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Binder–substrate interactions in granulation: a theoretical approach based on surface free energy and polarity

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Summary

The interfacial works of cohesion and adhesion (between substrate and binder) in addition to the spreading coefficients of one phase on the other have been calculated for a number of pharmaceutical solids and polymeric binders using literature values of surface free energies and polarities. For low polarity substrates (polarity < 0.2) calculations have shown that polyvinyl pyrrolidone or starch would be the optimum binder while for higher polarity substrates (polarity > 0.4) the cellulose derivatives or acacia would be the optimum binder, consistent with the trends reported in the literature. The spreading coefficients have implications in that it is possible to hypothesise two distinct modes of granule formation.

Introduction

Pharmaceutical powders often exhibit poor flow and compaction characteristics and are formulated as granules with binding agents to enhance tablet properties. Considerable research has been conducted in an attempt to correlate binder physical properties with subsequent granule and tablet properties often with limited success (Krycer et al., 1983a, 1983b;, Reading and Spring, 1984). Krycer et al. (1983a) concluded that significant determinants of granule and tablet strength are the wetting of the substrate by the binder, binder cohesion and binder–substrate adhesion. Recent work, based on a simple but crude model of calculating the intensity of the molecular interactions in a two-component system using partial solubility parameters, has shown that it is possible to predict the properties of granules and tablets involving a number of powder substrates granulated with the polymers hydroxypropyl methylcellulose, methylcellulose and polyvinyl pyrrolidone (Rowe, 1988). The present approach extends this concept using surface free energy and polarity terms instead of partial solubility parameters.

Theoretical considerations

The interfacial energy between any two phases, γ_{12}, can be estimated by knowing the individual surface free energies, γ_1, and γ_2, and the energy associated with the interactions taking place across the interface. This relationship can be written in the form (Wu, 1973):

$$\gamma_{12} = \gamma_1 + \gamma_2 - W^{d}_{a_{12}} - W^{p}_{a_{12}} \quad (1)$$

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where $W_{a_{12}}^{d}$ and $W_{a_{12}}^{p}$ are the non-polar and polar components of the work of adhesion, $W_{a_{12}}$.

$$\text{i.e. } W_{a_{12}} = W_{a_{12}}^{d} + W_{a_{12}}^{p} \tag{2}$$

Wu (1973) has converted Eqn. 1 into a more useful form applicable to a wide range of materials by expressing the components of the work of adhesion in terms of the non-polar (γ^{d}) and polar (γ^{p}) components of the surface energy of each of the two phases:

$$\gamma_{12} = \gamma_1 + \gamma_2 - \frac{4\gamma_1^{d} \cdot \gamma_2^{d}}{\gamma_1^{d} + \gamma_2^{d}} - \frac{4\gamma_1^{p} \cdot \gamma_2^{p}}{\gamma_1^{p} + \gamma_2^{p}} \tag{3}$$

This equation can be extended in several ways, firstly to calculate the surface free energy of a solid γ_1, from the equilibrium contact angle (θ) of a liquid of surface free energy γ_2. In this case the linking equation is that of Young-Dupré, i.e.

$$\gamma_1 = \gamma_2 \cos\theta + \gamma_{12} \tag{4}$$

Substituting Eqn. 4 into Eqn. 3 to eliminate γ_{12} (Wu and Brzozowski, 1971):

$$(1 + \cos\theta)\gamma_2 = 2\left[\frac{2\gamma_1^{d} \cdot \gamma_2^{d}}{\gamma_1^{d} + \gamma_2^{d}} + \frac{2\gamma_1^{p} \cdot \gamma_2^{p}}{\gamma_1^{p} + \gamma_2^{p}}\right] \tag{5}$$

This equation contains two unknown quantities, γ_1^{d} and γ_1^{p}, when the contact angle is measured and the non-polar and polar components of the testing liquid are known. If, however, two liquids are used, the equation may be solved. Conversely, provided the surface free energy and its non-polar and polar components of the solid substrate are known, it is possible to calculate the non-polar and polar components of the second phase from its surface free energy and contact angle with the substrate.

Secondly, Eqn. 3 can be used in the calculation of the spreading coefficient (λ) of one phase on the other phase:

$$\text{i.e. } \lambda_{12} = W_{a_{12}} - W_{c_1} \tag{6}$$

$$\lambda_{21} = W_{a_{21}} - W_{c_2} \tag{7}$$

where W_c is the work of cohesion of either phase 1 or phase 2, i.e.

$$\lambda_{12} = 4\left[\frac{\gamma_1^{d} \cdot \gamma_2^{d}}{\gamma_1^{d} + \gamma_2^{d}} + \frac{\gamma_1^{p} \cdot \gamma_2^{p}}{\gamma_1^{p} + \gamma_2^{p}} - \frac{\gamma_1}{2}\right] \tag{8}$$

$$\lambda_{21} = 4\left[\frac{\gamma_1^{d} \cdot \gamma_2^{d}}{\gamma_1^{d} + \gamma_2^{d}} + \frac{\gamma_1^{p} \cdot \gamma_2^{p}}{\gamma_1^{p} + \gamma_2^{p}} - \frac{\gamma_2}{2}\right] \tag{9}$$

A comparison of all these equations show that it is possible to calculate the work of cohesion of each of the two phases, the work of adhesion between the two phases and the spreading coefficients of each phase on the other simply from a knowledge of the surface free energy and fractional polarity (defined as the ratio of the polar component to the total surface free energy) of each of the constituents in a two-phase system. This concept has been applied to the binary system of organic compounds granulated with polymeric binders.

Results

Numerical values for the surface free energies and polarities of all of the substrates and binders used in subsequent calculations are given in Tables 1 and 2, respectively. All of the data for the organic substrates were obtained by the application of Eqn. 5 from contact angle measurements. In the case of the polymeric binders, surface free energies were estimated from surface tension measurements of their aqueous solutions in the range of concentration independence. In the case of acacia and starch, polarities were estimated by the application of Eqn. 5 by first calculating γ_1^{d}, and γ_1^{p} for the substrate used by Krycer et al. (1983a) taking the author's reported values for the surface tensions and contact angles of the aqueous solutions of the two binders, hydroxypropyl methylcellulose and polyvinyl pyrrolidone, of known polarity (Table 1) and then resubstituting for the reported surface tensions and contact angles of the aqueous solution of acacia and starch.

The calculated work of cohesion for all the substrates and binders are shown in Table 3 where

TABLE 1

Numerical data on organic substrates

Substrate	Surface free energy ($mN \cdot m^{-1}$)	Fractional polarity	Reference
Griseofulvin (A)	32.2	0.06	Hansford et al. (1980)
Griseofulvin (B)	30.6	0.11	
β-Sitosterol	34.9	0.11	Zografi and Tam (1976)
Phenacetin	58.3	0.21	
Indomethacin	61.8	0.24	
Hydrocortisone acetate	63.4	0.26	
Hydrocortisone	68.7	0.34	
Benzoic acid	61.7	0.37	
Ethinamate	70.0	0.39	
Aspirin	67.5	0.42	

N.B. Griseofulvin was processed by two different crystallisation/milling procedures (Hansford et al., 1980).

it can be seen that, apart from the low polarity substrates griseofulvin and β-sitosterol, the works of cohesion of all the substrates are higher than those of the binders. Inspection of the calculated work of adhesion and spreading coefficient data for all the substrates granulated with the binders, hydroxypropyl methylcellulose, methylcellulose and polyvinyl pyrrolidone (Table 4), shows that while polyvinyl pyrrolidone has the highest work of adhesion there is an indication that the work of adhesion has reached a maximum for this binder.

TABLE 2

Numerical data on the polymeric binders

Binder	Surface free energy ($mN \cdot m^{-1}$)	Fractional polarity	References
Hydroxypropyl methylcellulose	48.4	0.62	Manufacturer's data
Methylcellulose	50.0	0.58	
Polyvinyl pyrrolidone	53.6	0.47	Krycer et al. (1983a)
Acacia	50.6	0.57	
Starch	58.7	0.51	

TABLE 3

Calculated work of cohesion for substrates and binders

Material	Work of cohesion ($mN \cdot m^{-1}$)
Griseofulvin (A)	64.4
Griseofulvin (B)	61.2
β-Sitosterol	69.8
Phenacetin	116.6
Indomethacin	123.6
Hydrocortisone acetate	126.8
Hydrocortisone	137.4
Benzoic acid	123.4
Ethinamate	140.0
Aspirin	135.0
Hydroxypropyl methylcellulose	96.8
Methylcellulose	100.0
Polyvinyl pyrrolidone	107.2
Acacia	101.2
Starch	117.4

The spreading coefficient data show very interesting trends in that for the spreading of the binder over the substrate (λ_{12}) there is an increase from negative values for low polarity substrates rising through zero to large positive values for the higher polarity substrates. The polarity at which the spreading coefficient, λ_{12}, becomes positive appears to be dependent on the binder, being 0.24 for the polyvinyl pyrrolidone, 0.26 for methylcellulose and 0.34 for hydroxypropyl methylcellulose. In the case of the spreading coefficient for the spreading of the substrate over the binder (λ_{21}), all systems apart from griseofulvin and β-sitosterol granulated with polyvinyl pyrrolidone show negative values.

Data for the two binders, acacia and starch (Table 5), show the same overall trends as the other binders with the data for acacia being similar in magnitude to that for methylcellulose and that for starch being similar in magnitude to that for polyvinyl pyrrolidone.

Discussion

The trend in the work of adhesion data for the 3 binders in Table 4, i.e. hydroxypropyl methylcellulose < methylcellulose < polyvinyl pyrrolidone,

TABLE 4

Calculated work of adhesion (W_a) and spreading coefficient (λ) for substrates granulated with hydroxypropyl methylcellulose (HPMC), methylcellulose (MC) and polyvinyl pyrrolidone (PVP)

λ_{12} = spreading coefficient of polymeric binder over substrate; λ_{21} = spreading coefficient of substrate over polymeric binder.

Substrate	HPMC ($mN \cdot m^{-1}$)			MC ($mN \cdot m^{-1}$)			PVP ($mN \cdot m^{-1}$)		
	W_a	λ_{12}	λ_{21}	W_a	λ_{12}	λ_{21}	W_a	λ_{12}	λ_{21}
Griseofulvin (A)	53.1	−43.7	−11.3	56.7	−43.3	−7.7	65.7	−41.5	+1.3
Griseofulvin (B)	57.3	−39.5	−3.9	60.5	−39.5	−0.7	68.4	−38.8	+7.2
β-Sitosterol	59.3	−37.1	−10.2	63.3	−36.7	−6.5	72.4	−34.8	+2.6
Phenacetin	88.0	−8.8	−28.6	92.5	−7.5	−24.1	103.5	−3.7	−13.1
Indomethacin	92.3	−4.5	−31.3	96.8	−3.2	−26.8	107.8	+0.6	−15.8
Hydrocortisone acetate	95.6	−1.2	−31.2	100.1	+0.1	−26.7	110.6	+3.4	−16.2
Hydrocortisone	105.2	+8.4	−32.2	107.4	+9.4	−28.0	118.5	+11.3	−18.9
Ethinamate	108.3	+11.5	−31.7	112.2	+12.2	−27.8	120.5	+13.3	−19.5
Aspirin	108.3	+11.5	−26.7	111.9	+11.9	−23.1	119.2	+12.0	−15.8

compare favourably with those predicted from interaction data calculated from solubility parameter data for substrates of similar polarity (Rowe, 1988) except that in the previous work the trend was reversed for the substrates of polarity in excess of 0.45. However, inspection of the data in Table 4 clearly shows that while the calculated work of adhesion data of polyvinyl pyrrolidone appears to have reached a plateau, the data for the other two binders are still rising implying that if surface free energy data were available for some higher polarity substrates the trends observed here would be reversed.

TABLE 5

Calculated work of adhesion (W_a) and spreading coefficient for substrates granulated with acacia and starch

Substrate	Acacia ($mN \cdot m^{-1}$)			Starch ($mN \cdot m^{-1}$)		
	W_a	λ_{12}	λ_{21}	W_a	λ_{12}	λ_{21}
Griseofulvin (A)	57.6	−43.6	−6.8	66.4	−51.0	+2.0
Griseofulvin (B)	61.3	−39.9	0.0	69.2	−48.2	+8.0
β-Sitosterol	64.2	−37.0	−5.6	73.3	−44.1	+3.4
Phenacetin	93.7	−7.5	−22.9	106.2	−11.2	−10.4
Indomethacin	98.0	−3.2	−25.6	110.9	−6.5	−12.7
Hydrocortisone acetate	101.2	0.0	−25.6	114.1	−3.3	−12.7
Hydrocortisone	110.5	+9.3	−26.9	123.2	+5.8	−14.2
Ethinamate	113.2	+12.0	−26.7	125.7	+8.3	−14.3
Aspirin	112.9	+11.7	−22.1	124.6	+7.2	−10.4

The relationship observed between ideal interfacial adhesive bond strength (σ_{12}) data from previous studies (Rowe, 1988) and work of adhesion ($W_{a_{12}}$) data is not surprising since they are directly related (Gardon, 1967).

$$\sigma_{12} = \frac{1.03 W_{a_{12}}}{d_{12}} \tag{10}$$

where d_{12} is the equilibrium separation between the centres of neighbouring sites, i.e. approximately 10^{-9} m for van der Waals bonds. Inspection of the results given in Table 6 for benzoic acid, where all the relevant data is known in the literature, shows that this relationship does indeed hold and can be used to estimate works of adhesion for

TABLE 6

Comparison between the calculated work of adhesion (W_a) and the ideal interface adhesive bond strength (σ) for benzoic acid granulated with hydroxypropyl methylcellulose (HPMC), methylcellulose (MC) and polyvinyl pyrrolidone (PVP)

All calculations using data given in Tables 1 and 2 or solubility parameter data given by Barton (1983) and Rowe (1988).

Binder	W_a ($mN \cdot m^{-1}$)	σ ($MN \cdot m^{-2}$)
HPMC	101.8	109.3
MC	105.5	107.8
PVP	113.5	112.0

other substrates from solubility parameter data. If this is done for theophylline (polarity 0.45) and caffeine (polarity 0.60) granulated with hydroxypropyl methylcellulose, methylcellulose and polyvinyl pyrrolidone, then works of adhesion will be of the order of 147.3, 128.3 and 118.1 $mN \cdot m^{-1}$ respectively for theophylline, and 143.6, 125.5 and 114.4 $mN \cdot m^{-1}$ respectively for caffeine. It is interesting to note that these calculations certainly confirm the attainment of a plateau value in the work of adhesion for polyvinyl pyrrolidone and the reversal of trends seen for the lower polarity substrates.

For optimum spreading of a polymeric binder over a substrate, λ_{12} should always be positive. Wu (1973) has shown that for optimum thermodynamic spreading of two phases of equivalent surface free energy the polarity of the two phases should be the same. However, when the surface free energy of one phase is much smaller than that of the other phase, complete wetting may still occur even although the polarities may be relatively widely part. The latter is generally the case for binder–substrate interaction in pharmaceutical granulation although for the very low polarity substrates, e.g. griseofulvin and β-sitosterol, granulated with either polyvinyl pyrrolidone or starch, spreading of the substrate on the binder would appear to be more energetically favourable. This spreading data has important implications in that it suggests the hypothesis of two distinctly different modes of granule formation. In the case where λ_{12} is positive the binder will form a strongly adhering film around the substrate and hence in the aggregate or granule there would always be a bond formed at all points of contact between the substrate particles. This would result in a strong dense granule, the strength being dependent on the strength (i.e. the work of cohesion) of the binder. In the case where λ_{21} is positive, the substrate adheres to the binder but there will be no film around the substrate. Bonds would not always be formed at points of contact between substrate particles only through isolated patches of binder. This would result in a porous open granule of generally lower strength. However, in both cases granulation would occur.

It will be noticed that no mention has been made of the solvent system used to dissolve the binder or on the addition of surfactants, both of which are known to affect the granule properties (Krycer et al., 1983a and b). Both will temporarily affect the spreading of the binder and hence the interfacial area of contact between the substrate and the binder. In the case where λ_{12} is positive, the effect on granule properties is unlikely to be great. However, in the case where λ_{21} is positive, changing the conditions of application of the binder to increase the spreading of it over the substrate will be advantageous.

It is important to relate these concepts to granulation data in the literature. Inspection of the data in Tables 4 and 5 would suggest that for low polarity substrates it would be pertinent to use either polyvinyl pyrrolidone or starch as a binder while for higher polarity substrates either acacia or hydroxypropyl methylcellulose would be the binder of choice. Formulation data given in Dictionnaire Vidal (1986) would support these predictions in that all the griseofulvin formulations are granulated with either polyvinyl pyrrolidone and/or starch while for theophylline granulations acacia would appear to be the binder of choice. In addition, recent experiments by Krycer et al. (1983a) for paracetamol (polarity unknown but likely to be, from solubility data, of the order of 0.5) and by Reading and Spring (1984) for sand (polarity of the order of 0.8) have both shown the superiority of the cellulose derivatives in the formation of strong granules.

The data presented here, in addition to that presented earlier (Rowe, 1988), clearly show the applicability of these approaches in the prediction of binder–substrate interactions in granulation. It must be emphasised that a complete analysis of granule strength should also include rheology and fracture mechanics but the concept of the optimisation of formulations based on the known or measured polarities of the substrate and binder clearly has potential use in product development.

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