International Journal of Pharmaceutics, 56 (1989) 117–124
Elsevier

IJP 01898

Polar/non-polar interactions in the granulation of organic substrates with polymer binding agents

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(Received 27 February 1989)
(Accepted 1 May 1989)

Key words: Granulation; Polymer; Interaction; Polarity

Summary

Calculations of the thermodynamic works of cohesion and adhesion (between substrate and polymer binder) based on a knowledge of either the partial cohesion/solubility parameters or surface free energies of the constituents have shown that there is a parabolic relationship between the reduced spreading coefficient (defined as the ratio of the work of adhesion to the work of cohesion) and the fractional polarity of the substrate. The relationship is independent of the method used to calculate these two dimensionless parameters but is specific for each polymer binder. It is possible, using the relationship, to explain the apparently anomalous results in the literature regarding the rank ordering of polymer binders and to predict the optimum binder for any particular substrate.

Introduction

Powders are often formulated with polymer binding agents to enhance flow and compaction characteristics. Krycer et al. (1983) concluded that significant determinants for optimum granulation are the spreading of the binder over the substrate, binder-substrate adhesion and binder cohesion. Recent work (Rowe, 1988, 1989a, 1989b) has shown that it is possible to assess the relative influence of these factors using calculations of the thermodynamic works of cohesion and adhesion based on a knowledge of either the partial cohesion/solubility parameters (Rowe, 1988) or the surface free energies (Rowe, 1989a) on both the substrates and binders leading to statements regarding film formation, granule morphology, fracture processes and granule strength (Rowe, 1989b). Although there are common concepts underlying the calculations in both approaches (Gardon, 1977) and indeed, in the special case where complete data on both cohesion parameters and surface free energies for both substrate and binder are known, the results are directly comparable (Rowe, 1989a), no attempt has been made to fully integrate and compare the results from both approaches to investigate commonalities. This has been attempted in this paper using the common dimensionless parameters of fractional polarity and reduced spreading coefficient (the ratio of the calculated work of adhesion to the calculated work of cohesion of the binder) for a wide range of organic substrates (drugs and excipients) granulated with a number of polymer binders.

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Theoretical Considerations

If ${}^{S}\gamma$, ${}^{S}\delta$ and ${}^{B}\gamma$, ${}^{B}\delta$ are the surface free energies and cohesion/solubility parameters of the substrate and binder respectively with subscripts d and p denoting their dispersion and polar components, then it is possible to calculate all the dimensionless parameters:

(1) fractional polarity $x_p = \dfrac{\gamma_p}{\gamma} = 1 - \left(\dfrac{\delta_d}{\delta}\right)^2$

(2) reduced spreading coefficient λ

$$= \frac{\text{work of adhesion } (W_a)}{\text{work of cohesion of binder } (W_c)}$$

$$= \{\text{strength of adhesive interactions } (\sigma_{BS})\}/$$

$$\{\text{strength of cohesive interactions in binder } (\sigma_{BB})\}$$

where $W_c = 2{}^{B}\gamma$

$$W_a = 4\left[\frac{{}^{B}\gamma_d \cdot {}^{S}\gamma_d}{{}^{B}\gamma_d + {}^{S}\gamma_d} + \frac{{}^{B}\gamma_p \cdot {}^{S}\gamma_p}{{}^{B}\gamma_p + {}^{S}\gamma_p}\right]$$

$\sigma_{BB} = 0.25{}^{B}\gamma^2$

$\sigma_{BS} = 0.25\phi{}^{B}\delta{}^{S}\delta$

and ϕ the interaction parameter is given by (Wu, 1973):

$$\phi = 2\left[\frac{{}^{B}x_d \cdot {}^{S}x_d}{{}^{B}x_d g_1 + {}^{S}x_d g_2} + \frac{{}^{B}x_p \cdot {}^{S}x_p}{{}^{B}x_p g_1 + {}^{S}x_p g_2}\right]$$

where $g_1 = {}^{B}\gamma^2 \cdot {}^{B}V^{1/3}/{}^{S}\gamma^2 \cdot {}^{S}V^{1/3}$ being the molar volume and g_2 the reciprocal of g_1 (Rowe, 1988).

Results and Discussion

Analysis of surface free energy data

Figs. 1–5 show the results of plotting the reduced spreading coefficient (λ) against fractional polarity (x) for the materials listed in Table 1. As

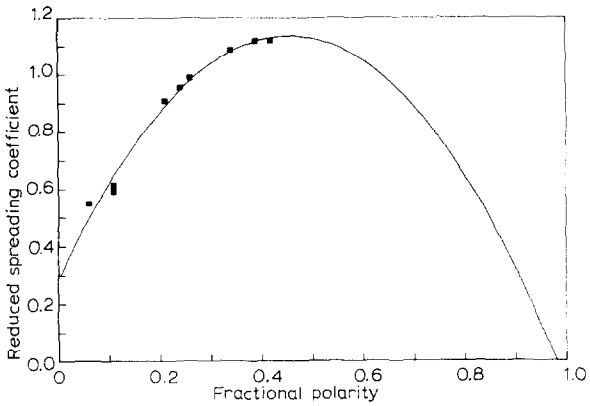

Fig. 1. Reduced spreading coefficient vs fractional polarity for hydroxypropyl methylcellulose (data calculated from surface free energies).

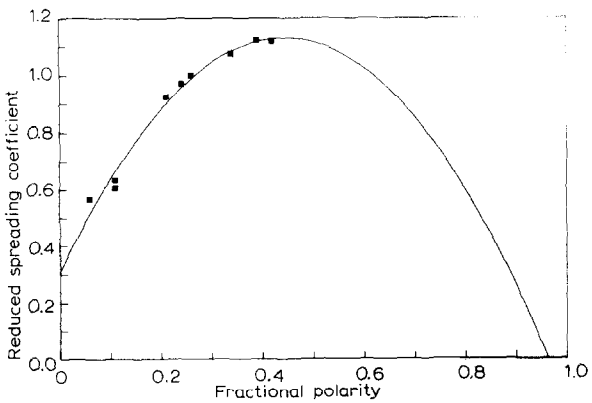

Fig. 2. Reduced spreading coefficient vs fractional polarity for methylcellulose (data calculated from surface free energies).

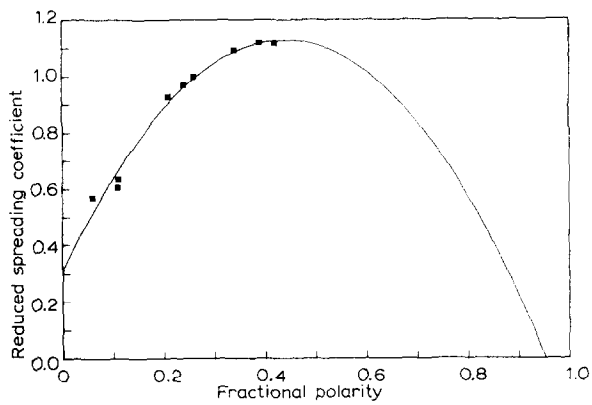

Fig. 3. Reduced spreading coefficient vs fractional polarity for acacia (data calculated from surface free energies).

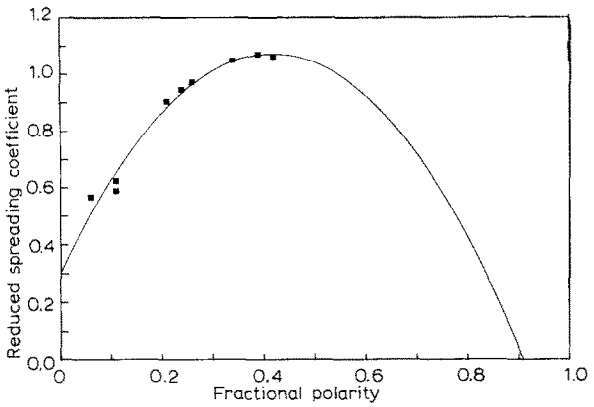

Fig. 4. Reduced spreading coefficient vs fractional polarity for starch (data calculated from surface free energies).

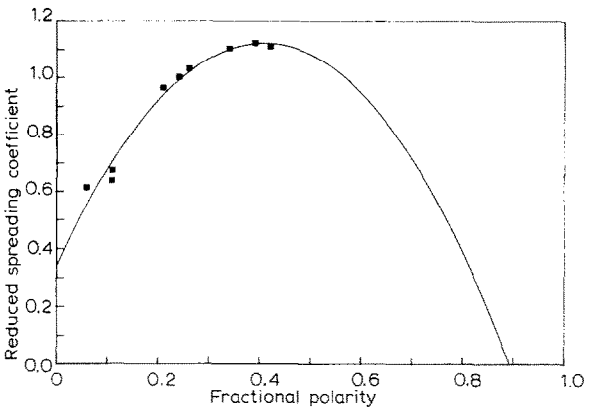

Fig. 5. Reduced spreading coefficient vs fractional polarity for polyvinyl pyrrolidone (data calculated from surface free energies).

predicted by Wu (1973) all the data can be fitted to a quadratic equation of the type

$$\lambda = c + ax + bx^2$$

where c, a and b are constants depending on the polymer binder used, with good correlations and low standard errors (Table 2). Solutions for the equations where $\lambda = 1$ provide information on the polarities of these substrates where film formation is likely to occur for each polymer binder. In this respect it is interesting to note that hydroxypropyl methylcellulose has the widest range (0.28–0.64) and starch the narrowest range (0.29–0.54). An interesting feature of the derived data (Table 2) are the calculated values for the fractional polarities at the maximum spreading coefficients. Theoretically (Wu, 1973), these values should be identical to the fractional polarities of the polymer binders but although they are in the correct rank order, i.e., hydroxypropylmethylcellulose > methylcellulose > acacia > starch > polyvinyl pyrrolidone, they are certainly not identical to the

TABLE 1

Surface free energy and molar volume data on substrates and polymer binders

Material	Molar volume (cm^3/mol) V	Surface free energy (mN/m) γ	γ_d	Fractional polarity x_p	Reference
Griseofulvin (A)	245.1	32.2	30.3	0.06	Hansford et al. (1980)
Griseofulvin (B)	245.1	30.6	26.8	0.11	
β-Sitosterol	406.9	34.9	31.2	0.11	Zografi and Tam (1976)
Phenacetin	143.2	58.3	45.8	0.21	
Indomethacin	265.2	61.8	47.3	0.24	
Hydrocortisone acetate	313.2	63.4	46.9	0.26	
Hydrocortisone	282.8	68.7	45.1	0.34	
Ethinamate	–	70.0	43.3	0.39	
Aspirin	–	67.5	39.4	0.42	
Hydroxypropyl methylcellulose	185.7	48.4	18.5	0.62	Rowe (1989a)
Methylcellulose	150.9	50.0	21.0	0.58	
Polyvinyl pyrrolidone	95.0	53.6	28.4	0.47	
Acacia	–	50.6	21.6	0.57	
Starch	–	58.7	29.0	0.51	

TABLE 2

Results of quadratic curve-fitting for data shown in Figs. 1–5 (n = 9)

Binder	Derived values			Correlation coefficient	Standard error	Polarity for $\lambda = 1$	Data at max	
	c	a	b				λ	x
HPMC	0.2848	3.737	−4.105	0.9912	0.0358	0.28–0.64	1.135	0.46
MC	0.3063	3.710	−4.183	0.9898	0.0372	0.26–0.62	1.129	0.44
Acacia	0.3038	3.755	−4.274	0.9899	0.0373	0.27–0.61	1.129	0.44
Starch	0.3020	3.690	−4.419	0.9866	0.0398	0.29–0.54	1.073	0.42
PVP	0.3388	3.858	−4.473	0.9861	0.0410	0.25–0.57	1.123	0.41

TABLE 3

Data on substrates used to test derived quadratic equations. **A.** *Surface free energy data;* **B**: *Cohesion / solubility parameter data*

A Substrate	Molar volume (cm^3/mol) V	Surface free energy (mN/m)		Fractional polarity x_p	Reference
		γ	γ_d		
Microcrystalline cellulose (Avicel)	216.0	63.9	29.1	0.54	Lee and Luner (1972)
Benzocaine	136.4	67.1	48.1	0.28	Zografi and Tam (1976)
Polymethylmethacrylate	85.6	45.4	33.0	0.27	Johnson and Zografi (1986)
B Substrate	Molar volume (cm^3/mol) V	Cohesion parameter ($MPa^{1/2}$)		Fractional polarity x_p	Reference
		δ	δ_d		
Microcrystalline cellulose (Avicel anhydrous)	216.0	29.3	19.4	0.76	Huu-Phuoc et al. (1987a)
Lactose (anhydrous)	236.8	39.9	19.6	0.76	Huu-Phuoc et al. (1986)
Polymethylmethacrylate	85.6	22.6	18.6	0.32	Barton (1983)
Polyvinylchloride	45.1	21.4	18.2	0.28	Barton (1983)

fractional polarities in Table 1. Comparisons of reduced spreading coefficients extrapolated using the quadratic equations given in Table 2 for other substrates (Table 3A) with those calculated using the standard equations for the same substrates show reasonably good agreement (Table 4) espe-

TABLE 4

Comparison of calculated with predicted values for λ *from curve-fitting data in Table 2*

Binder	Microcrystalline cellulose (Avicel)		Benzocaine		Polymethylmethacrylate	
	Predicted	Calculated	Predicted	Calculated	Predicted	Calculated
HPMC	1.106	1.132	1.009	1.032	0.995	0.852
MC	1.090	1.121	1.017	1.044	1.003	0.861
Acacia	1.085	1.115	1.020	1.043	1.006	0.859
PVP	1.039	1.082	1.047	1.070	1.035	0.880
Starch	1.006	1.041	0.989	1.008	0.976	0.824

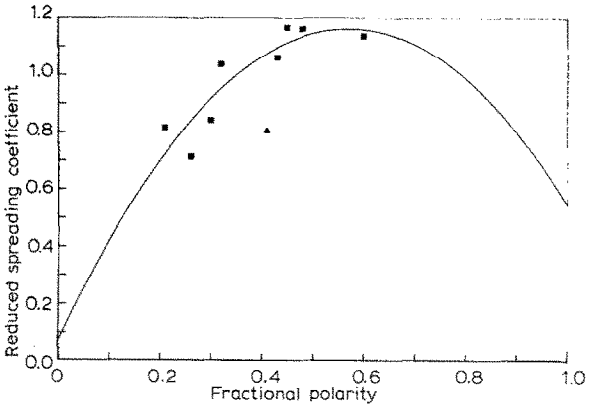

Fig. 6. Reduced spreading coefficient vs fractional polarity for hydroxypropyl methylcellulose (data calculated from cohesion/solubility parameters) data point for testosterone propionate (A); ▲, Omitted from analysis.

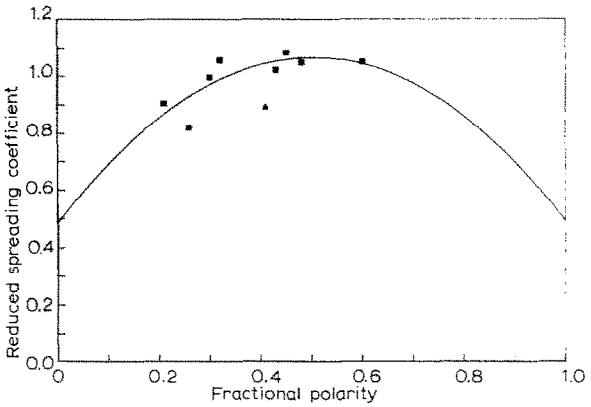

Fig. 8. Reduced spreading coefficient vs fractional polarity for polyvinyl pyrrolidone (data calculated from cohesion/solubility parameters) data point for testosterone propionate (A); ▲, Omitted from analysis.

cially for the microcrystalline cellulose (Avicel) and benzocaine, indicating that data using organic drugs can be extrapolated to other materials.

Analysis of cohesion / solubility parameter data

Figs. 6–8 show the results of plotting the reduced spreading coefficient (λ) against fractional polarity (x) for the materials listed in Table 5. As with the surface free energy data, all the data could be fitted to a quadratic equation although in this case the fit was not as good but still statistically significant. (For the derivation of the equations given in Table 6 the data for testosterone propionate (A) were omitted since it is obvious that the calculated polarity of this drug is at variance with its structure and properties). The trends shown are similar to those seen above for the surface free energy data although the actual values for the polarities of those substrates when film formation is likely to occur are different. However, the calculated values for the fractional polarities at maximum spreading are nearer those given for the polymer binders in Table 5. As with the surface free energy data the derived quadratic equations can be used to predict reduced spreading coefficients for other materials (Table 3B) with reasonable accuracy (Table 7).

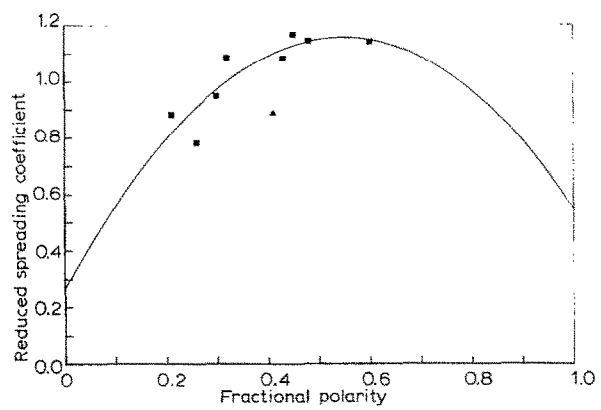

Fig. 7. Reduced spreading coefficient vs fractional polarity for methylcellulose (data calculated from cohesion/solubility parameters) data point for testosterone propionate (A); ▲, Omitted from analysis.

Combined data and practical significance

In view of the close similarity of the results obtained for the 3 polymer binders hydroxypropyl methylcellulose, methylcellulose and polyvinyl pyrrolidone using both surface free energy and cohesion/solubility parameter data, it would appear logical to combine all the results for each of these three polymers. Fig. 9 together with Table 8 summarise the results for 24 substrates. All the trends seen with the separate data are present in the combined data. An interesting feature is that the calculated polarities at maximum spreading are now much nearer to the polarities of the polymer binders i.e. 0.54 (0.60–0.62 for hydroxy-

TABLE 5

Cohesion / solubility parameter and molar volume data on substrates and polymer binders

Material	Molar volume (cm^3/mol) V	Solubility parameter ($MPa^{1/2}$)		Fractional polarity x_p	Reference
		δ	δ_d		
Caffeine (anhyd)	144	26.6	16.8	0.60	Huu-Phuoc et al. (1987b)
Caffeine	144	28.8	20.7	0.48	Martin et al. (1983)
Theophylline (anhyd)	124	28.6	21.3	0.45	Huu-Phuoc et al. (1987b)
Sulphadiazine	182	25.6	19.4	0.43	Martin et al. (1983)
Testosterone propionate (A)	294	19.4	14.9	0.41	James et al. (1976)
Phenobarbital	137	25.6	21.1	0.32	Martin et al. (1983)
Benzoic acid	100	21.8	18.2	0.30	Barton (1983)
Testosterone propionate (B)	294	20.5	18.8	0.26	Martin et al. (1983)
Tolbutamide	229	22.3	19.8	0.21	
Hydroxypropyl methylcellulose	185.7	22.8	14.4	0.60	Rowe (1988)
Methylcellulose	150.9	21.3	14.1	0.56	
Polyvinyl pyrrolidone	95.0	21.2	15.5	0.47	

TABLE 6

Results of quadratic curve fitting for data shown in Figs. 6–8 (n = 8)

Binder	Derived values			Correlation coefficient	Standard error	Polarity for $\lambda = 1$	Data at max	
	c	a	b				λ	x
HPMC	0.0683	3.833	−3.354	0.8989	0.0917	0.35–0.79	1.163	0.57
MC	0.2618	3.261	−2.972	0.8831	0.0781	0.32–0.77	1.156	0.55
PVP	0.4815	2.322	−2.308	0.8006	0.0634	0.34–0.66	1.065	0.50

TABLE 7

Comparison of calculated with predicted values for λ from curve-fitting data in Table 6

Substrate	HPMC		MC		PVP	
	Predicted	Calculated	Predicted	Calculated	Predicted	Calculated
Microcrystalline cellulose (Avicel anhydrous)	1.044	0.990	1.024	0.890	0.913	0.765
Lactose (anhydrous)	1.044	0.956	1.024	0.857	0.913	0.738
Polymethylmethacrylate	0.952	0.885	1.001	0.997	1.037	0.988
Polyvinylchloride	0.879	0.732	0.942	0.867	0.951	0.948

TABLE 8

Results of quadratic curve-fitting for data shown in Fig. 9 (n = 24)

Binder	Derived values			Correlation coefficient	Standard error	Polarity for $\lambda = 1$	Data at max	
	c	a	b				λ	x
HPMC	0.3196	2.958	−2.721	0.8926	0.0887	0.33–0.75	1.124	0.54
MC	0.3241	3.244	−3.282	0.9373	0.0636	0.30–0.69	1.126	0.50
PVP	0.3981	3.072	−3.416	0.9314	0.0598	0.29–0.61	1.088	0.44

propyl methylcellulose, 0.50 (0.56–0.58) for methylcellulose and 0.44 (0.47) for polyvinyl pyrrolidone.

It is important to relate these concepts to granulation data in the literature. In this context the reduced spreading coefficient is important in that it defines the ease of film formation of the polymer binder over the substrate and thus the production of 'strong' granules. Inspection of the data especially in Table 8 and Fig. 9 shows that there is no single universal optimum binder, and each substrate has to be taken individually. This then goes some way to explaining the apparently anomalous results in the literature when comparing the polymer binders polyvinyl pyrrolidone, acacia, starch and cellulose derivatives, where for paracetamol, Krycer et al. (1983) found a rank order of cellulose derivative (hydroxypropyl methylcellulose) > acacia > polyvinyl pyrrolidone > starch, but for sulphamethoxazole, Agrawal and Prakasam (1988) found a rank order of polyvinyl pyrrolidone > acacia > starch > cellulose derivative (sodium carboxymethylcellulose). Unfortunately definitive polarity values for these two substrates are unknown. However, from solubility data it can be inferred that paracetamol will have a polarity in excess of 0.5 while sulphamethoxazole will have a polarity somewhat less that of sulphadiazine, i.e. < 0.43 (Sunwoo and Eisen, 1971).

These data clearly have applications in the choice of optimum binders for specific substrates since for low polarity substrates it would be pertinent to use either polyvinyl pyrrolidone or starch while for high polarity substrates either acacia or a cellulose derivative would be recommended. Formulation data in Dictionnaire Vidal (1988) for drugs of known polarity are in general agreement with these predictions (Table 9).

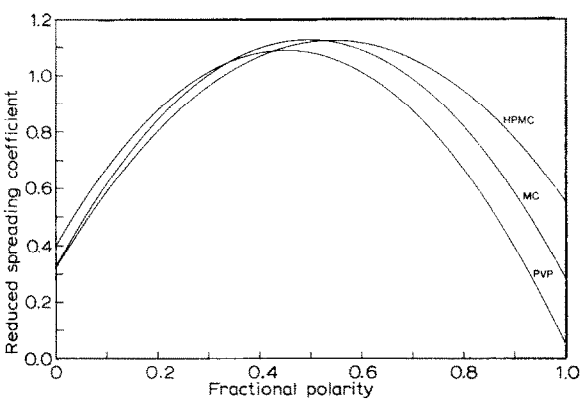

Fig. 9. Reduced spreading coefficient vs fractional polarity for hydroxypropyl methylcellulose (HPMC), methylcellulose (MC) and polyvinyl pyrrolidone (PVP) (combined data).

TABLE 9

Binders used in formulation (data ex Dictionnaire Vidal, 1988)

Substrate	Fractional polarity	Binder
Griseofulvin	0.1	Starch and polyvinyl pyrrolidone
Tolbutamide	0.21	Starch
Phenobarbital	0.32	Starch
Sulphadiazine	0.43	Starch
Theophylline	0.45	Acacia/sodium carboxymethyl cellulose

It must be emphasised that this approach is based solely on the hypothesis that optimum spreading of the binders is the main criterion for a successful formulation. Clearly other criteria such as fast disintegration and dissolution and good flow properties are also important. However the concept of optimising formulations based on the known or measured polarities of substrate and binder undoubtedly has potential use in product development.

References

Agrawal, Y.K. and Prakasam, K., Effect of binders on sulfamethoxazole tablets. *J. Pharm. Sci.*, 77 (1988) 885–888.

Barton, A.F.M., *Handbook of Solubility Parameters and Other Cohesion Parameters*. CRC, Baton Rouge, FL, 1983.

Dictionnaire Vidal, 63rd edn., O.V.P., Paris, 1988.

Gardon, J.L., Critical review of concepts common to cohesive energy density, surface tension, tensile strength, heat of mixing, interfacial tension and butt joint strength. *Prog. Org. Coatings*, 5 (1977) 1–20.

Hansford, D.T., Grant, D.J.W. and Newton, J.M., Surface energetics of the wetting of a hydrophobic powder. *J. Chem. Soc. Faraday I*, 76 (1980) 2417–2431.

Huu-Phuoc, N., Phan Tan Luu, R., Munafo, A., Ruelle, P., Nam-Tran, H., Buchmann, M. and Kesselring, U.W., Determination of partial solubility parameters of lactose by gas-solid chromatography. *J. Pharm. Sci.*, 75 (1986) 68–72.

Huu-Phuoc, N., Nam-Tran, H., Buchmann, M. and Kesselring, U.W., Experimentally optimised determination of the partial and total cohesion parameters of an insoluble polymer (microcrystalline cellulose) by gas-solid chromatography. *Int. J. Pharm.*, 34 (1987a) 217–223.

Huu-Phuoc, N., Nam Tran, H., Buchmann, M. and Kesselring, U.W., Determination of partial and total cohesion parameters of caffeine, theophylline and methyl-p-hydroxybenzoate by gas-solid chromatography. *J. Pharm. Sci.*, 77 (1987b) 406–410.

James, K.C., Ng, C.T. and Noyce, P.R., Solubilities of testosterone propionate and related esters in organic solvents. *J. Pharm. Sci.*, 65 (1976) 656–659.

Johnson, B.A. and Zografi, G., Adhesion of hydroxypropyl cellulose films onto low energy solid substrates. *J. Pharm. Sci.*, 75 (1986) 529–533.

Krycer, I., Pope, D.G. and Hersey, J.A., An evaluation of tablet binding agents. Part I. Solution binders. *Powder Technology*, 34 (1983) 39–51.

Lee, S.B. and Luner, P., The wetting and interfacial properties of lignin. *Tappi*, 55 (1972) 116–121.

Martin, A.N., Swarbrick, J. and Cammarata, A., *Physical Pharmacy. Physical Chemical Principles in the Pharmaceutical Sciences*, 3rd edn., Lea & Febiger, Philadelphia, 1983, p. 286.

Rowe, R.C., Binder-substrate interactions in tablets; a theoretical approach based on solubility parameters. *Acta Pharm. Technol.*, 34 (1988) 144–146.

Rowe, R.C., Binder-substrate interactions in granulation; a theoretical approach based on surface free energy and polarity. *Int. J. Pharm.*, 52 (1989a) 149–154.

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

Sunwoo, C. and Eisen, H., Solubility parameters of selected sulfonamides. *J. Pharm. Sci.*, 60 (1971) 238–244.

Wu, S., Polar and non-polar interactions in adhesion. *J. Adhesion*, 5 (1973) 39–55.

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