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The use of surface energy and polarity determinations to predict physical stability of non-polar, non-aqueous suspensions

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Summary

Suspensions of five model micronised particles (indomethacin, isoprenaline, aspirin, polytetrafluoroethylene (PTFE) and beclomethasone, which were selected for their range of surface energies and polarities) in a non-polar, non-aqueous liquid (Arcton 113 – a model aerosol propellent) were prepared and assessed for ease of solid dispersion, tendency for solid aggregation and the extent of adherence of solid to the container walls (the effect of coating the container walls in order to alter its surface energy and polarity was also investigated). The surface energies and polarities of all the solids, the materials used to make and/or coat the container, and Arcton 113 were estimated from the necessary contact angle and surface tension measurements. The experimentally observed properties of the suspensions were compared to the theoretical interactions, i.e., ease of dispersion was found to correlate with the work of cohesion of the particles and the spreading coefficients of the powders over Arcton 113; the extent of aggregation of the particles correlated with their polarity (and was unrelated to the liquid properties), whilst the extent of adherence of particles to the surface of the container correlated with the difference between the works of adhesion between the particles and the container and the works of adhesion between the particles and Arcton 113 (changing the surface properties of the container resulted in different extents of adherence, but all results approximately fitted one master curve). By obtaining estimates of surface energies and polarities, it should be possible to predict the ease of manufacture and the physical stability of many non-aqueous, non-polar suspensions, such as metered dose inhaler products. It is well known that processing (e.g., milling) can affect powder surface energies, and the possibility that processing stages can be planned to optimise a product's physical stability is discussed.

Introduction

Non-aqueous, non-polar suspensions are used in the production of metered dose inhalers. With such systems it is usual to suspend the drug in a liquid propellant, which is currently a chlorofluorocarbon. In order for the drug to penetrate deep into the lung and remain there, it is necessary for the drug particles to be between 2 and 5 μm in size. To obtain this particle size, the drug must be micronised and subsequently be delivered in this micronised form. The problems that inevitably occur with such systems is that the high surface area, and the associated surface free energy, of

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the drug will tend to result in aggregation of the drug and/or adhesion to the container wall, as the system attempts to minimise total surface free energy. The purpose of this study was to investigate the extent to which aggregation and adhesion to the container can be predicted by estimates of surface free energies, and if such predictions are possible, whether improvements to formulations could be made from such a theoretical basis.

Recent publications (Rowe, 1989a,b, 1990; Young and Buckton, 1990; Zajic and Buckton, 1990) have demonstrated that surface free energies and polarity estimates allow reasonable predictions to be made of the behaviour of dosage forms. This previous work has dealt with such aspects as the choice of binder for wet granulation (e.g., Rowe, 1989a,b; Zajic and Buckton, 1990), predicting the properties of formed tablets on the basis of the interactions between the binder and the drug (Rowe, 1990), and the tendency of drugs to aggregate in aqueous suspensions (Young and Buckton, 1990). In such complex systems (as those already investigated), it is a little surprising that the surface energetics have played such a major role as to allow predictions of behaviour, as many other factors are likely to be involved in the interactions. With non-polar, non-aqueous suspensions, however, it is likely that surface energetic interactions will play a very significant role in determining the behaviour, as other parameters (e.g., electrostatic charges) will not be significant in these suspensions.

Theory

The theory for the determination of surface energies and polarities is based on the reciprocal mean approach of Wu (1973). Essentially, if a contact angle (θ) is measured against two liquids of known surface energy (γ) and polarity, then it is possible to estimate the surface energy and polarity of the solid (for details see, for example, Zografi and Tam (1976)).

Having obtained the surface free energies and polarities for the solids and the liquids, it is possible to consider the potential for cohesion, adhesion and spreading, as the work of cohesion (W_c) (of phase 1) is:

$$W_c = 2\gamma_1 \tag{1}$$

the work of adhesion (W_a) between phases 1 and 2 is:

$$W_a = 4\left[\frac{\gamma_1^d \cdot \gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p \cdot \gamma_2^p}{\gamma_1^p + \gamma_2^p}\right] \tag{2}$$

(where the superscripts designate polar (p) and dispersion (d) contributions to the surface energy) and the spreading coefficient (λ_{12}) of phase 1 over phase 2 is the difference between the works of adhesion and cohesion, i.e.

$$\lambda_{12} = 4\left[\frac{\gamma_1^d \cdot \gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p \cdot \gamma_2^p}{\gamma_1^p + \gamma_2^p} - \frac{\gamma_1}{2}\right] \tag{3}$$

The spreading coefficient of phase 2 over phase 1 (λ_{21}) can be calculated in a similar manner.

Materials and Methods

Materials

Five powders were selected for use in this study. Two powders were chosen on the basis that they are used for inhalation therapy (beclomethasone (3.8 μm) and isoprenaline (3.3 μm), both ex-Lilly Research), whilst the other solids were selected, as models, on the basis that they would provide a range of surface energies (aspirin (5.8 μm, Monsanto), indomethacin (3.0 μm, Becpharm) and polytetrafluoroethylene (PTFE) (6.6 μm, Goodfellow). The median particle sizes that are quoted above were determined using laser diffraction (Malvern, 2600c) after sonication (in an ultrasonic bath) in the presence of a surfactant (to prevent aggregation). The energy of the ultrasonic bath was not sufficiently great to induce size reduction, and the sizes were determined in solvents in which the solids were insoluble. Arcton 113 (ICI) was used as a model propellant (as it has similar physical properties to those which are currently used for metered dose inhalers, with the exception that it is liquid at room temperature). The liquids used for contact angle measurements were water (double distilled) and methylene iodide (Aldrich). Other liquids used were 'Repelcoat' (BDH) and octadecyltrimethylchlorosilane (OTMCS).

Methods

Measurement of surface energies and polarities of the liquids

As described under Theory, all the surface energies and polarities were assessed by use of two probes; in the case of determinations for liquid samples, this involved using a clean glass plate (to measure surface tension, i.e., zero contact angle) and then to measure a contact angle between the liquid and Parafilm. As the surface energy of paraffin is well known it is possible to determine the surface energy (i.e., the surface tension) and the polarity of the unknown liquid (see Zografi and Tam (1976)). The equipment used for both the surface tension measurements and the measurements of contact angle was a Cahn Dynamic Contact Angle Analyser.

Assessment of the surface energies and polarities of the solids

The powders were compacted into thin rectangular plates and contact angles were measured using water and methylene iodide as probe liquids (see Zajic and Buckton (1990) for details of the method). From these contact angles, and the surface energies and polarities of the probe liquids, the surface energies and polarities of the solids were calculated. For PTFE a solid plate was used to obtain an assessment of the surface energy, and this was assumed to be the same as that of the particulate sample.

Preparation of the suspensions

The suspensions were prepared individually by adding 10 mg (accurately weighed) of drug to 15 ml of Arcton 113 in a scintillation vial. Wetting was achieved by shaking, followed by sonication as described below. The concentration (10 mg/15 ml) was selected to allow direct use in the Malvern 2600c laser diffraction particle sizer (without the need for dilution). All drugs investigated were essentially insoluble in Arcton 113.

Assessment of the suspensions

In considering the properties of the suspensions, three parameters were assessed: the initial ease of dispersion, the degree of aggregation and the extent of adhesion of the powder to the container.

Ease of dispersion

As an indication of the ease of dispersion, the solids were introduced into the Arcton 113 and the particle size was assessed using a laser diffraction method (Malvern, 2600c). In all cases (except PTFE), the measured size was greater than the primary size of the particles, indicating that dispersion was not instantaneous. Different samples of the suspensions were then sonicated for a defined time and then immediately sized (Malvern, 2600c). The duration of sonication that was needed to achieve a suspension of the primary particle size was taken as an indication of the ease of dispersibility.

Degree of aggregation

Once the suspensions had been formed, and sonicated to reach their primary particle size, they were stored in sealed glass bottles at a constant temperature of 25°C. Numerous replicate suspensions of each solid were prepared at the same time and stored together. At selected time intervals (1, 2, 3, 4, 5, 7, 14 and 28 days), five bottles of each suspension were removed from storage and the particle size was measured, by gently pouring the suspension into the measuring cell of the Malvern (each individual suspension was only removed and measured once: for further time intervals other bottles were removed from storage, and these had not been disturbed since manufacture). The sizing process was repeated until the sizes reached a plateau value.

Adhesion to the container wall

Suspensions of four of the solids (indomethacin, isoprenaline, aspirin and PTFE) were prepared as before, and stored for 1 week at 25°C. In

TABLE 1

The values of cosine of contact angle (θ) for the various solids with water and methylene iodide, together with the calculated surface energies and polarities for the solids and liquids

	Cos θ		Surface energy (mN/m)			% polarity
	Water	Methylene iodide	γ^d	γ^p	Total	
Indomethacin	0.0187	0.9974	50.3	2.4	52.7	4.6
Isoprenaline	0.9334	0.8198	42.1	33.6	75.7	44.4
Aspirin	0.4053	0.8725	44.4	12.6	56.9	22.1
PTFE	−0.4089	0.1137	19.5	0.0	19.5	0.0
Beclomethasone	0.0499	0.8689	44.0	3.9	47.9	8.1
Repelcoat	0.6068	0.6251	34.3	21.9	56.2	39.0
OTMCS	−0.6029	−0.3200	10.3	−0.8	9.5	0.0
Clean glass	1.000	0.7530	39.3	39.0	78.3	49.8
Water	–	–	72.8	48.8	24.0	67.0
Methylene iodide	–	–	50.4	0.0	50.4	0.0
Arcton 113	–	–	19.0	0.0	19.0	0.0

this case, the bottle was accurately weighed before adding the suspension, and then weighed again after pouring the suspension out of the container, rinsing the container with Arcton 113, and allowing the residual Arcton 113 to evaporate (to constant weight).

Results and Discussion

The contact angles of water and methylene iodide on the solids are presented in Table 1, as are the surface energies and fractional polarities of the powders, the liquids, glass and the coated glass samples. The values of the work of cohesion of the solids, and the works of adhesion between the solids and Arcton 113 are listed in Table 2, along with the spreading coefficients of solid over liquid, and liquid over solid. The values of the works of adhesion and the spreading coefficients of the solids and clean glass are presented in Table 3, and for the solids and the coated glass in Table 4.

Ease of dispersion

Comparisons of the time required to achieve the primary particle size for the suspensions (i.e., an assessment of ease of dispersion) and the surface energy and polarity data revealed that a relationship exists between the work of cohesion (of the solids) and the sonication time (Fig. 1). From Fig. 1 it can be concluded that the greater the work of cohesion the harder it will be to

TABLE 2

Calculated works of cohesion (W_c) of the solids, the works of adhesion (W_a) between the solids and Arcton 113, and the spreading coefficients of solid (S) over liquid (L) and liquid over solid (all values quoted in mN/m)

	W_c	Arcton 113		
		W_a	λ_{LS}	λ_{SL}
Indomethacin	105.4	55.2	17.2	−50.2
Isoprenaline	151.4	52.4	14.4	−99.0
Aspirin	113.9	53.3	15.2	−60.6
PTFE	39.0	38.5	0.5	−0.5
Beclomethasone	95.8	53.2	15.1	−42.6

TABLE 3

Calculated work of adhesion (W_a) and spreading coefficients (λ) for solid powders (S) and glass (G) (all values in mN/m)

	Clean glass		
	W_a	λ_{LS}	λ_{SL}
Indomethacin	97.4	−8.0	−59.2
Isoprenaline	153.5	2.1	−3.1
Aspirin	121.4	7.5	−35.1
PTFE	52.1	13.1	−104.4
Beclomethasone	97.2	1.4	−59.4

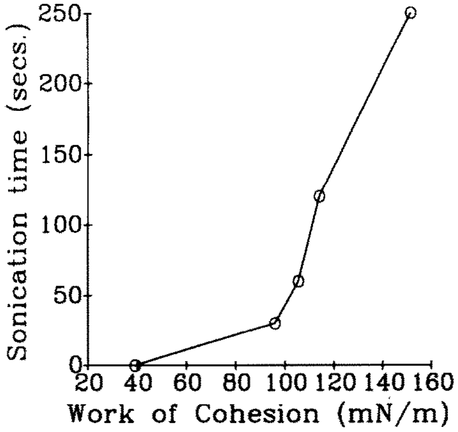

Fig. 1. Sonication time required to reach primary particle size for suspensions of various solids in Arcton 113, as a function of the work of cohesion of those solids.

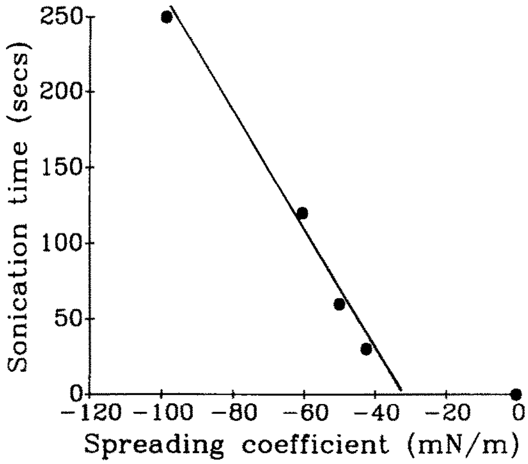

Fig. 2. Sonication time required to reach primary particle size for suspensions of solids in Arcton 113 as a function of the spreading coefficient of the solids over Arcton 113.

disperse the powder in the liquid; this is as expected and demonstrates that surface energies are of potential value in predicting the behaviour of non-polar non-aqueous suspensions. The spreading coefficients of the solid over the liquid and conversely of the liquid over the solid can also be compared with the ease of dispersion (sonication time), as it is not unreasonable to assume that the properties of the liquid (as well as W_c) will contribute to the ease of dispersion. The values of λ_{LS} are all positive (Table 2) and (with the exception of PTFE) are all similar (approx. 15 mN/m); this indicates that the liquid will spread over the solids (ironically with the possible exception of PTFE which has a very low value of λ_{LS} despite its easy dispersion in Arcton 113), and it may be the very fact that Arcton 113 spreads so easily over the solids that results in the ease of dispersion being so strongly linked to W_c (i.e., the ease of dispersion seems to relate to the ease with which the solid-solid cohesion can be disrupted, rather than any problems with distribution in the liquid). If the sonication time is plotted as a function of the spreading coefficient of the solid over the liquid (λ_{SL}) (Fig. 2), a linear relationship ($r = 0.99$) is observed which intersects the x-axis at −33 mN/m. This intercept indicates that dispersion may be spontaneous as long as λ_{SL} is greater than −33 mN/m. The figure of −33 mN/m has no obvious origin, and it seems likely that the intercept should theoretically be at −18 mN/m (which is the approximate surface energy of Arcton 113), in which case if

TABLE 4

Calculated work of adhesion (W_a) and spreading coefficients (λ) for various powders and coated glass substrates (G) (all values in mN/m)

	OTMCS			Repelcoat		
	W_a	λ_{SG}	λ_{GS}	W_a	λ_{SG}	λ_{GS}
Indomethacin	29.2	−76.2	10.2	90.3	−15.1	−22.2
Isoprenaline	29.8	−121.6	10.8	128.7	−22.7	16.2
Aspirin	30.0	−83.9	11.0	109.4	−4.5	−3.1
PTFE	27.0	−12.0	8.0	49.7	10.7	−62.7
Beclomethasone	29.3	−66.5	10.2	90.3	−5.5	−22.2

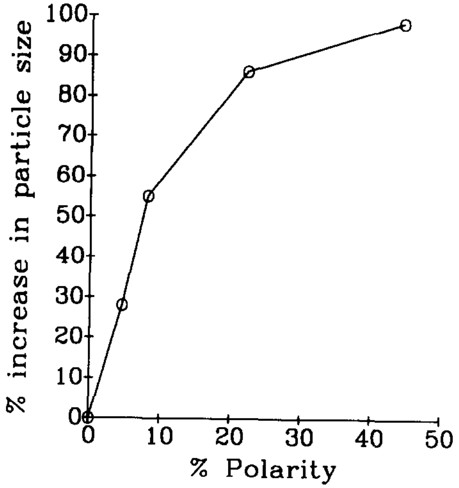

Fig. 3. Percentage increase in particle size after storage (plateau value) as a function of the % polarity of the solid.

λ_{SL} is greater than the surface energy of the non-polar liquid that is used to form the suspension, then spreading will not be spontaneous. A similar hypothesis has been presented before (Young and Buckton, 1990) for aqueous suspensions, where it was suggested that solids would spontaneously disperse in the liquid if the spreading coefficient was greater than the dispersion component of the surface energy of water.

Degree of aggregation

The degree of aggregation, as assessed by increases in particle size, has been calculated as the % increase in size above the primary particle size. Having recorded these figures, it was apparent that no correlation existed with either λ_{SL} or λ_{LS} neither was there any correlation with values of W_c or W_a, however, a near-exponential relationship exists between the increase in size and the % polarity of the solid (Fig. 3), ranging from PTFE which is non-polar and does not aggregate, to isoprenaline which is 44.4% polar and which aggregates substantially. Thus, for suspensions in a completely non-polar liquid, the tendency to aggregate can be predicted on the basis of the polarity of the solid, and is apparently unrelated to the surface energy of the liquid. It is interesting that the water content of a powder is often quoted as influencing the extent of aggregation in non-aqueous suspensions; as the tendency for water to sorb will be directly related to the polarity, this is totally in agreement with the results presented here.

As the degree of aggregation in such systems is apparently independent of the non-polar liquid (i.e., entirely dependent upon the % polarity of the solid), it follows that any factors which affect the surface energy (and more particularly the % polarity of the solid) will affect this aspect of physical stability of such suspensions. It has been reported before (e.g., Buckton et al., 1988) that physical treatment of powders, such as the milling technique, will alter the surface energy. Thus, the tendency to aggregate is likely to be very dependent upon the powder processing history, and any changes in surface energies of the powder that occur with age (either during storage prior to formation of the suspension, or after the suspension has been made). Research is continuing into these aspects, but it seems possible that the appropriate selection of processing procedure may be of value in optimising the physical stability of such systems.

Adhesion to the container wall

The results for the weight of solid adhering to the glass containers were significantly different, ranging from 3.65 ± 0.77 mg ($n = 19$) for isoprenaline to 0.06 ± 0.09 ($n = 10$) for PTFE. There was no obvious correlation between the W_c or spreading coefficient values and the amount adhering, however, as may be expected, a relationship was detected between the work of adhesion between the particles and the glass (Fig. 4). It is perhaps more appropriate to consider the difference in W_a between the particle and glass and the particle and the liquid (Fig. 5). The exponential relationship in Fig. 5 is seen to pass through the origin, and it is reasonable to assume that adhesion to the glass will occur if W_a to the glass is greater than W_a between the particles and Arcton 113.

When the glass container is coated, in order to change its surface energy and polarity, the amount of drug adhering was found to change. Coating with Repelcoat yields a surface with a lower surface energy and polarity than glass (Table 1)

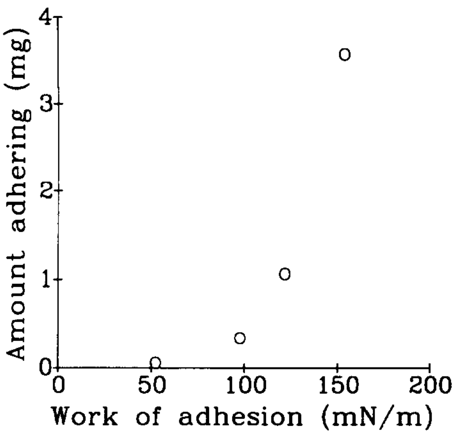

Fig. 4. The weight of solid adhering to the container as a function of the work of adhesion between the solid and glass.

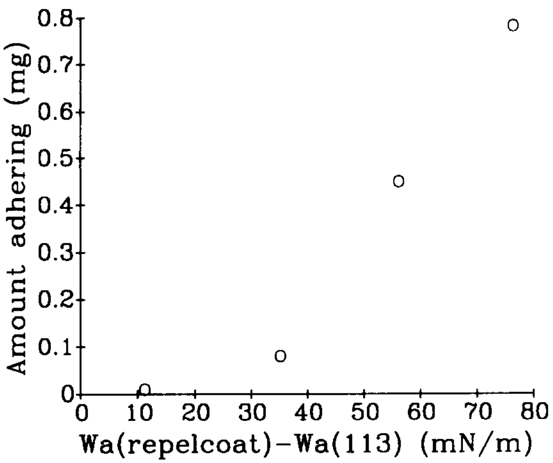

Fig. 6. The weight of solid adhering to the container wall as a function of the difference between the works of adhesion between the solids and Repelcoated glass and the works of adhesion between the solids and Arcton 113.

and thus the calculated works of adhesion between the solid model drugs and the Repelcoated surface are lower. The plot of amount of drug adhering to the Repelcoated container as a function of the difference between W_a between the particles and the container and W_a between the particles and Arcton 113 is presented in Fig. 6. It can be seen that the amount of drug adhering is significantly lower than for the clean glass container (Fig. 5). If the glass is coated with OTMCS the surface has zero polarity and a very low surface energy (Table 1), consequently the values of W_a for the model drugs onto this surface are also very low, resulting in the difference between W_a (particles/OTMCS) and W_a (particles/Arcton 113) being negative in all cases; consequently it is not surprising that (within experimental error) no adhesion of particles was detected for the

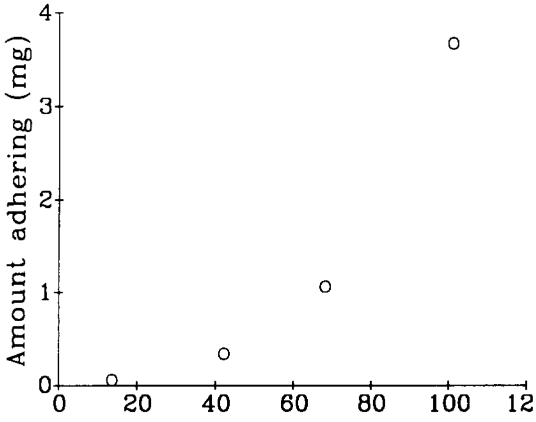

Fig. 5. The weight of solid adhering to the container wall as a function of the difference between the works of adhesion between the solids and glass and the solids and Arcton 113.

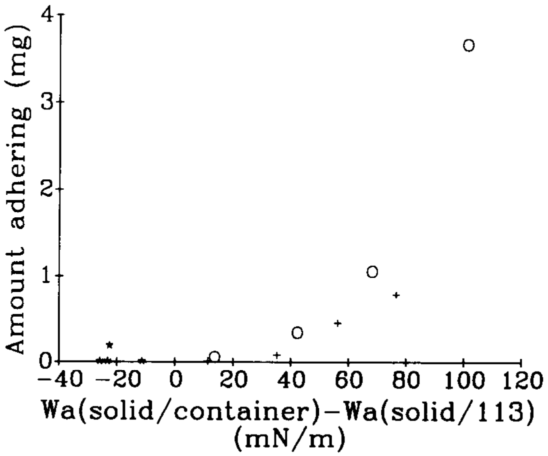

Fig. 7. The weight of solids adhering to the container wall as a function of the difference between the works of adhesion between the solids and the containers and the solids and Arcton 113 (○) Glass container; (+) Repelcoated glass container; (∗) OTMCS coated glass container.

OTMCS coated glass, indicating that this would lead to an improvement in the quality of a metered dose inhalation formulation, e.g., isoprenaline adherence was reduced from approx. 35% onto glass, to 0% onto OTMCS.

The differences in the works of adhesion between the surfaces of the different containers and the model drug particles and between the particles and Arcton 113 are all presented together in Fig. 7. Within the limits of experimental error, the points on Fig. 7 fit to a single-exponential curve, passing through the origin. Thus, this curve should provide a method by which the extent of drug loss to a container can be estimated if W_a (container/particle)-W_a (particle/liquid) is calculated from surface energy and polarity data.

Conclusion

For each of the three parameters investigated (ease of dispersion, particle aggregation and adhering of particles to the container wall), an aspect of the surface energy and polarity data was found to correlate with the experimental data (the W_c of the particles and the spreading coefficients with ease of dispersibility; the % polarity of the particles with the degree of aggregation; a difference between W_a values with the amount adhering to the container walls).

Predictions made using surface energy and polarity data would allow a logical and reliable approach to the formulation of non-polar, non-aqueous suspension, such as metered dose inhalers. Furthermore, a detailed understanding of how and why processing (e.g., choice of micronisation technique) affects the surface energy and polarity of solids may allow processing to be selected to optimise the product's physical stability.

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References

Buckton, G., Choularton, A., Beezer, A.E. and Chatham, S.M., The effect of the comminution technique on the surface energy of a powder. *Int. J. Pharm.*, 47 (1988) 121–128.

Rowe, R.C., Surface free energy and polarity effects in the granulation of a model system. *Int. J. Pharm.*, 53 (1989a) 75–78.

Rowe, R.C., Polar/non-polar interactions in the granulation of organic substrates with polymeric binders. *Int. J. Pharm.*, 56 (1989b) 117–124.

Rowe, R.C., Correlation between predicted binder spreading coefficients and measured granule and tablet properties in the granulation of paracetamol. *Int. J. Pharm.*, 58 (1990) 209–214.

Wu, S., Calculation of interfacial tension in polymer systems. *J. Polym. Sci. C.*, 34 (1973) 39–55.

Young, S.A. and Buckton, G., Particle growth in aqueous suspensions: the influence of surface energy and polarity. *Int. J. Pharm.*, 60 (1990) 235–241.

Zajic, L. and Buckton, G., The use of surface energy values to predict optimum binder selection for granulations. *Int. J. Pharm.*, 59 (1990) 155–164.

Zografi, G. and Tam, S.S., Wettability of pharmaceutical solids: estimates of solid surface polarity. *J. Pharm. Sci.*, 65 (1976) 1145–1149.