{eff} cannot simply be predicted from the particle size and packing data, and, therefore, advancing water contact angle measurement relies on a comparison of the wetting behaviour of water with that of a perfectly wetting liquid. It is pertinent, therefore, to consider the role of liquid surface tension on morphine sulfate particle wettability to establish a perfectly wetting liquid. Zisman (1964) related the surface tension of various wetting liquids to the contact angle and defined a critical surface tension of wetting (γ_c). Liquids with surface tensions less than the critical value (i.e. $\gamma_{lv} < \gamma_c$) are deemed to be perfectly wetting, and their contact angle on the surface in question is zero. For partially wetting liquids ($\gamma_{lv} > \gamma_c$), the contact angle and liquid surface tension are related by the expression:

$$\cos\theta = 1 - k[\gamma_{lv} - \gamma_c] \quad (3)$$

A combination of Eqs. (1) and (3) leads to:

$$2h^2\eta/t\gamma_{lv} = r_{eff}(1 - k[\gamma_{lv} - \gamma_c]) \quad (4)$$

For a range of single-component wetting and partially wetting liquids, $2h^2\eta/t\gamma_{lv}$ is plotted against γ_{lv} in Fig. 3, and is equivalent to a Zisman plot. For liquids of surface tensions in the range 18 to ~ 40 mN m^{-1}, this plot is independent of γ_{lv} and therefore these liquids can be considered perfectly wetting. The contact angles are equal to zero. Thus, $1 - k[\gamma_{lv} - \gamma_c] = 1$ in Eq. (3) and can be substituted into Eq. (4) such that $2h^2\eta/t\gamma_{lv} = r_{eff}$. From the plot in Fig. 3, r_{eff} is estimated to be 0.32×10^{-6} m, which compares favourably with r_{eff} values determined directly from Eq. (1) using either chloroform or diethyl ether as the perfectly wetting liquid, as shown in Table 4. Liquids with surface tensions greater than 40 mN m^{-1} are considered partially wetting. The critical surface tension (γ_c) is the point at which there is a transition in the wettability data, i.e. ~ 40 mN m^{-1}. No significant difference in γ_c values were observed for the different morphine sulfate samples investigated; this is in agreement with measurements made using skin flotation (not included).

Table 4
Effective capillary radii for wetted morphine sulfate samples (assuming perfectly wetting)

Morphine sulfate sample	Average effective capillary radius, r_{eff}		
	Ethanol/water (μm)	Chloroform (μm)	Diethyl ether (μm)
A	0.229	0.603	0.581
B	0.431	0.745	0.549
C	0.218	0.591	0.599
D	0.160	0.400	0.396
E	0.313	0.393	0.415
F	–	0.317	0.316
G	–	0.300	0.343

In the case of wetting liquids, it is often uncertain whether or not thin film equilibria are achieved during the time scale of the experiment. Liquid penetration rates depend on whether or not equilibrium wetting films have been established ahead of the macroscopic wetting front (Good, 1973). Formation of thin films and/or condensation would be expected to be a distinct function of the surface tension of the wetting liquid. With this in mind, liquid penetration studies of morphine sulfate particle beds using cyclohexane, *n*-hexane, diethyl ether and chloroform probe the geometry of the particle bed rather than surface chemical effects. Effective capillary radii calculated assuming perfect wetting are given in Table 4. The values obtained for diethyl ether and chloroform are in good agreement, whereas values for ethanol/water mixtures are significantly different.

The unusual wetting behaviour of morphine sulfate powders by binary solvent mixtures is further demonstrated in Fig. 4. The wetting rate was effectively independent of surface tension over a wide range and Zisman behaviour was not observed. Possible problems arising during wettability testing with binary solvent mixtures include preferential adsorption of one component onto the drug surface (Good, 1977; Buckton and Newton, 1985, 1986b). In morphine sulfate powders, polarity and vapour–solid interactions may affect liquid penetration rates. Methanol/water mixtures at surface tension values similar to those of single-component liquids yielded significantly lower wetting rates, implying that advancing methanol/water contact angles exist. The use of binary solvent mixtures for probing morphine sulfate wettability, and hence contact angle determination, is seriously questioned. The following sections will only be concerned with single-component wetting liquids.

3.2.3. Particle contact angles

Advancing water-particle contact angles for the powdered morphine sulfate samples were determined from Eq. (1), using the average water wetting rate and the average r_{eff} values; these are given with their respective errors in Table 5. (Sessile drop contact angles determined for morphine sulfate compacts are also included in Table 5; these were determined by extrapolation of data of

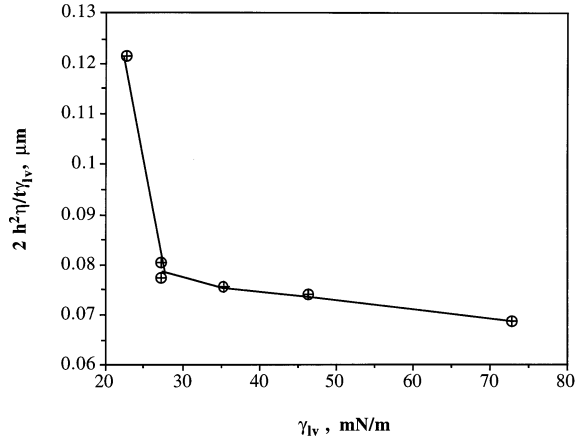


Fig. 4. Morphine sulfate wetting rates (adjusted for viscosity and surface tension) as a function of the surface tension of binary (methanol/water) wetting liquids (refer to Table 1).

Table 5
Particle contact angles for morphine sulfate samples

Morphine sulfate sample	Capillary penetration (Washburn)		Sessile drop[a]	
	Advancing water-particle contact angle (°)	Standard deviation (°)	Advancing water-particle contact angle (°)	Standard deviation (°)
A	68.4	1.7	44.6	1.3
B	70.5	1.8	–	–
C	71.8	2.6	–	–
D	57.0	2.4	42.6	0.7
E	69.3	1.6	45.2	0.9
F	76.0	1.9	–	–
G	78.9	1.1	–	–

[a] Contact angles extrapolated from θ versus t at $t \rightarrow 0$.

the kind shown in Fig. 1 back to time 0. Qualitative agreement between the different experimental approaches is apparent.) In the liquid penetration rate approach, it is assumed that the solid surface is covered by a duplex film in equilibrium with the saturated vapour of the wetting liquid (i.e. the liquid is volatile). Should this not be the case, the 'dry' solid will wet faster. This has not been found to be an issue for, say, mineral particles and quartz particles where cyclohexane is used as a wetting liquid and water is the non-wetting liquid (Diggins et al., 1990; Subrahmanyam et al., 1996). Contact angles in this previous case were determined with a reported precision of $\pm 2°$ and are similar to those obtained here for morphine sulfate.

Particle contact angles of the different morphine sulfate samples are observed in the range 57–79°, this difference is significant and may well be influential in controlling their properties, e.g. dissolution rates and rheology, and their processing behaviour, e.g. tabletisation, granulation and coating. The reasons for the observed differences in particle wettability are explored in the following sections.

3.3. Particle contact angle, particle properties and surface chemistry

3.3.1. Crystal structure, particle shape and surface morphology

In an attempt to investigate wettability differences, the crystalline nature of morphine sulfate samples was determined by powder XRD. In all cases, the determined XRD patterns were representative of fully crystalline morphine sulfate pentahydrate $((C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O)$, in an orthorhombic crystalline form. That is, no differences in the crystal form of the different samples were identified. It can be concluded that contact angle differences are not due to significant differences in the crystal structure or crystalline form. It may, however, be hypothesised that contact angle variability is due to different levels of exposure of the different crystal faces, which have varying proportions of hydrophilic and hydrophobic groups.

SEM was used to determine differences in particle shape, crystal habit, crystalline state (i.e. single crystal versus agglomerates) and surface morphology for the different morphine sulfate samples. SEM micrographs at $\sim 500\times$ magnification are given in Fig. 5, along with the average aspect ratios. The presence of particles of sizes from 1 to 100 μm in each sample was confirmed. It was also shown that the proportion of particles < 10 μm is highly variable from sample to sample, e.g. sample E contains a greater percentage of finer material than sample A (cf. Fig. 5a,e). This finding is in agreement with the determined r_{eff} values from wettability measurements, i.e. Sample A has the greatest r_{eff} and the lowest surface area. The significant particle shape and size differences, as indicated in Fig. 5, may be responsible for wettability differences and be influential during processing.

Morphine sulfate particles in the majority of the samples appear as well-formed single crystals with aspect ratios greater than 2.5. Sample D (Fig. 5d) is the exception, displaying particles with poorly defined crystalline faces, significantly lower aspect ratios and some evidence of polycrystallinity. Powder XRD did, however, confirm the fully crystalline nature of sample D. Interestingly, sample D is the least hydrophobic of the samples characterised. Further differences in the crystal shape of the samples are apparent; however, no simple correlation between aspect ratio and contact angle has been found.

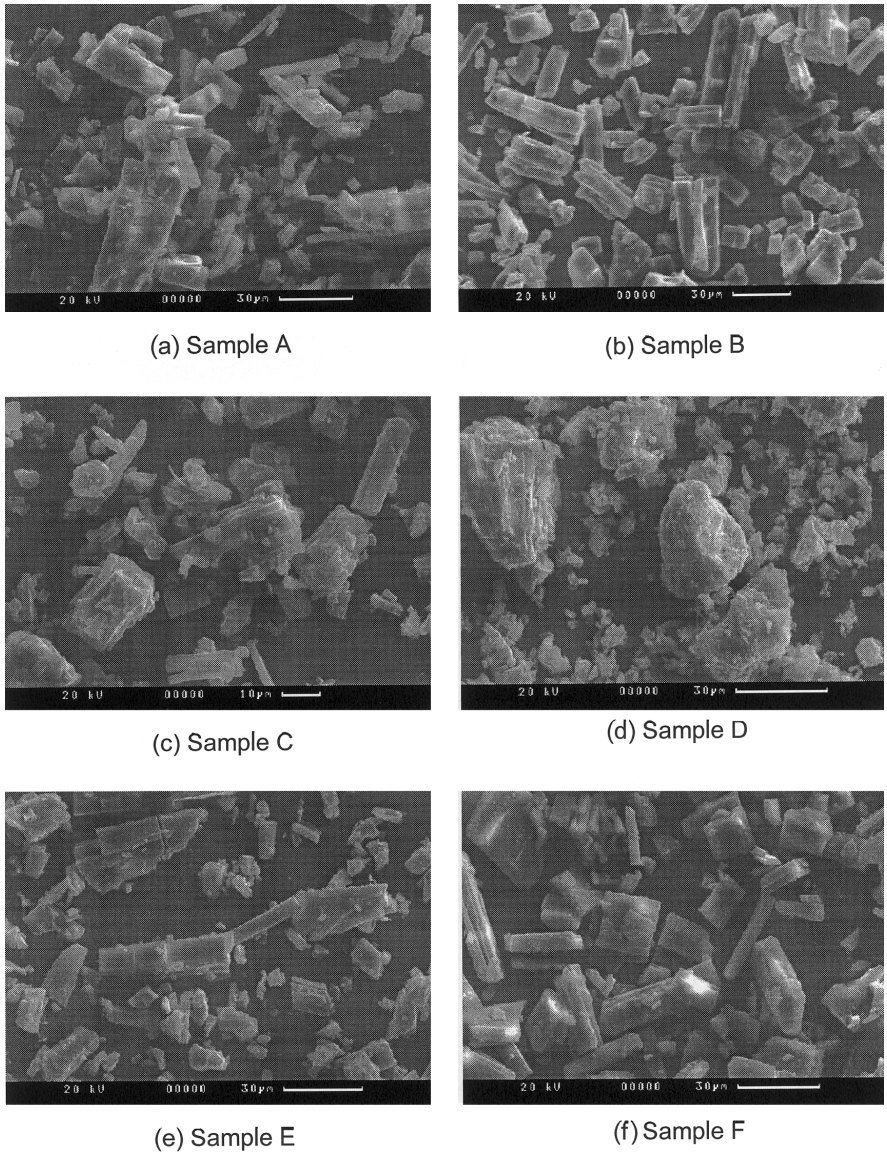
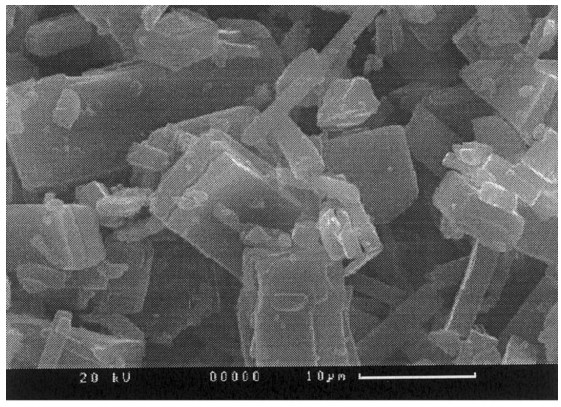


Fig. 5. SEM images (× 500) of morphine sulfate samples: (a) sample A, average aspect ratio = 4.07; (b) sample B, average aspect ratio = 3.95; (c) sample C, average aspect ratio = 2.96; (d) sample D, average aspect ratio = 1.60; (e) sample E, average aspect ratio = 2.85; (f) sample F, average aspect ratio = 3.71; and (g) sample G, average aspect ratio = 2.98.



(g) Sample G

Fig. 5. (*Continued*)

Table 6
Elemental composition from XPS analysis of powdered morphine sulfate samples

Element	Peak	Binding energy[a] (eV)	Atomic concentration (%)				
			Sample B	Sample D	Sample E	Sample F	Sample G
Carbon	1s	286.5	72.97	73.63	72.62	72.31	72.07
Oxygen	1s	531.4	20.81	21.87	21.06	20.91	21.32
Nitrogen	1s	400.9	3.77	2.97	4.05	4.44	4.22
Sulphur	2p	167.5	2.45	1.53	2.28	2.34	2.39

[a] Binding energies, except for C 1s, are corrected for charging.

3.3.2. X-ray photoelectron spectroscopy

XPS was used to characterise the surface chemistry of the individual samples of morphine sulfate powders. Spectra were obtained from an area of particles (on a sample stage) of $\sim$ 0.5 cm^2. This sampling approach analyses several thousand particles, in a range of orientations, and ensures a surface chemical analysis that is representative of the average particle in a particular sample. Small-spot XPS analysis may be used to determine the surface chemistry of an individual crystal face of a single morphine sulfate particle, but this may not be representative of the complete sample.

XPS spectra of the morphine sulfate samples contain signals due to only the elements carbon, nitrogen, sulfur and oxygen, with no evidence of surface impurities that are likely to affect surface wettability. XPS peak shapes for the major elements are sample independent, suggesting that there are no differences in the chemical environment (e.g. oxidation state) of elements in the surface layer, and in qualitative terms, the surface speciation of the morphine sulfate samples are identical. However, the surface atomic concentration data given in Table 6 identify significant quantitative differences in the surface chemistry of the different morphine sulfate samples. That is, the relative abundance of the different elements in the surface layer is sample dependent. XPS, as used here for powdered samples, has an analysis depth of $\sim$1 nm (based on C 1s photoelectron signals), which is comparable with the size of the morphine ion. The orientation of the morphine ion at the crystal surface will therefore influence the relative signal intensities from different atoms within the overall molecular ion. That is, atoms at the crystal surface will give considerably greater XPS photoelectron signals than those in the sub-surface region.

If we consider the chemical structure of the morphine and sulfate ions as shown in Fig. 6, both hydrophobic and hydrophilic regions can be identified. The sulfate and hydroxyl groups represent the more hydrophilic regions and the bulk of the morphine ion the hydrophobic region, respectively. With this in mind, it is clear that oxygen atoms are associated with the hydrophilic moieties, and nitrogen atoms with the hydrophobic moieties of a morphine sulfate ion pair or ionic crystal. This association is exemplified by comparing the relative atomic concentrations (see Table 6) of morphine sulfate samples D and F, i.e. the low level of surface oxygen for sample F corresponds to its relatively high contact angle. This is further highlighted in Fig. 7, where the nitrogen-to-oxygen atomic concentration ratio is shown to

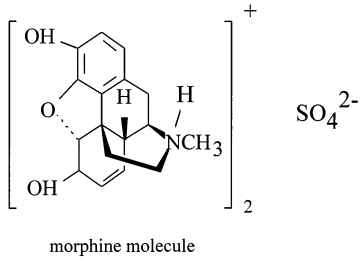


Fig. 6. Chemical structure of morphine sulfate (molecular weight = 668.76).

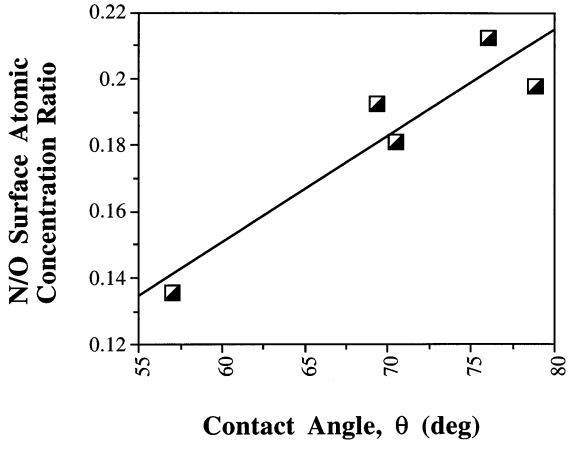


Fig. 7. Nitrogen-to-oxygen atomic concentration ratio (determined by XPS) of powdered morphine sulfate samples as a function of particle contact angle.

correlate directly with the contact angle of the morphine sulfate particles. The fact that varying proportions of hydrophilic (O-containing) and hydrophobic (N-containing) groups correlate with particle contact angle gives credence to the hypothesis that wettability variation is due to different surface exposure of the hydrophilic and hydrophobic faces of morphine sulfate crystals.

Evidence has been presented to suggest that the observed contact angle variability is due to differences in surface chemistry, which are controlled by the crystal dimensions and the average aspect ratio of morphine sulfate crystals in a particular sample. Further work is clearly required to fully establish the interplay between crystal habit and particle contact angle for morphine sulfate and other pharmaceutical powders. In considering this work, it would be advantageous to utilise monodispersed pharmaceutical powders, and use surface analytical techniques with greater surface sensitivity and better spatial resolution than the XPS as used here. Time-of-flight secondary ion mass spectroscopy and low-angle XPS on a single-crystal surface have potential in this regard. Studies of the specific chemical features of individual crystal faces that relate to wettability are under way; these will be reported separately.

4. Conclusions

Sessile drop measurements are inappropriate for determining the advancing water contact angle of morphine sulfate powders. A capillary penetration technique has determined significant differences in the wettability of morphine sulfate samples from different sources. A range of perfectly wetting liquids have been identified and the critical surface tension for wetting estimated to be $\sim$ 40 mN m^{-1}. The Washburn method enabled particle contact angles to be determined with good reproducibility. Morphine sulfate particle samples showed significant contact angle variability (57–79°), which may influence their processing behaviour.

Contact angle variability was shown to be independent of crystal structure (XRD), but to correlate with both the aspect ratio (SEM) of the

morphine sulfate crystals and the nitrogen-to-oxygen surface atomic concentration ratio (XPS). The relative exposure of different crystal faces is considered to play an important role in controlling the wettability of morphine sulfate powders.

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