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Particle growth in aqueous suspensions: the influence of surface energy and polarity

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Summary

The aggregation of drug particles in suspensions can cause products to be spoiled. In this paper the role of surface energetics in controlling the dispersion of powders in water is considered, by use of a spreading coefficient. The contact angles, surface energies and the polarities were determined for a series of barbiturate powders. Contact angles were measured using a Wilhelmy plate technique. Aqueous suspensions of each powder were prepared and the change in particle size was monitored over a period of hours and days. By extrapolation the limiting size of the aggregates was calculated and this was related to the original particle size of each powder. The powders were largely hydrophobic in nature, and as such were difficult to disperse in the liquid. It was determined that dispersion was possible only if the negative spreading coefficient of water over the powder did not have a significantly larger value than the dispersion component of the water. This has been explained in terms of the hydrophobic powder tending to interact with the dispersive, rather than the polar, entities in the water. For powders which spontaneously dispersed in the water a good correlation existed between the increase in particle size noted in the suspension and the spreading coefficient.

Introduction

In a number of recent publications (e.g. Rowe 1989a,b; Zajic and Buckton, 1990), the roles of surface free energy and polarities, expressed as a spreading coefficient, have been considered with respect to optimum binder selection for granulation.

The underlying theory is derived from the reciprocal mean approach to the determination of polar and dispersion components of surface en-

ergies that was suggested by Wu (1971):

$$\gamma_{12} = \gamma_1 + \gamma_2 - 4 \left[\frac{\gamma_1^d \cdot \gamma_2^d}{\gamma_1^d + \gamma_2^d} - \frac{\gamma_1^p \cdot \gamma_2^p}{\gamma_1^p + \gamma_2^p} \right] \quad (1)$$

where γ_{12} is the interfacial energy between phases 1 and 2, which each have a surface energy consisting of a polar and dispersion component (represented by p and d, respectively).

The spreading coefficient of phase 1 over phase 2 (γ_{12}) can be calculated by taking the differences between the works of cohesion and adhesion for the two phases:

$$\gamma_{12} = 4 \left[\frac{\gamma_1^d \cdot \gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p \cdot \gamma_2^p}{\gamma_1^p + \gamma_2^p} - \frac{\gamma_1}{2} \right] \quad (2)$$

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

In this work, the system under consideration is the behaviour of powders dispersed in a suspension system. It is obvious that a number of factors will influence the properties of powders in suspension, these may include surface charge, size, shape and surface energy. Having accepted the range of factors that are involved, it is also true that the role of surface energetics in controlling aggregation may well be a significant one, with systems always tending to move to a state of minimum interfacial free energy. In the case of a hydrophobic solid one might expect the powder to aggregate to minimise the solid/liquid interface; with a hydrophilic powder the opposite might be true. To investigate this situation a series of drugs with different surface energies were dispersed in their saturated solutions in water and their particle sizes were measured over a period of time. The change in particle size was related to the spreading coefficient of the water over the drug.

Materials and Methods

Sieved size fractions of barbiturate powders (45–63 μm) were used as model drugs, these were BP quality amylobarbitone, phenobarbitone and butobarbitone, and barbitone (Fisons). The reason for selection was that these powders are known to have a range of wettabilities.

Assessment of surface energies

The contact angle between the powder and the test liquids was measured using a Wilhelmy plate technique, as described before (Zajic and Buckton, 1990). For most of the powders non-polar liquids formed a zero contact angle and were, therefore, not used in the calculation of the surface energies. Water (reverse osmosis) and ethylene glycol (BDH) were used as both produced a finite contact angle for each of the powders.

The powders were prepared into rectangular plates 10 mm wide, 50 mm long and 1 mm thick. Their perimeters were measured using a micrometer. A highly polished stainless-steel punch and die was used to prepare the plates, with the force (10

ton) being applied from a hydraulic press, with a 15 s dwell time. The die was then unbolted and dismantled to facilitate easy removal of the formed compact.

The compact was used as the Wilhelmy plate by connection to an electro-microbalance (C.I. Electronics), and the test liquid was raised to contact the powder by means of a motorised platform. Results were calculated as described previously (Zajic and Buckton, 1990) and are averages of at least five determinations.

Suspension preparation and testing

The suspensions were prepared individually by adding about 15 ml of the appropriate saturated barbiturate solution to the sieved size fraction. Minimal attrition was used during preparation. The quantity of powder used was varied (range 20–40 mg) in order to prepare suspensions that were suitable for direct use in the laser diffraction particle size analyser (Malvern, 2600C). The saturated solutions (in reverse osmosis water) were passed through a 0.22 μm filter prior to use. A large number of suspensions of each powder were stored in glass bottles in a 25 °C incubator.

The initial particle size of the powder was measured by making up a series of suspensions in saturated solutions of the barbiturates containing 0.2% Tween 85. These suspensions were treated in an ultrasonic bath for 10 min before particle size analysis.

At regular intervals over a period of one week a bottle of each suspension (a single 15 ml sample) was removed from the incubator and transferred to the particle size analyzer. The suspensions were agitated gently to redisperse the sedimented powder and were stirred in the chamber of the instrument (in-built magnetic stirrer). After testing the samples were discarded. Each experiment for later storage times was undertaken on a different undisturbed suspension.

Results

Contact angles and spreading coefficients

With the exception of amylobarbitone, the increase in weight noted on the electromicrobalance

was significantly lower for the first immersion than for subsequent immersions of the same plate of powder. The values for the first immersion could not be reproduced with any accuracy. For all measurements subsequent to the initial wetting, the angles were at worst accurate to $\pm 5^\circ$. This reproducibility is significantly better than might be expected when using other techniques of contact angle measurement, for example contact angles for water measured on the same powders using a sessile drop method showed a range of $\pm 10^\circ$ (Buckton and Newton, 1986a). The contact angles that are measured on compressed powder discs are always measured on a bed that has been saturated with the wetting liquid prior to measurement (e.g. Lerk et al., 1977), the decision to ignore the first immersion will result in a measurement that is in keeping with the established practice in this field of study.

The values of the contact angles that have been calculated for immersion of the powder plates into water and ethylene glycol are presented in Table 1. The reproducibility of the data provides confidence in the results, but reservations have to be expressed. Contact angles on systems that have been compressed may not be indicative of the nature of the original powder surface due to surface adaptation during powder compression (Buckton and Newton, 1986a).

It surface energy measurements are to be used as a predictive aid it is essential that the technique used to assess surface energy is simple, rapid and provides reproducible results; this method was chosen on that basis.

The results obtained for the contact angles of water on barbiturate powders in this work differ

TABLE 1

Contact angles for the barbiturate powders

Powder	Liquid	
	Water ($^\circ$)	Ethylene glycol ($^\circ$)
Amylobarbitone	66.1	30.6
Barbitone	47.2	17.4
Butobarbitone	41.6	37.1
Phenobarbitone	52.6	20.6

TABLE 2

Surface energies of the barbiturates and the spreading coefficient of water over the powders

Powder	γ	γ^d (mN/m)	γ^p	λ_{12}
Amylobarbitone	43.4	25.3	18.0	-43.0
Phenobarbitone	50.3	23.8	26.5	-28.3
Barbitone	53.3	23.1	30.3	-22.9
Butobarbitone	56.0	16.0	40.0	-4.5

Spreading coefficients calculated using (water) $\gamma = 72.0$, $\gamma^d = 23.2$, $\gamma^p = 48.8$ mN/m and (ethylene glycol) $\gamma = 48.9$, $\gamma^d = 33.4$, $\gamma^p = 15.5$ mN/m.

from published values that were obtained using the sessile drop approach (Buckton and Newton, 1986a). The previously published data (Buckton and Newton, 1986a) are: amylobarbitone, 68° ; phenobarbitone, 64° (drop height method (Mohammed, 1983)); barbitone, 62° ; and butobarbitone, 56° . The rank order of the contact angles does, however, remain the same. The ranking of contact angles for these powders obtained by use of a liquid penetration technique was different (Buckton and Newton, 1986b), where amylobarbitone was deemed to be the most hydrophobic followed by phenobarbitone, butobarbitone and barbitone respectively. The relative merits and demerits of different techniques for assessing the contact angles of powders are beyond the scope of this work.

Using Eqn 2, the spreading coefficient of the water over the powder was calculated, these values being presented in Table 2. As was mentioned in the Introduction, it is also possible to calculate a spreading coefficient of the powder over the liquid; the physical significance of such a value is uncertain and even though the values when calculated were positive for all the barbiturates (showing that the process is favoured) the results have not been quoted.

Suspension particle size analysis

The median particle size (by volume) of the various powders was plotted as a function of $\log(\text{time})$. The graphs (Fig. 1) approximated to straight lines and were used to calculate a limiting size (time tending to infinity) for the different

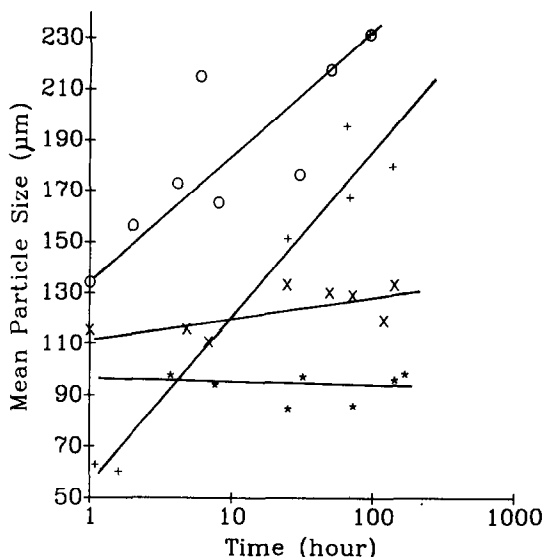


Fig. 1. Particle size of the powders, when suspended in water, as a function of time (age of suspension). (x) Amylobarbitone, (+) barbitone, (*) butobarbitone, (O) phenobarbitone.

suspensions. The initial and limiting particle sizes are listed in Table 3. The original sizes were those recorded with surfactant and ultrasonic treatment, these were all measured on 45–63 μm sieved size fractions of the powders. The initial size measured was in the expected range for each of the powders, with the exception of phenobarbitone which had a much smaller size than the lower sieve size. The initial size of phenobarbitone suspended in its saturated solution without surfactant and sonification was in the region of 100 μm .

The pattern of the size distribution changes suggested agglomeration rather than the growth of crystals. For example phenobarbitone suspensions displayed a bimodal distribution with peak max-

ima at sizes of approx. 100 and 200 μm . As the storage time continued the 100 μm peak (known to consist of aggregates) decreased in magnitude, but did not shift in size, while the 200 μm peak showed a corresponding increase in magnitude but no shift in size.

Discussion

It is a well known phenomenon that small suspended particles (meaning sub-micron particles) will have an increased tendency to dissolve and will then precipitate out, over a period of time, onto large crystal to cause an overall increase in size of the suspended particles. Two factors cause this to happen, one is the state of dynamic equilibrium that exists in these systems and the other is temperature oscillation which causes changes in solubility. In the current work sub-micron particles were not present and temperature of storage was controlled at a constant level. Crystal growth is not likely to proceed by a dissolution of one size of particle and the formation of another larger size. It is possible that crystals that have aggregated together will become welded together by crystallisation onto their surfaces; such processes would not negate the issue being expressed in this work.

The relationship between the limiting particle size and the prime particle size of the powder is not linear (Table 3). Based on this small sample it may be observed that the limiting size in suspension is a property of the drug and not related to initial particle size. It might be expected, however, that for very small and very large particles this finding will not be true.

In Fig. 2 the increase in size, i.e., the difference between the prime particle size and the limiting particle size, is plotted as a function of the spreading coefficient of water over the powders. The barbitone, butobarbitone and phenobarbitone powders fit a linear relationship which passes through the origin. The results obtained when using amylobarbitone do not fit onto this line. The interesting difference between amylobarbitone and the other powders is that amylobarbitone is the only one which does not allow water to penetrate

TABLE 3

Median prime particle size and median limiting particle size of the powders studied

Powder	Prime size (μm)	Limiting size (μm)
Amylobarbitone	40.6	137
Barbitone	71.2	270
Butobarbitone	47.7	93
Phenobarbitone	14.2	265

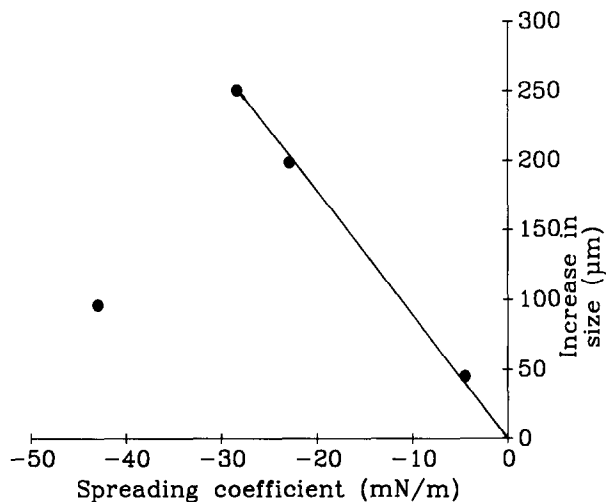


Fig. 2. Increase of particle size in suspension as a function of the spreading coefficient of water over the powders.

spontaneously its loosely packed bed (Buckton and Newton, 1986b). Amylobarbitone is also the only powder which has a contact angle of over 90° as assessed by liquid penetration experiments (Buckton and Newton, 1986b). Consequently, with amylobarbitone the hydrophobic nature resulted in a suspension which was almost impossible to disperse. The true nature of agglomeration was hard to assess as only a small proportion of the powder was displaced from the surface. The implication can be drawn that the use of spreading coefficients provides a good assessment of the degree of aggregation that can be expected in suspension, provided it is possible to disperse the powder to an adequate extent.

Fig. 3 shows the plot of limiting particle size as

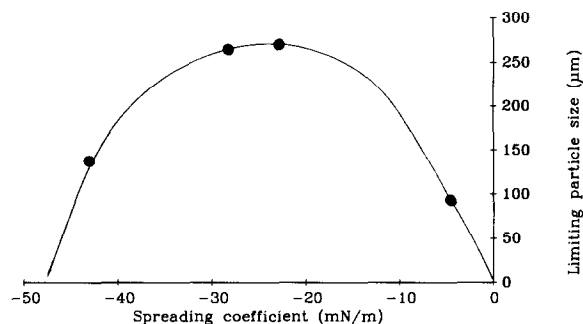


Fig. 3. Limiting particle size in suspension as a function of the spreading coefficient in water.

a function of the spreading coefficient of the water over the powder. A parabolic relationship exists between these two parameters. In a recent publication relating to the spreading of polymeric binders over powders (Rowe, 1989c), the fractional polarity of the surface energy of a solid was found to show a parabolic relationship with the dimensionless reduced spreading coefficient. Such a fit to a quadratic relationship was predicted by Wu (1973).

The line fitted to Fig. 3 passes through the origin, reaches a plateau at a value of the spreading coefficient in the region of the dispersion component of the surface energy of water and then passes through the x -axis again at a point which is approximately equal to twice the dispersion component of the surface energy of water.

The increase in limiting particle size from a spreading coefficient of zero is to be expected; here the prediction is that the solid will have a greater tendency to aggregate rather than disperse as the spreading becomes less favoured. The implication of this plot is that the drug will tend to disperse and indeed become more soluble as the value of the spreading coefficient approaches zero. With respect to dispersibility, this observation is supported by the fact that butobarbitone, which has the smallest negative spreading coefficient, decreased in median size over the period of storage, albeit by a very small amount from about $97 \mu\text{m}$ to a limiting size of $93 \mu\text{m}$; butobarbitone did remain aggregated, as predicted from the negative spreading coefficient, and as proved by the fact that it did not reach its primary median particle size, $47 \mu\text{m}$. The concept of solubility increasing as the spreading coefficient tends to a positive value is not straightforward; firstly, saturated solutions are used in this work so powders cannot reduce in size below their prime particle size, secondly, the relationship between surface energies of powders and their solubilities is not a simple one (Buckton and Beezer, 1989). Interpretations of the results should, therefore, be restricted to aspects of dispersibility; thus, if a powder has a spreading coefficient of zero the predicted size would be zero, and this should be taken to imply that the size would be the prime particle size and that aggregation would not occur.

The other side of the parabolic curve, where the spreading coefficient has a negative value in excess of the dispersion component of the continuous phase, is the region in which the powder will not spontaneously disperse in the liquid. This observation is of particular value when using compressed powder methods of contact angle determination. The reason for this is that with liquid penetration techniques the dividing line between a powder which will allow penetration and one which will not is 90° ; with compressed discs the contact angle values are invariably lower than those obtained by liquid penetration. The results in Table 1 demonstrate this point, i.e., there is no obvious reason as to why one should conclude that a powder with a contact angle of 52.6° (phenobarbitone) should be just at the borderline of allowing water penetration, but that a powder with a contact angle of 66.1° should not allow water to penetrate. This becomes clear in Fig. 3, however, as the spreading coefficient of amylo-barbitone is well past the plateau response. In this system it would be possible to predict that any powder which had a negative spreading coefficient in excess of the dispersion component of water would be difficult to disperse, and that any powder with a negative spreading coefficient significantly greater than the dispersion component of water would not disperse spontaneously. Any powder with a lower negative dispersion component would achieve better dispersion and thus a reduction in its tendency to aggregate.

The physical significance of the maximum occurring at the value equal to the dispersion component of the continuous phase (Fig. 3) can be explained as follows. It is clear that such hydrophobic powders will attempt to interact with the dispersive rather than the polar entities of the continuous phase. All the values of the spreading coefficient are negative and thus describe the disfavoured interaction between water and the powders. However, the dispersion component of the surface energy of water provides a driving force to allow dispersion. The powder will be dispersible as long as the resistance to dispersion (the difference between the works of cohesion and adhesion, i.e. the negative spreading coefficient) is not greater than the potential favourable interac-

tion given by the dispersive component of the continuous phase.

Conclusion

In an attempt to test the use of spreading coefficients as a method of predicting the aggregation of powders dispersed in suspension in water, two factors have come to light:

Firstly, for a crude and simple predictive test the results for powders which are spontaneously wetted by water provide an excellent fit to a straight line when increase in size is plotted as a function of spreading coefficient.

Secondly, it was discovered that the non-dispersing powder had a spreading coefficient which had a larger negative value than the value of the dispersion component of the continuous phase. The parabolic relationship between size and spreading coefficient (Fig. 3) provides a master curve which will demonstrate whether a powder can be expected to disperse in water. This is something that is not easy to judge by having only a contact angle that was measured on a compressed powder system.

It will now be necessary to continue this line of research to look at different continuous phases and different solids to determine how generally applicable the findings are.

The results are encouraging when it is considered that only surface energy has been considered in this work and that many other factors play a role controlling suspension stability.

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