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A relationship between surface free energy and polarity data and some physical properties of spheroids

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Abstract

Spherical particles have been produced by extrusion and spheronisation of a wet mass of lactose, microcrystalline cellulose and indomethacin (as a model drug), and of mixtures of microcrystalline cellulose, barium sulphate and glyceryl monostearate (to test the general applicability of the surface energy predictions). The surface energies of the powders were estimated from contact angle measurements. The work of cohesion of each powder, and the work of adhesion between pairs of powders were assessed, as were spreading coefficients of the powders over each other. It was found that the spheres produced without indomethacin (lactose and microcrystalline cellulose only) required a significantly higher force to cause crushing, and were also of higher density than any of the four batches which contained different levels of indomethacin. The batches with added indomethacin had similar physical properties irrespective of indomethacin loading. Spheroids containing glyceryl monostearate and barium sulphate had much higher porosities and lower crushing strengths than the indomethacin based formulations. These differences are explained in terms of much lower works of adhesion and cohesion for barium sulphate and glyceryl monostearate than were obtained for the other materials. The differences in the properties of the spheroids have been explained in terms of interfacial phenomena, and in particular the relative works of adhesion between the solids.

Keywords: Extrusion; Spheronisation; Surface energy; Spreading; Indomethacin; Lactose; Microcrystalline cellulose; Barium sulfate; Glyceryl monostearate

1. Introduction

The production of spherical particles by extrusion and spheronisation involves the preparation of a moist powder mass, which is then forced through a die to produce extrudate. The extrudate is then transferred to a spheroniser, which consists of a rapidly rotating scored plate; the toroidal movement of the extrudate causes chopping, rounding and densification of the particles (Newton, 1994). Obtaining a formulation which has the correct physical properties to both extrude and spheronise, and yield a product of uniform quality can, in certain circumstances, present difficulties. Successful formulations are achieved when the correct balance between plasticity and brittleness of the initial wet mass is obtained.

At present, whilst it is known that the interaction between the liquid phase and the powder

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mass seems to be critical and that certain powder mixes do not allow either extrudates and/or spheroids to be formed, there is little quantitative information relating to the required properties of the powder mix. The aim of this study was to investigate the potential for the application of interfacial parameters to aid in the understanding of the processes of extrusion and spheronisation, and to assess the possibility of using such measurements to predict the composition of formulations with optimum properties.

A number of publications have demonstrated that interfacial energy terms may be used to predict the interaction between different components of formulations, e.g., binders in granulations (e.g., Rowe, 1989a,b), powder dispersion in aqueous (Young and Buckton, 1990) and non-aqueous (Parsons et al., 1992a) suspensions, and the tendency for suspended material to adhere to the walls of different containers (Parsons et al., 1992a). Each of the publications referred to considered comparatively simple formulations (inasmuch as there was a high probability that the interaction under investigation (e.g., binder/substrate) would be a dominant factor in the properties of the system (e.g., granule strength), the current study is considerably more difficult, as the processes of extrusion and spheronisation are complex, and the important interactions within the formulation are as yet largely unquantified.

There are a number of ways of considering interfacial interactions, including the work of adhesion (W_a) between two phases, the work of cohesion (W_c) of any one phase, and the tendency for one phase to spread over another (represented by λ, the spreading coefficient, which is $W_a - W_c$). Numerically, the work of cohesion is equal to twice the surface energy of that phase. Surface energy values are easy to measure for liquids (as the surface tension), but must be estimated for solids from contact angle data. A well documented, approach to the estimation of solid surface energies is to use the reciprocal mean equation of Wu (1973), in the manner described by Zografi and Tam (1976). Using this approach it is possible to estimate the surface energy and its constituent polar [1] and dispersion contributions, from contact angle measurements made on the test solid using two liquids (each of known surface tension and polarity). Having obtained the surface energy values, it is possible to calculate data for W_a and W_c (in the case shown for phase 1):

$$W_a = 4\left[\frac{\gamma_1^p \cdot \gamma_2^p}{\gamma_1^p + \gamma_2^p} + \frac{\gamma_1^d \cdot \gamma_2^d}{\gamma_1^d + \gamma_2^d}\right] \quad (1)$$

$$W_c = 2\gamma_1 \quad (2)$$

where superscripts p and d refer to polar and dispersion components of the surface energy terms (γ), and subscripts identify phases 1 and 2.

2. Materials and methods

2.1. Materials

Indomethacin was obtained from Bechpharm (median particle size 57.0 ± 1.9 μm (Malvern Master Sizer), melting range 154.3–155.8°C, and density 1.36 g/cm^3 (Beckman air pycnometer)). Powdered excipients were lactose EP (Meggle-Wasseburg; 16.8 ± 0.4 μm, density 1.54 g/cm^3), microcrystalline cellulose (MCC) (Avicel PH-101 (FMC); 53.8 ± 0.5 μm, density 1.54 g/cm^3), glyceryl monostearate (Pfaltz and Bauer; < 125 μm, density 0.98 g/cm^3) and barium sulphate (BDH; 16.3 ± 0.8 μm, density 4.38 g/cm^3). Liquids used were freshly distilled water and propylene glycol (Macarthy).

2.2. Assessment of the surface energy of the powders

The powders were compacted into plates by compressing 150 mg of powder in a rectangular

[1] The 'polar' contribution to surface energy has now been recognised to originate from interactions between acidic and basic sites of the materials. Any exhaustive treatment of interfacial phenomena must be based on Lewis acid-Lewis base interactions, rather than 'polar' forces (Fowkes, 1987). However, within the context of the current study, which attempts to probe the possibility of use of interfacial phenomena to understand behaviour in such complex systems, the acid-base components have not been extracted.

Table 1
A summary of the formulations used in this study

Code	Lactose (%)	Microcrystalline cellulose (%)	Indomethacin (%)	Barium sulphate (%)	Glyceryl monostearate (%)
0	62.5	37.5			
I_1	59.4	37.5	3.1		
I_2	56.25	37.5	6.25		
I_3	50.0	37.5	12.5		
I_4	37.5	37.5	25.0		
I_5	25.0	37.5	37.5		
B		20.0		80.0	
BG		20.0		50.0	30.0

All the powders were mixed in the above proportions then mixed with water in the powder/water ratio of 8:3.

punch and die (20.00×7.07 mm) in a Specac hydraulic press at 5000 kg force for 5 min. The plates had an average thickness of 0.95 ± 0.05 mm. The width and thickness of each plate was measured individually using a micrometer, and each individual measurement (rather than the mean value) was used in subsequent calculations. The liquid surface tensions and the contact angles of the liquids on the plates were determined by use of a Cahn Dynamic Contact Angle Analyser (using a Wilhelmy plate method), by immersing the plates 2.0 mm into the liquid (water and propylene glycol) at a speed of 20.0 μm/s (see Zajic and Buckton (1990) for further details of the experimental system).

2.3. Production of the spheres

The powders were mixed for 20 min (Turbula mixer T2C) in the proportions shown in Table 1. The mixing time was investigated and found to be optimal by sampling for content uniformity at different positions at different time intervals (UV assay for indomethacin at a wavelength of 264 nm). The dry mixture was transferred to a planetary mixer (Kenwood Chef) and the wet mass was produced by adding the water during mixing at 90 rpm for 10 min. The quantity of water added was always in the powder mixture/water ratio of 8:3. The formed wet mass was allowed to stand in a sealed plastic bag for 12 h to ensure good water distribution.

The mass was extruded using a ram extruder mounted in a mechanical press (Lloyds instruments MX50). The ram extruder consisted of a stainless-steel barrel of 2.54 cm internal diameter and 20 cm length, with a centrally mounted die (radius 1 mm, length 4 mm) in the base plate. The wet mass was extruded at a constant speed of 400 mm/min, and the portion of extrudate ob-

Table 2
Measured properties of spheres

Code (see Table 1)	Crushing force (kg) ($n = 10$)	Density (g cm^{-3}) ($n = 5$)	Porosity (%)	OPCS (°)	Median diameter (IQR) (mm)
0	1.85 ± 0.32	1.52 ± 0.01	1.6	18.3	1.34 (0.24)
I_1	1.44 ± 0.18	1.47 ± 0.01	4.4	17.0	1.29 (0.26)
I_2	1.49 ± 0.26	1.46 ± 0.01	4.7	22.0	1.21 (0.36)
I_3	1.17 ± 0.24	1.45 ± 0.01	4.7	23.8	1.07 (0.28)
I_4	1.40 ± 0.17	1.45 ± 0.01	3.3	21.2	1.27 (0.32)
I_5	1.21 ± 0.16	1.44 ± 0.01	2.5	18.9	1.31 (0.26)
B	0.49 ± 0.15	3.14 ± 0.03	15.3	16.8	1.39 (0.19)
BG	0.24 ± 0.09	1.42 ± 0.02	38.0	24.5	1.25 (0.43)

IQR, interquartile range.

Table 3
Surface tension and the polar and dispersion components of the liquids used for contact angle determinations (all in mN m^{-1})

	γ	γ^d	γ^p
Water	72.0	21.7	50.3
Propylene glycol	38.0	28.6	9.4
Decane	24.0	24.0	0.0

tained during steady-state flow was collected and spheronised (Harrison et al., 1985).

The spheroniser (Caleva) consisted of a 27.5 cm diameter radially cut plate which was rotated at 1000 rpm for 20 min. The spheroniser was only partially covered to allow water vapour to escape. The spheres were dried in a fluid bed drier (60°C air flow for 20 min) (PRL Engineering).

2.4. Characterisation of the process and products

The spheres obtained were assessed in terms of their particle size distribution (Endecott analytical sieves, after shaking for 10 min), strength (CT40 Engineering Systems), density (Beckman air pycnometer) and shape (using the one plane critical stability (OPCS) model (Chapman et al., 1988)). The OPCS system describes the theoretical angle through which the spheroid must be tilted before it will roll under gravity, thus the lower the value the more spherical the particle.

3. Results

The properties of the spheres that were obtained for the various formulations are presented in Table 2. The surface energy terms of the liquids used for contact angle measurements are listed in Table 3, and the values of contact angle (expressed in the more appropriate form of cos θ (Parsons et al., 1992b)) formed by the two liquids on the three powders are presented in Table 4, together with the calculated values for the solid surface energy terms. Calculated works of adhesion, works of cohesion and spreading coefficients are presented in Table 5.

4. Discussion

The densities of the spheres containing various proportions of indomethacin, lactose and microcrystalline cellulose (Table 2) were found to change from 1.52 ± 0.01 g cm^{-3} for the formulation with no indomethacin present, to approx. 1.46 g cm^{-3} for the batches of spheres with indomethacin. This difference is significant at $p < 0.05$. Despite the fact that indomethacin has a slightly lower density than either MCC or lactose (1.36, 1.54 and 1.54 g cm^{-3}, respectively), it is extremely unlikely that the inclusion of such small quantities of the drug could be directly

Table 4
Contact angle data and calculated surface free energy terms for the components of the spheres

(a) Using water and propylene glycol as test liquids

	Cos $\theta \pm$ SD(water)	Cos $\theta \pm$ SD (propylene glycol)	γ (mJ m^{-2})	γ^d (mJ m^{-2})	γ^p (mJ m^{-2})
Indomethacin	0.284 ± 0.051	0.861 ± 0.049	36.7	19.6	17.1
Lactose	0.853 ± 0.042	0.952 ± 0.016	62.2	17.3	44.9
Microcrystalline cellulose	0.879 ± 0.065	0.958 ± 0.028	63.9	17.3	46.6
Glyceryl monostearate	0.274 ± 0.048	0.810 ± 0.030	35.7	18.0	17.7

(b) Using decane and propylene glycol as the test liquids

	Cos $\theta \pm$ SD (decane)	Cos $\theta \pm$ SD (propylene glycol)	γ (mJ m^{-2})	γ^d (mJ m^{-2})	γ^p (mJ m^{-2})
Barium sulphate	0.991 ± 0.025	0.888 ± 0.002	32.6	24.8	7.8

Contact angle data are means of at least six replicate plates

responsible for this change. Simply working on the basis of weighted means, a powder mixture of 5 parts of lactose and 3 parts of MCC would have a density of 1.54 g cm^{-3}, and a powder mixture of 3 parts indomethacin, 2 parts lactose and 3 parts of MCC would have a density of 1.48 g cm^{-3}, thus the change in density of the indomethacin should contribute only slightly to the change in density of the sphere, consequently, it is far more likely that the change in density of the spheres is due to a repacking of the systems due to different interactions within the moist mass as a consequence of the inclusion of the indomethacin (this cannot be proved, but only hypothesised from the observations), than to any intrinsic difference in the densities of the raw materials. Similarly, the force required to break the spheres is reduced from 1.85 kg to about 1.4 kg (statistically significant at $p < 0.05$). For both the changes in strength and density, there is no evidence of a gradual change in response with increased concentration of indomethacin, but rather all formulations with indomethacin present are essentially similar, but different from the formulation which has just lactose and MCC. This observation is perhaps surprising, when it is considered that the indomethacin content is varied from about 3 to 37.5%. The OPCS (shape) and the median size of the six formulations are not significantly different, and equally the fact that the formulation without added indomethacin has the narrowest size distribution (smallest inter-quartile range) cannot be regarded as being a significant difference.

The differences in properties of the formulation with just lactose and microcrystalline cellulose, compared to the five formulations with varying amounts of added indomethacin can be explained by considering the data in Table 5. Firstly, it is seen that the spreading coefficient values are significant and positive for the spreading of indomethacin over both lactose (12.9) and MCC (13.46 mJ m^{-2}), but only marginally positive for the spreading of lactose over MCC (1.7 mJ m^{-2}). This implies that the drug will have a greater tendency to spread over (or in this case disperse in) the excipients than will the excipients have to mix with each other. This extension of interfacial phenomena to solid/solid interactions is unconventional, however, it is not entirely unprecedented (e.g., Rowe (1989c) investigated the spreading of dry coloured powders over each other with some success). Care must be taken with such interfacial predictions not to assume that the powders are really spreading (in the true sense of the word), but to assert that the interaction between powders with a high spreading coefficient is likely to be more favourable than that between those with a low spreading coefficient. Currently, there is no evidence to suggest that solid/solid mixing efficiency can be predicted in terms of spreading coefficients, although as a low spreading coefficient is indicative of a low tendency for surfaces to interact it might be expected that in an energetic mixer particles may associate with other particles in order to minimise 'interfacial' (particle/particle) tensions. It is possible then, that the high spreading coefficients for indomethacin over the excipients will translate into a greater tendency for it to be uniformly dispersed.

Secondly, the values for W_a between indomethacin and the excipients (86.8 mJ m^{-2} indomethacin/lactose, 86.0 mJ m^{-2} in-

Table 5
Works of adhesion (W_a) for the different powders and spreading coefficients of the powder (1) over powder (2) and vice versa

	W_a (mJ m^{-2})	λ_{12} (mJ m^{-2})	λ_{21} (mJ m^{-2})
1:IND 2:LAC	86.3	12.94	−38.16
1:IND 2:MCC	86.8	13.46	−41.04
1:LAC 2:MCC	126.1	1.68	−1.72
1:MCC 2:BaS	67.4	−60.41	2.29
1:MCC 2:GM	86.6	−41.23	15.15
2:BaS 2:GM	63.3	−1.77	−8.09

Table 6
Surface tension and the polar and dispersion components of the liquids used for contact angle determinations (all in mN m^{-1})

	γ	γ^d	γ^p
Water	72.0	21.7	50.3
Propylene glycol	38.0	28.6	9.4
Decane	24.0	24.0	0.0

domethacin/MCC) were much lower than between MCC and lactose (126 mJ m^{-2}). This implies that (bearing in mind the reservations relating to use of interfacial phenomena to application in solid/solid interfaces) bonds between lactose and MCC will have a tendency to be stronger than bonds between indomethacin and either of the excipients.

The implications of the interfacial predictions are that the indomethacin will have a tendency to spread readily throughout the excipients, but that bonds formed between the indomethacin and the excipients will tend to be weaker than those between the two excipients. These predictions are in good agreement with the observed results, in that the formulation without added indomethacin was more dense, and required a higher force to break the spheres, i.e., the values of W_a (126 mJ m^{-2}) and W_c for the two excipients (124 mJ m^{-2} for lactose and 128 mJ m^{-2} for MCC) all suggest strong bonding. When indomethacin is added, even at low % content, it spreads readily through the mixture, but results in lower bonding strengths (W_a approx. 86 mJ m^{-2}), thus the sphere is not pulled together so strongly (lower density), and is broken with a lower applied force. On this basis it is not surprising that the properties of the spheres with indomethacin present do not change with increased drug loading, as the forces will be essentially identical.

Having considered the behaviour of different proportions of the same ingredients in the spheroid, it is interesting to consider how well the surface energy predictions compare with the observed behaviour for totally unrelated systems. Considering the other formulations in Table 2 it can be seen that the crushing force was greatly reduced (in comparison with the indomethacin based formulations) for the formulation containing barium sulphate and microcrystalline cellulose, and reduced still further when glyceryl monostearate was added to these two ingredients. The porosities for these two formulations are also very much higher than those for the indomethacin based spheroids. For these (non-indomethacin) formulations it is not reasonable to consider the changes in product density as glyceryl monostearate has a comparatively low whilst barium sulphate has a very high density.

From the data in Table 5 it can be seen that barium sulphate has the lowest work of adhesion values (being low with both glyceryl monostearate and microcrystalline cellulose, 63.3 and 67.4 mJ m^{-2}, respectively, compared with 126.1 mJ m^{-2} for lactose and microcrystalline cellulose). These low work of adhesion values correlate well with the observations of weak highly porous spheroids. Furthermore, if the spreading coefficients are considered, the glyceryl monostearate is predicted to disperse over the microcrystalline cellulose, this favourable dispersion linked with the low adhesive interaction and low cohesive strength of the glyceryl monostearate again correlate well with the observations of a weaker product.

In this particular study, it is reasonable to assume that interfacial considerations, rather than any other aspect of the formulation dominates the process, on the basis that these interfacial considerations fit in well with the measured properties. However, it is clear that an essential part of the formulation of spheroids relates to the interaction of water with the excipients (in particular the role of MCC), and as this is not considered by these interfacial calculations, it would only be possible to compare directly formulations made under the same conditions (in terms of processing, water and MCC content) for changes in, for example, drug content. Furthermore, the solubility of different excipients in the water will in certain circumstances cause different interfacial phenomena to dominate. It follows that an element of quantitative prediction should be possible based on measurements on similar formulations, but only qualitative prediction would be possible when comparing the indomethacin formulations with those containing glyceryl monos-

tearate and barium sulphate (and a different quantity of microcrystalline cellulose).

The conclusion to this study is that interfacial phenomena play a vital role in determining the behaviour of wet powder masses, and the properties of the spheroids that are produced from them, however, due to the extreme complexity of the formulations and the processing stages, it remains to be seen how generally applicable the predictions obtained from surface energy data will be.

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