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Research Paper

Can the Organization of a Binary Mix Be Predicted from the Surface Energy, Cohesion Parameter and Particle Size of Its Components?

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Purpose. The aim of this study was to relate the organization of several binary mixes with three physical parameters (surface energy, cohesion parameter, and particle size) of various materials blended with each other.

Methods. Four pharmaceutical compounds were selected for their surface energies and cohesion parameters. Binary mixes were prepared from different sieved fractions. The frequency and nature of the interactions between the particles were observed by scanning electron microscopy.

Results. As expected, interactions were determined by both the energetics and the relative particle size of the two compounds blended, the latter determining the mode of interaction. However, particle size was not the only factor influencing the organization of the blends as, sometimes, small particles of a material would not adhere to the coarser particles of the other. Thus, a surface energy derived parameter $|^{B/A}\lambda - {}^{A/B}\lambda|$ appears to be a valuable estimating tool of the potentiality of interaction between the particles blended. No correlation between the cohesion parameters of the compounds and the organization of the resulting blends could be found.

Conclusions. Surface energy and particle size play a major role in the organization of a binary blend. However, they cannot explain separately the interactions observed between the fractions blended as reliable predictions require the use of both characteristics.

KEY WORDS: cohesion parameter; spreading coefficient; strength of interaction; surface energy; particle size.

INTRODUCTION

Blending of powders is an essential operation in pharmacy and other industries. It has been intensively studied. The process of powder mixing has been described by several theories. The random mixing theory proposes that mixing is a statistical process in which the bed of particles is repeatedly split and recombined until there is an equal chance of any individual particle being at any given point in the mix at any one time. Mechanisms of random mixing were early described by Lacey (1) as including shear, diffusion and convection. At equilibrium, the distribution of particles can be described by a binomial distribution. The theory of non-random mixing assumes that the probability of finding any constituent particle in a mix is not equal. The mixing is incomplete. This is the most frequent case when mixed particles do not interact physically except under the force of gravity. In contrast, particles may interact to produce ordered mixes as early described by Hersey (2). For example, fine particles may adhere at the surface of coarser ones to form ordered units. At equilibrium, the ordered mixing theory predicts that the standard deviation of the distribution will be zero if the sample is larger than the ordered unit. As discussed by Lai and Hersey (3), the standard deviation sample size relationship is true only when the carrier is monosized. A real mix will behave somewhere between all the different possibilities described above. A theory of total mixing was presented by Staniforth (4) which accounts for powder mixes formed by particles that are not totally randomly distributed, nor completely ordered. This theory accepts that ordering and randomisation coexist. The final organization of the blend depends on gravity and surface electrical forces. These forces may vary with the particle size distribution of the materials. Another way to classify the degree of homogeneity of a mix has been proposed by Egermann (5): ideally ordered, ordered, pseudo-random, random and incomplete (or segregated) mixtures.

However, despite all the theories and approaches developed, a simple and very important question is still without answer at the moment: what will be, *a priori*, the organization of a mix simply prepared from two powders A and B? The answer clearly depends on the adhesive interactions between the two powders and their cohesiveness. From the different theories on surface free energy and cohesion parameter, it is possible to derive various interesting parameters of interactions between two materials (6,7) such as the spreading ($^{B/A}\lambda$) and reduced spreading coefficients ($^{B/A}\lambda_r$), the interaction parameter ($^{AB}\phi$), and the strength of interaction ($^{AB}\sigma$). They have already been used with success in the pharmaceutical field (8–10). However, these parameters are not likely to be used routinely to predict the organization of an ordered (interactive) or a random (non interactive) mixture because they do not include a major parameter: the particle sizes of the mixed components. As it is well-known, the relative particle size of two blended fractions is a major factor influencing the organization of binary blends.

Some theories have been proposed to estimate the force between two particles, depending on their sizes. The pioneer work in this area was done by Derjaguin (11) who defined the force between two spheres in terms of the energy per unit area of two flat surfaces at a specific distance. Later, the case of adhesion between elastic spheres was examined using the so-called JKR theory (12). These approaches have their own limitations as the particles are supposed spherical, non-porous (so that the effect of capillary condensation on adhesion can be neglected), and non-elastic (for the Derjaguin approximation), an ideal case never encountered in pharmaceutical technology. In practice, adhesion and cohesion can be estimated by several techniques, e.g., flow characteristics, scanning electron microscopy, UV fluorescence microscopy, specific sieve technique, vibration technique and by way of Jenike shear cells. An interesting method of quantification of the adhesion forces between

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fine and coarse particles in ordered mixes involves centrifugation (13). The ordered units are held behind a screen in an ultracentrifuge rotor tube insert. When the force generated by ultracentrifugation becomes greater than the inter-particle adhesion forces, the ordered units break down into their component particles. This technique was later applied with success to ternary systems (14).

In this study, we tried to use the surface energy and cohesion parameter concepts while taking into account the effect of particle size and to see if we could relate these parameters with the observed organization of various binary blends. We selected two active ingredients (niflumic acid, ibuprofen) and two excipients (ethyl cellulose, hydroxypropyl methylcellulose) because niflumic acid and ibuprofen have different total surface energies but similar polarity, whereas ethyl cellulose and hydroxypropyl methylcellulose have close total surface energies but different polarities. Fractions of different sizes were isolated by a sieve method. Finally, each fraction of each material was blended with the others and the resulting interactions were evaluated by scanning electron microscopy and related to surface energy and cohesion parameters.

MATERIALS AND METHODS

Materials

Analytical grades of diethylene glycol, 2-aminoethanol, diiodomethane, aniline, dibutyl phthalate were purchased from Sigma (Buchs, Switzerland) and used to determine the surface energies of the constituants: niflumic acid (Hexachimie, Agen, France), ibuprofen (Unipex, Rueil-Malmaison, France), ethyl cellulose 10 mPa.s (Dow Europe, Horgen, Switzerland), and hydroxypropyl methylcellulose USP type 2910 (Shin Etsu, Tokyo, Japan). All materials were kindly supplied by UPSA, Agen, France.

Preparation of the Binary Mixes

Six series of binary mixes were prepared: niflumic acid with ethyl cellulose or with hydroxypropyl methylcellulose, ibuprofen with either ethyl cellulose or hydroxypropyl methylcellulose, niflumic acid with ibuprofen and finally, ethyl cellulose with hydroxypropyl methylcellulose. Blends were made from the powders as received or after sieving using an Alpine air-jet sieve (Augsburg, Germany) equipped with 20, 32, 45, 63, and 125 μm sieves (Fritsch GmbH, Idar-Oberstein, Germany). It was not possible to obtain a 63–125 μm fraction for ibuprofen as the original powder did not contain enough particles of this size. Using a Turbula (Basel, Switzerland) blender, identical true volumes of each powder were blended for 20 minutes in a 25-mL cylindrical glass container, filled up to 14 mL (56%) to ensure optimum blending. To obtain identical real volumes, the true density (ρ) of each powder (A or B) and the bulk density (D) of each particle size fraction are needed. These densities were determined with a Beckman (Irvine, California, USA) air comparison pycnometer model 930 and a 20 mL volumetric flask, respectively. Then, the following equations were used to determine the weight (w) of each fractions:

$$w_A = \frac{14 \cdot D_A \cdot D_B \cdot \rho_A}{D_B \cdot \rho_A + D_A \cdot \rho_B} \tag{1a}$$

$$w_B = \frac{14 \cdot D_A \cdot D_B \cdot \rho_B}{D_B \cdot \rho_A + D_A \cdot \rho_B} \tag{1b}$$

Scanning Electron Microscopy

Samples were mounted directly onto a SEM sample stub using a double sided adhesive carbon layer and coated with a 150 Å thick gold film under reduced pressure (Balzers Sputter Coater SCD004, Balzers, Principality of Liechtenstein). Photographs were taken using a Jeol scanning electron microscope 6400 (Tokyo, Japan) at magnifications of 100x and 500x.

Determination of Surface Energies

Surface energies were determined from contact angle measurements by measuring the height and width of a drop of liquid onto the surface of a tablet made of the investigated compound with a Lorentzen and Wettre anglometer type 28 (Stockholm, Sweden). Measurements were made 10 times under normal atmospheric conditions. Several solvents were tested to obtain three acceptable solvents with one being mostly disperse. The disperse and polar surface tension fractions (γ_d and γ_p, respectively) of each powder were determined from the known characteristics of the solvents used, given by Panzer (15) and the model developed by Fowkes (16) and expanded by Wu (17).

THEORETICAL BACKGROUND

Calculation of Cohesion Parameters

Cohesion parameters were calculated as described by Barton (18) using the group contribution method of van Krevelen for niflumic acid and ibuprofen, and the specific method for polymers of Hoy. Molar volumes of niflumic acid and ibuprofen were determined using the group contribution method of Fedors (19).

Interaction Parameters: Spreading Coefficients and Strength of Interaction

Two different spreading coefficients have been proposed. Using the harmonic mean equation, Wu (6) determined the optimum wettability condition for adhesion and defined the spreading coefficient of B on A (${}^{B/A}\lambda$) as:

$${}^{B/A}\lambda = {}^{A}\gamma - {}^{B}\gamma - {}^{BA}\gamma \tag{2}$$

expanded to:

$${}^{B/A}\lambda = 4\left[\frac{{}^{B}\gamma_d \cdot {}^{A}\gamma_d}{{}^{B}\gamma_d + {}^{A}\gamma_d} + \frac{{}^{B}\gamma_p \cdot {}^{A}\gamma_p}{{}^{B}\gamma_p + {}^{A}\gamma_p} - \frac{{}^{B}\gamma}{2}\right] \tag{3}$$

where ${}^{A}\gamma$ and ${}^{B}\gamma$ are the surface tensions of two materials, and d, p refer to dispersity and polarity, respectively. When ${}^{B/A}\lambda$ is positive or nil, spreading (or complete wetting) will occur.

Rowe (7) defined a reduced spreading coefficient (${}^{B/A}\lambda_r$) as the ratio of the work of adhesion to the work of cohesion of the binder, thus:

$$^{B/A}\lambda_r = \frac{2}{^{B}\gamma}\cdot\left[\frac{^{A}\gamma_d\cdot{}^{B}\gamma_d}{(^{A}\gamma_d+{}^{B}\gamma_d)}+\frac{^{A}\gamma_p\cdot{}^{B}\gamma_p}{(^{A}\gamma_p+{}^{B}\gamma_p)}\right] \qquad (4)$$

Here, wetting will occur when $^{B/A}\lambda_r \geq 1$. Based on the Leenard-Jones pair potential function, Rowe (20) could calculate the relative strength of interaction ($^{AB}\sigma$ in $ML^{-1}T^{-2}$) of two surfaces A and B from their cohesion parameters ($^{A}\delta$, $^{B}\delta$) and an interaction parameter ($^{AB}\phi$):

$$^{AB}\sigma = 0.25\ {}^{AB}\phi\ {}^{A}\delta\ {}^{B}\delta \qquad (5a)$$

$$^{BB}\sigma = 0.25\ {}^{B}\delta^2 \qquad (5b)$$

$$^{AA}\sigma = 0.25\ {}^{A}\delta^2 \qquad (5c)$$

where $^{AB}\phi$, the interaction parameter, is defined from the harmonic mean equation as (6):

$$^{AB}\phi = 2\cdot\left[\frac{^{A}x_d\cdot{}^{B}x_d}{(^{A}x_d\cdot g_1+{}^{B}x_d\cdot g_2)}+\frac{^{A}x_p\cdot{}^{B}x_p}{(^{A}x_p\cdot g_1+{}^{B}x_p\cdot g_2)}\right] \qquad (6)$$

Quantities x_d and x_p are the fractional non-polarity and polarity, respectively, $(x_d + x_p = 1)$ for each material and the parameters g_1 and g_2 are the ratio of the surface tensions of the materials:

$$x_d = \frac{\gamma_d}{\gamma} \qquad (7a)$$

$$x_p = \frac{\gamma_p}{\gamma} \qquad (7b)$$

$$g_1 = \frac{^{A}\gamma}{^{B}\gamma} \qquad (8a)$$

$$g_2 = \frac{1}{g_1} \qquad (8b)$$

Comparing the relative values of the adhesion strength of interaction with the cohesion strength of each material (Eqs. 5b, c), predictions of the possible interactions between the materials can be made. The predictions from the spreading coefficients and the strength of interaction are presented in Figure 1.

Adhesion Force as a Variable Dependent on Particle Size

From the Derjaguin approximation, it is possible to relate the adhesion force F_{adh} of two rigid (incompressible) non-porous macroscopic spheres of radius R_A and R_B to their work of adhesion W_{adh} by (21):

$$F_{adh} = 2\pi\left(\frac{R_A R_B}{R_A + R_B}\right)\cdot W_{adh} \qquad (9)$$

where the work of adhesion between two particles can be calculated from their disperse (γ_d) and polar (γ_p) surface energy fractions:

$$W_{adh} = 4\cdot\left[\frac{^{A}\gamma_d\cdot{}^{B}\gamma_d}{(^{A}\gamma_d+{}^{B}\gamma_d)}+\frac{^{A}\gamma_p\cdot{}^{B}\gamma_p}{(^{A}\gamma_p+{}^{B}\gamma_p)}\right] \qquad (10)$$

As already indicated in the introduction, this model was later extended to elastic spheres in the so-called JKR theory (12). We will not present the equations here as, according to this theory, a finite elastic modulus while having an effect on the contact area between the two particles has no effect on the adhesion force. Therefore the Derjaguin model is satisfactory for our purpose.

RESULTS AND DISCUSSION

Surface Energies and Interaction Parameters

Contact angle measurements and corresponding partial surface energies of the four materials are presented in Table I. To reduce the experimental errors, three different solvents were used for the determination of the surface energies instead of the two minimum necessary, as usually done with this technique. Surface energy data were then calculated using the three possible couples of solvents, and the three sets of results were averaged. It is interesting to note that niflumic acid and ibuprofen have different total surface energies but present similar polarity (x_p) and dispersity (x_d). Ethyl cellulose and hydroxypropyl methylcellulose have close total surface energies. However, hydroxypropyl methylcellulose is more polar. The advantages of choosing products with different surface energies keeping

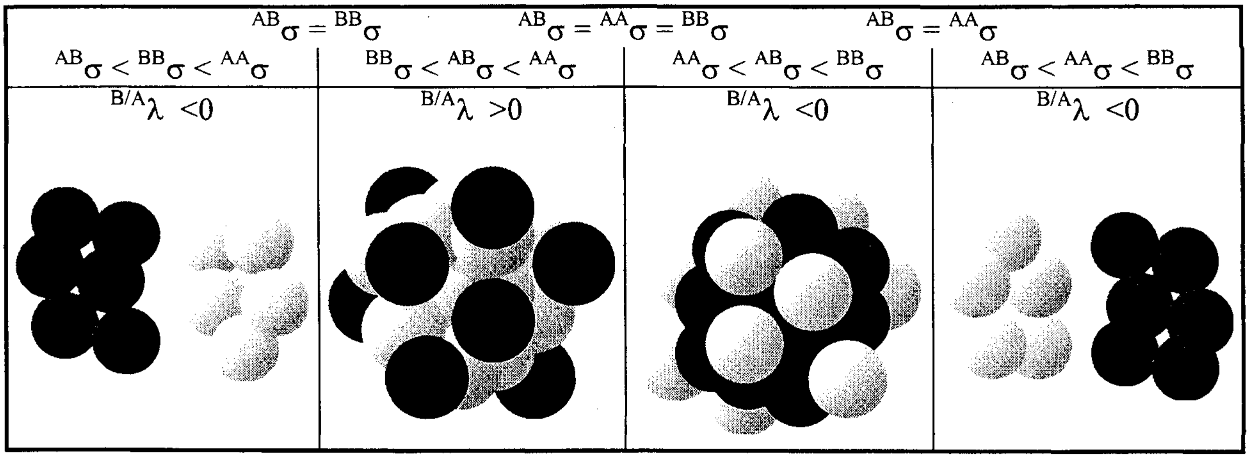

Fig. 1. Influence of cohesion parameter of two materials A (○) and B (●) on strength of interaction ($^{AB}\sigma$, $^{AA}\sigma$, $^{BB}\sigma$) and spreading coefficient ($^{B/A}\lambda$), together with possible predictions. Adapted from (22).

Table I. Contact Angles and Corresponding Partial Surface Energies of Niflumic Acid (NA), Ibuprofen (Ibu), Ethyl Cellulose (EC), and Hydroxypropyl Methylcellulose (HPMC)

	Averaged contact angle (°)					Surface energy (Nm^{-1})		
	Diethylene glycol	2-Amino-ethanol	Diiodo-methane	Dibutyl phthalate	Aniline	γ_d	γ_p	γ
NA	23.6	21.3	49.4	[a]	[a]	26.2	19.7	45.9
Ibu	41.4	39.0	[a]	21.1	[a]	21.3	17.2	38.5
EC	56.3	53.0	54.8	[a]	[a]	25.0	10.8	35.8
HPMC	38.2	63.8	[a]	[a]	44.2	17.0	17.0	34.0

[a] Non-satisfactory solvent for the compound.

either the total surface energy or the dispersity (thus the polarity) constant have already been discussed elsewhere (22).

Calculated spreading coefficients of the active ingredients over the polymers and vice-versa are presented in Table III. Generally, both types of spreading coefficient predict the same trends of spreading. This means that when the spreading coefficient of B over A is positive, the reduced spreading coefficient is greater than one (B should spray over A). There is a discrepancy between both parameters only when spreading of ethyl cellulose over ibuprofen is considered. In this case, the spreading coefficient of ethyl cellulose over ibuprofen is positive (ethyl cellulose should spray over ibuprofen), whereas the reduced spreading coefficient is less than one (ibuprofen should spray over ethyl cellulose or no interaction should happen). We decided to use only the original spreading coefficient ($^{B/A}\lambda$) as it was easier to handle positive or negative values rather than values larger or smaller to one.

Adhesion Force as a Variable Dependent on Particle Size

From Equations 9 and 10, it is possible to simulate the influence of particle size and surface energy on the adhesion force between two particles (Figure 2). The adhesion force between two particles of different materials will be maximum if they have same polarity and very different particle sizes. This prediction is reasonable as a small particle will tend to stick to a coarser one. However, the adhesion force between a particle A and a particle B 100 times smaller is lower than between the same particle A and a particle B 100 times larger. This is not completely satisfactory as the adhesion force should be the same when the relative particle size is kept constant.

One of the limitations of Equations 9 and 10 is that they consider the materials as non-porous. As it has been observed in practice, when one of the material is porous, the surface asperities will entrap the smaller particles of the other material. This was observed between large recrystallized mannitol crystals and small potassium sorbate particles (23). As described by Staniforth (24), the formation of an adhesive couple between two materials will prevent segregation. Furthermore, the force required to pull a particle from an asperity of another particle will be much larger than the force necessary to cause removal by rolling if the coarse particles are non-porous. In a recent publication, Xie (25) tried to include the porosity parameter to define the van der Waals force between two spheres. Using a sandwich contact system as a model of asperity, Xie was able to conclude that when two rough spheres come into contact, they could be treated as smooth when the surface asperities were less than 0.01 μm, whereas if the surface asperities were larger, the surface asperities rather than the parent particles will begin to dominate the van der Waals forces. In our study, niflumic acid and ibuprofen particles are non-porous crystals, hydroxypropyl methylcellulose amorphous particles are slightly porous and amorphous ethyl cellulose particles are porous particles.

Blends of Niflumic Acid with Ethyl Cellulose or Hydroxypropyl Methylcellulose

To test the predictions from the different models, we blended several fractions of different sizes of various materials and estimated their organization. Interactions between the components were assessed from the frequency and nature of aggregates $(A/B)^i$ observed by electron microscopy, where A/B were niflumic acid, ibuprofen, ethyl cellulose or hydroxypropyl methylcellulose and i the frequency, ranging from 1 to 3, of adhesion of A over B particles. The results from Table IV show the drastic influence of particle size of the fractions on the

Table II. Strengths of Interaction of Niflumic Acid (NA), Ibuprofen (Ibu), Ethyl Cellulose (EC) and Hydroxypropyl Methycellulose (HPMC)

	Strength of Interaction (MPa)			
	NA	Ibu	EC	HPMC
NA	124.0	103.5	119.5	155.3
Ibu	103.5	90.2	100.3	134.5
EC	119.5	100.3	119.6	153.1
HPMC	155.3	134.5	153.1	202.6

Table III. Spreading Coefficient ($^{B/A}\lambda$) of Niflumic Acid (NA), Ibuprofen (Ibu), Ethyl Cellulose (EC) and Hydroxypropyl Methylcellulose (HPMC) over Each Other

$^{B/A}\lambda$ A↓B→	NA	Ibu	EC	HPMC
NA	0.0	−8.1	−12.7	−14.1
Ibu	6.7	0.0	− 4.4	− 5.0
EC	7.5	1.0	0.0	− 4.8
HMPC	9.8	4.1	− 1.0	0.0

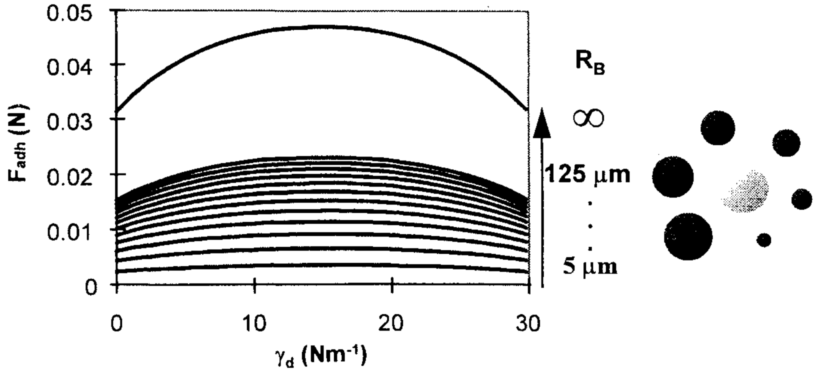

Fig. 2. Influence of particle size and surface energy on the adhesion force between two particles. The upper line describes the theoretical maximum adhesion force between particles A and B when B has an infinite radius. Particle A (○): 125 µm, γ_t = 30 Nm^{-1}, γ_d = 15 Nm^{-1}. Particle B (●): 5–125 µm, γ_t = 30 Nm^{-1}, γ_d = 0–30 Nm^{-1}.

interactions observed in the resulting blends. Examples of the influence of particle size on different blends of niflumic acid and ethyl cellulose are presented in Figure 3. Independently of all the calculated parameters (spreading coefficients and strength of interaction), it seems that the main parameter influencing the interaction, and, more importantly, the way of interaction between each fraction is the particle size of the blended fractions. When a fine material is in presence of a coarse one, the fine adheres to the coarse. This table also indicates that the larger the difference in particle size, the more frequent the interaction, whereas when the fractions have the same size range, the observed interaction is either non-existent (ethyl cellulose and niflumic acid) or very low (ethyl cellulose and hydroxypropyl methylcellulose). This last result is consistent with the work of Lai and Hersey (3). Simulating the properties of powder mixtures when the size and size distribution of the carrier particle of ordered powder mixture are being altered, these authors concluded that the use of a narrow size range of a carrier particles had dual advantages of both increasing the homogeneity and maintaining that homogeneity by avoiding "ordered unit segregation", while mono-sized carrier particles will produce uniform mixture. This is in fact the case when both materials do not interact because of their similar particle size.

Blends of Ibuprofen with Ethyl Cellulose or Hydroxypropyl Methylcellulose

If the relative particle size of each fraction dominates the phenomena leading to an ordered mixture, the same experiment with another active ingredient should give similar results. Blending ibuprofen with either ethyl cellulose or hydroxypropyl methylcellulose gives a completely different pattern of behaviour as indicated in Table V. Only small particles of hydroxypropyl methylcellulose adhere to aggregates of ibuprofen and in a single case only ibuprofen crystals adhere to larger particles of ethyl cellulose. Moreover, instead of having small particles of active ingredient concentrating in the interstitial pores of ethyl cellulose, like niflumic acid, ibuprofen seems to be a very cohesive material giving systematically non-interactive aggregates even for crystal sizes under 45 µm. This is clearly illustrated by the two SEM pictures (Figure 4) of the 125-63 µm fraction of ethyl cellulose blended with the 20–32 µm fractions of niflumic acid (A) or ibuprofen (B). It could be argued that the relative size of the two components is not enough to describe the system because the surface of contact available between them also depends on their shapes. However, since both niflumic

Table IV. Interactions (A/B)^{i} Observed in Binary Blends where A, B Represent Niflumic Acid (NA), Ethyl Cellulose (EC) or Hydroxypropyl Methylcellulose (HPMC), and i the Frequency, Ranging from 1 (low) to 3 (high), of Adhesion of Particles A on Particles B

	Niflumic acid (NA)			
	63–125 µm	45–63 µm	32–45 µm	20–32 µm
EC				
63–125 µm	-/-[a]	(NA/EC)^{2}	(NA/EC)^{3}	(NA/EC)^{3}
45–63 µm	(EC/NA)^{1}	-/-	-/-	(NA/EC)^{2}
32–45 µm	(EC/NA)^{1}	(EC/NA)^{2}	(EC/NA)^{1}	-/-
20–32 µm	(EC/NA)^{3}	(EC/NA)^{3}	(EC/NA)^{3}	-/-
HPMC				
63–125 µm	-/-	(NA/HPMC)^{1}	(NA/HPMC)^{3}	(NA/HPMC)^{2}
45–63 µm	(HPMC/NA)^{2}	(HPMC/NA)^{1}	(NA/HPMC)^{1}	(NA/HPMC)^{2}
32–45 µm	(HPMC/NA)^{2}	(HPMC/NA)^{2}	(HPMC/NA)^{1}	(NA/HPMC)^{2}
20–32 µm	(HPMC/NA)^{2}	(HPMC/NA)^{2}	(HPMC/NA)^{2}	(NA/HPMC)^{2}

[a] Absence of interaction.

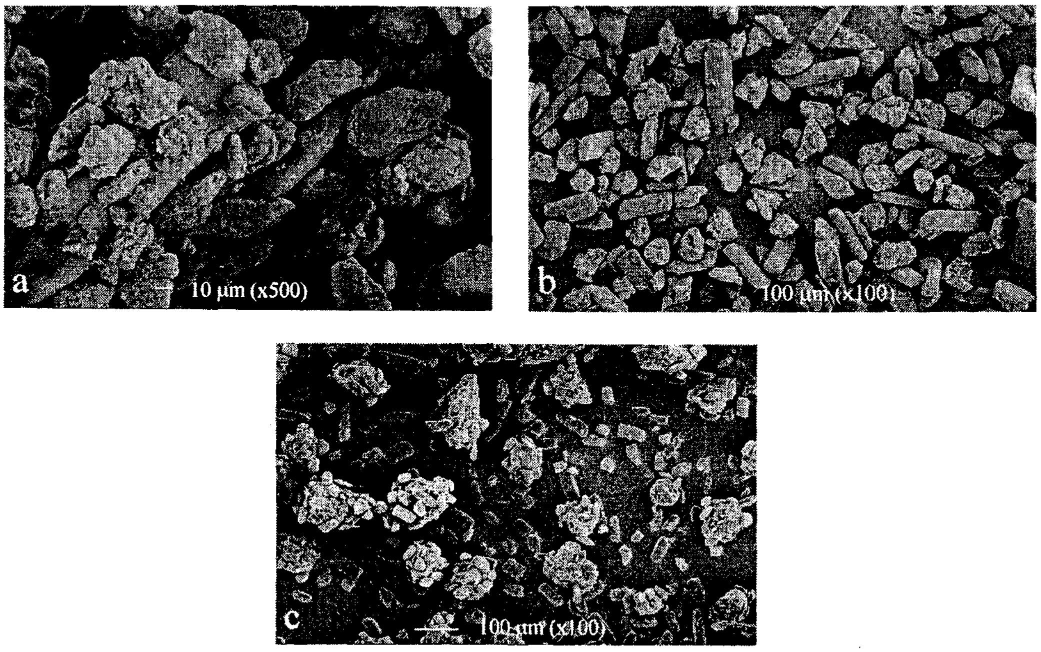

Fig. 3. SEM pictures (×500 or ×100) of various fractions of niflumic acid (NA) with ethyl cellulose (EC); a: NA 63–125 μm/EC 20–32 μm; b: NA 45–63 μm/EC 45–63 μm; c: NA 20–32 μm/EC 63–125 μm.

acid and ibuprofen crystals are parallelepipeds, this is not the case here.

Blends of Niflumic Acid with Ibuprofen

Blending similarly shaped niflumic acid and ibuprofen particles still shows the cohesiveness of ibuprofen (Table VI). These observations are surprising as we could expect a possible interaction of the clusters of ibuprofen with the smaller particles of niflumic acid from the larger spreading coefficient of ibuprofen over niflumic acid compared to the spreading coefficients of ibuprofen over ethyl cellulose and hydroxypropyl methylcellulose (Table III).

Table V. Interactions (A/B)^{i} Observed in Binary Blends where A, B Represent Ibuprofen (Ibu), Ethyl Cellulose (EC) or Hydroxypropyl Methylcellulose (HPMC), and i the Frequency, Ranging from 1 (low) 3 (high), of Adhesion of Particles A on Particles B

	IBUPROFEN (Ibu)		
	45–63 μm	32–45 μm	20–32 μm
EC			
63–125 μm	(Ibu/EC)^{1}	(Ibu/Ibu)^{2}	(Ibu/Ibu)^{3}
45–63 μm	-/-^{a}	(Ibu/Ibu)^{2}	(Ibu/Ibu)^{3}
32–45 μm	-/-	(Ibu/Ibu)^{2}	(Ibu/Ibu)^{3}
20–32 μm	-/-	EC^{2}(Ibu/Ibu)^{2}	EC^{1}(Ibu/Ibu)^{2}
HPMC			
63–125 μm	-/-	(Ibu/Ibu)^{2}	(Ibu/Ibu)^{3}
45–63 μm	-/-	(Ibu/Ibu)^{2}	(Ibu/Ibu)^{3}
32–45 μm	-/-	HPMC^{1}(Ibu/Ibu)^{2}	(Ibu/Ibu)^{3}
20–32 μm	(HPMC/Ibu)^{1}	HPMC^{1}(Ibu/Ibu)^{2}	HPMC^{3}/(Ibu/Ibu)^{3}

[a] Absence of interaction.

Blends of Ethyl Cellulose with Hydroxypropyl Methylcellulose

This case is particularly interesting as almost no interactions are observed between the particles even when the 125-63 μm fraction of ethyl cellulose is blended with the 20–32 μm fraction of hydroxypropyl methylcellulose (Figure 4c). The only slight interaction observed was between the 20–32 μm fraction of ethyl cellulose and the 32–45 μm fraction of hydroxypropyl methylcellulose. These observations reinforce those made when ibuprofen was blended with ethyl cellulose (Figure 4b), showing that the relative particle size of the compounds blended was not the only factor influencing the organization of the blend. The model from the cohesion parameters fails to predict the absence of interaction as it predicts a strong adhesion of ethyl cellulose over the particles of hydroxypropyl methylcellulose (${}^{HPMC/HPMC}\sigma > {}^{HPMC/EC}\sigma > {}^{EC/EC}\sigma$). However, the spreading coefficient seems more interesting as the spreading coefficients of ethyl cellulose over hydroxypropyl methylcellulose (${}^{EC/HPMC}\lambda$) and hydroxypropyl methylcellulose over ethyl cellulose (${}^{HPMC/EC}\lambda$) are both negative. Both spreadings have the same sign because ethyl cellulose and hydroxypropyl methylcellulose have very close total surface energies. As shown earlier, spreading will occur if the spreading coefficient is positive or nil. Therefore, the absence of interaction between ethyl cellulose and hydroxypropyl methylcellulose could have been predicted from the values of their spreading coefficients.

On the other hand, the presumed predictions from Tables II and III using the surface energy and cohesion parameter approaches cannot explain alone all the sets of results (Tables IV–VI). In fact, the two approaches may even give opposite predictions (e.g., in the case of niflumic acid, the calculated strengths of interaction indicate that ethyl cellulose should not interact with niflumic acid and niflumic acid should coat the hydroxypropyl methylcellulose whereas spreading coefficients

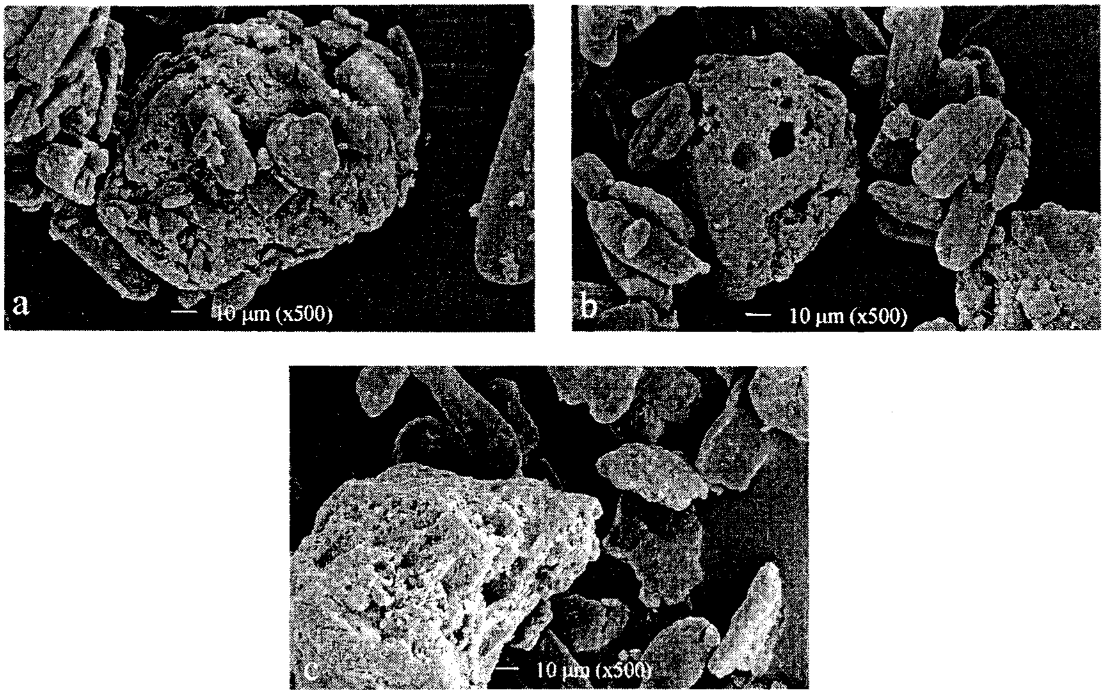

Fig. 4. SEM pictures of the 125–63 μm fraction of ethyl cellulose blended with the 20–32 μm fractions of niflumic acid (a), ibuprofen (b) or HPMC (c).

predict that both ethyl cellulose and hydroxypropyl methylcellulose should coat the niflumic acid). More importantly, both approaches can only predict a one-way interaction. Clearly, this is not what was observed.

The Parameter $|^{B/A}\lambda - {}^{A/B}\lambda|$

Despite the qualitative way used to estimate the importance of the interaction between the different materials, we tried to relate the number of cases where interactions were observed to the derived parameters obtained from the surface energies and cohesion parameters of the blended materials.

We could not relate the interactions observed with the cohesion parameters or the strength of interaction as several discrepancies exist between the observed and calculated interaction. For example, the calculated adhesion forces (Table II) predict that the adhesion of the niflumic acid / hydroxypropyl methylcellulose pair should be similar to the adhesion of the ethyl cellulose / hydroxypropyl methylcellulose pair ($^{NA/HPMC}\sigma \approx {}^{EC/HPMC}\sigma \approx 154$ MPa). Clearly, this is not what was observed by electronic microscopy.

However, the absolute difference between the spreading coefficients of each active ingredient over each excipient and *vice versa* seems interesting as this quantity increases with the number of interaction. This difference is not nil as the absolute value of the spreading coefficient of B over A is different from the absolute value of the spreading coefficient of A over B ($|^{B/A}\lambda| \neq |^{A/B}\lambda|$). Therefore, the quantity $|^{B/A}\lambda - {}^{A/B}\lambda|$ represents the distance between the two spreading coefficients on the spreading coefficient scale. The corresponding values for each mix are given in Table VII. They are plotted in Figure 5 against the number N of cases where interactions between active ingredient and polymer were observed in each binary mix. For exam-

Table VI. Interactions Observed in Blends of Niflumic Acid (NA) with Ibuprofen (Ibu)

	Ibuprofen		
	45-63 μm	32-45 μm	20-32 μm
Niflumic acid			
63–125 μm	(Ibu/NA)^1	(Ibu/Ibu)^2 and (Ibu/NA)^1	(Ibu/Ibu)^3/NA^1
45–63 μm	(Ibu/Ibu)^2	NA^1/(Ibu/Ibu)^2	(Ibu/Ibu)^3/NA^3
32–45 μm	NA^1/(Ibu/Ibu)^1	-/-^{a}	NA^1/(Ibu/Ibu)^2
20–32 μm	-/-	-/-	NA^1/(Ibu/Ibu)^2

^{a} Absence of interaction.

Table VII. Number N of Cases Where Interactions Were Observed Between the Different Particle Size Fractions of a Specific Blend *Versus* the Parameter $|^{B/A}\lambda - {}^{A/B}\lambda|$ of Each Blend

	Number of interactions observed			
Materials	A/B	B/A	Total	$|^{B/A}\lambda - {}^{A/B}\lambda|$ (Nm^{-1})
NA/HPMC	5	7	12	24.0
NA/EC	4	4	8	20.2
NA/Ibu	4	1	5	14.9
Ibu/HPMC	5	0	5	9.1
Ibu/EC	2	1	3	5.4
EC/HPMC	1	0	1	3.7

Note: NA, niflumic acid; HPMC, hydroxypropyl methylcellulose; EC, ethyl cellulose; Ibu, ibuprofen.

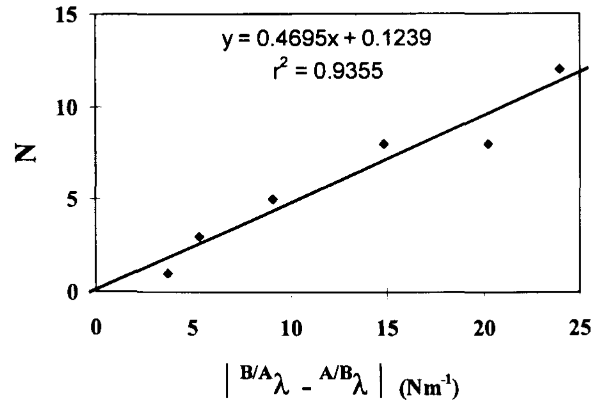

Fig. 5. Number (N) of cases where interactions were observed in Ibu/EC, Ibu/HPMC, NA/EC, NA/HPMC, Ibu/NA and EC/HPMC blends *versus* $|{}^{B/A}\lambda - {}^{A/B}\lambda|$. Ibu, ibuprofen; EC, ethyl cellulose; HPMC, hydroxypropyl methylcellulose; NA, niflumic acid.

ple, between ibuprofen and ethyl cellulose (Table V), N is equal to 3. In order to compare identical sets of data, we did not consider the 125–63 μm fraction of niflumic acid since this fraction could not be isolated from ibuprofen powder. Figure 5 seems to indicate a linear relationship between $|{}^{B/A}\lambda - {}^{A/B}\lambda|$ and N. Interestingly, this parameter can be simplified as two times the absolute value of the difference between the total surface energies of the components:

$$|{}^{B/A}\lambda - {}^{A/B}\lambda| = |{}^{AB}\gamma - {}^{BA}\gamma| = 2.|{}^{A}\gamma - {}^{B}\gamma| \qquad (11)$$

Equation 9 shows that the parameter $|{}^{B/A}\lambda - {}^{A/B}\lambda|$ is independent from the dispersity and polarity of the compounds used. From Figure 5 and the interactions observed in the different blends, we can propose to modify Figure 1 into Figure 6 to take into account the major role of particle size on the strength and frequency of interaction between the particles of a binary blend. Using this figure, it could have been possible to predict the organization of the blends between niflumic acid, ibuprofen, ethyl cellulose and hydroxypropyl methylcellulose from their surface energies. All the cases described in Figure 6 were observed except the last one as the materials chosen did not present such a large $|{}^{B/A}\lambda - {}^{A/B}\lambda|$ value.

We could not find any relationship between the solubility parameters or the strength of interaction and the observed interactions in the various blends. It should be reminded that cohesion parameters are related to the molecule (bulk property) whereas surface energies are an indication on the properties of the surface of the material which may be quite different from the properties of the inside of the particle. It is the forces arising from the surfaces along with gravity that will define the organization of the blend, not the bulk properties of the materials.

In the daily formulation work, blends are made of more than two components and not in 50/50 v/v ratios. As a first attempt towards this real world, we prepared some blends of niflumic acid with ethyl cellulose using three different ratios with increasing proportions of active ingredient: 10/90, 25/75 and 50/50. Results presented in Figure 7 show that even in small proportions, niflumic acid will interact with ethyl cellulose (Figure 7A). The coating of the ethyl cellulose particles will increase as long as there is some surface area available to the niflumic acid particles (Figure 7B). Once all the sites are occupied, the additional niflumic acid particles will lay aside the coating ethyl cellulose particles (Figure 7C). This suggests that when two interacting materials are blended, they will interact whatever their relative proportions as long as an area is available for interaction. In previous studies, Hersey (2) and Yip and Hersey (26) proposed that when a minor monosized ingredient is mixed with a major monosized diluent of higher mean particle size, the fine one should adhere to the coarse one, to yield ordered powder mixtures. Later, Egermann (27) proposed the concept of ordered and random adhesion. When ordered adhesion occurs, the same number of fines should adhere to the coarse particles, whereas in the case of random adhesion, a random variation of the number of adhering fines per coarse particle is assumed. In our case, it was difficult to estimate if the niflumic acid crystals were randomly dispersed or not on the surface of the ethyl cellulose particles. Our point was to verify that in case of interaction, the adhering material will interact with the coarse material whatever the proportions of the mix until full coverage of the coarse particles is reached.

Recently, another work concerning the use of surface energy measurements to predict mixing performance was published (28). Microcrystalline cellulose, magnesium stearate, titanium and iron oxides were blended with each other. After calculating the spreading coefficients of these powders onto glass, the adhesion tendencies to glass of the powder mixes and the pure powders were evaluated. In a previous communication (29), the authors reported that the adhesion ranged from non-

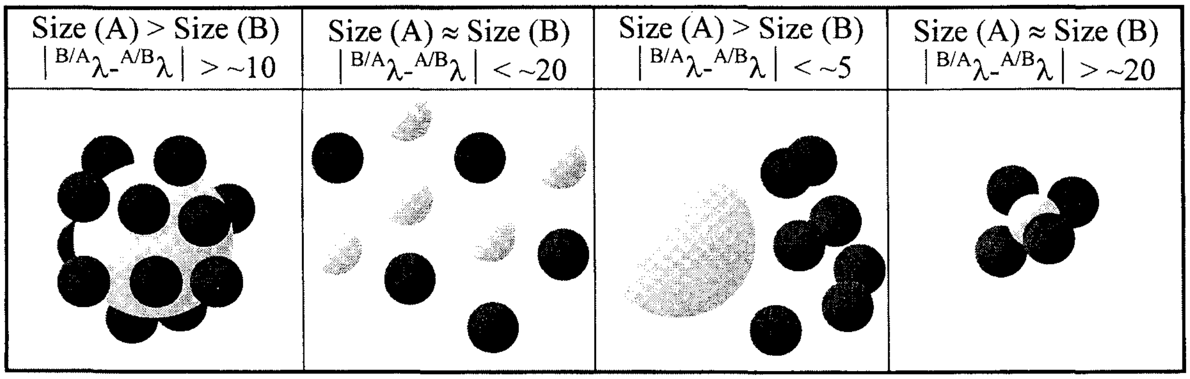

Fig. 6. Influence of particle size and surface energy on the organisation of a binary blends of two materials A (○) and B (●).

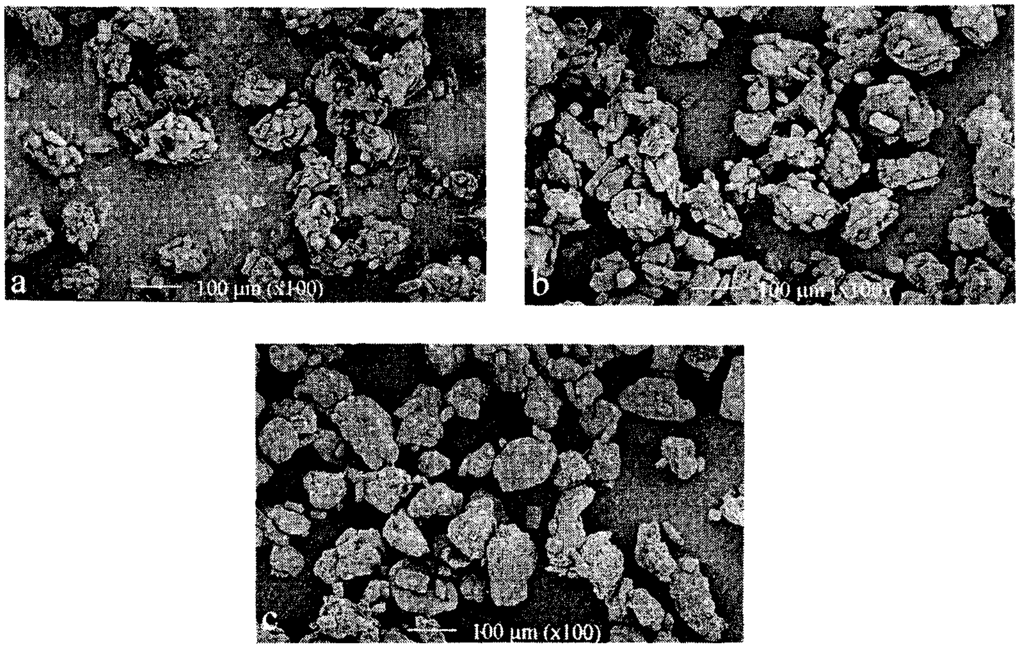

Fig. 7. SEM pictures (×100) of blends with various proportions of 63–125 µm niflumic acid with 20–32 µm ethyl cellulose (EC). a: NA 10 / EC 90; b: NA 25/EC 75; c: NA 50/EC 50.

adhering to strongly adhering. If we give a 0 score when no adhesion was observed, and 1, 2, and 3 when slight, moderate and strong adhesions to glass were observed and calculate the $|{}^{B/A}\lambda - {}^{A/B}\lambda|$ parameters from the spreading coefficients, we obtain a good correlation between the proposed scores and the $|{}^{B/A}\lambda - {}^{A/B}\lambda|$ parameters except in one case. This is in agreement with our results, as this score reflects the overall tendency of the materials to spread onto each other just as the parameter N defined in this paper.

CONCLUSIONS

In this study, we were able to demonstrate that although the surface energy and cohesion parameter were useful tools in predicting some interactions between powders, they were not able to predict reliably the presence and nature of interactions for the powders selected. To get an ordered mixture between an active ingredient (A) and another material (B), both should have a wide particle size distribution and present such surface energy as the absolute difference between ${}^{B/A}\lambda$ and ${}^{A/B}\lambda$ be as high as possible. In this case, the small particles of A and B will adhere to the coarse particles of B and A, respectively. If random homogeneity without interaction between the components is desired, A and B should have similar particle sizes and present a $|{}^{B/A}\lambda - {}^{A/B}\lambda|$ value as low as possible.

To validate this approach, more experiments are required with binary groups of materials presenting different $|{}^{B/A}\lambda - {}^{A/B}\lambda|$ values. We agree with Rowe (30) who recognised that the model used in the derivation of the equations involving solubility parameters was somewhat crude and oversimplified. Unless both surface energy and cohesion parameter approaches include the particle size factor as we tried to do it in this study, we believe that the derived parameters should be considered with care by the formulator when trying to predict powder interactions to optimise a formulation.

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REFERENCES

1. P. M. C. Lacey. Developments in the theory of particle mixing. *J. Appl. Chem.* **4**:257–268 (1954).
2. J. A. Hersey. Ordered mixing: a new concept in powder practice. *Powder Technol.* **11**:41–44 (1975).
3. F. K. Y. Lai and J. A. Hersey. Simulated ordered powder mixture. *Int. J. Pharm.* **36**:157–164 (1987).
4. J. N. Staniforth. Total mixing. *Int. J. Pharm. Tech. Prod. Mfr.* **2(1)**:7–12 (1981).
5. H. Egermann. Reply to comments on "Suggestions on the nomenclature of powder mixtures". *Powder Technol.* **30**:289–290 (1981).
6. S. Wu. Polar and non-polar interactions in adhesion. *J. Adhesion*, **5**:39–55 (1973).
7. R. C. Rowe. Polar/non-polar interactions in the granulation of organic substrates with polymer binding agents. *Int. J. Pharm.* **56**:117–124 (1989).
8. R. C. Rowe. Interactions in coloured powders and tablet formulations: a theoretical approach based on solubility parameters. *Int. J. Pharm.* **53**:47–51 (1989).
9. R.C. Rowe. Surface free energy and polarity effects in the granulation of a model system. *Int. J. Pharm.* **53**:75–78 (1989).
10. R. C. Rowe. Correlation between predicted binder spreading coefficients and measured granule and tablet properties in the granulation of paracetamol. *Int. J. Pharm.* **58**:209–213 (1990).
11. B. V. Derjaguin. Friction and adhesion. IV. The theory of adhesion of small particles. *Kolloid-Z*, **69**:155–164 (1934).
12. K. L. Johnson, K. Kendall and A. D. Roberts, *Proc. R. Soc. London*, Ser. A **324**:301–313 (1971).
13. J. N. Staniforth, J. E. Rees, F. K. Y. Lai, and J. A. Hersey. Determination of interparticulate forces in ordered powder mixes. *J. Pharm. Pharmacol.* **33**:485–490 (1981).

14. J. N. Staniforth, J. E. Rees, F. K. Y. Lai and J. A. Hersey. Interparticle forces in binary and ternary ordered powder mixes. *J. Pharm. Pharmacol.* **34**:141–145 (1982).
15. J. Panzer. Components of solid surface free energy from wetting measurements. *J. Colloid Interface Sci.* **44**:142–161 (1973).
16. F. M. Fowkes. Attractive forces at interfaces. *Ind. Eng. Chem.* **56(12)**:40–52 (1964).
17. S. Wu. Calculation of interfacial tension in polymer systems. *J. Polym. Sci.* **34**:19–30 (1971).
18. A. F. M. Barton, *Handbook of solubility parameters and other cohesion parameters*, CRC Press Inc., Boca Raton, 1991.
19. R. F. Fedors. A method for estimating both the solubility parameters and molar volumes of liquids. *Polym. Eng. Sci.* **14**:147–154 (1974).
20. R. C. Rowe. Binder-substrate interactions in tablets: a theoretical approach based on solubility parameters. *Acta Pharm. Technol.* **34**:144–146 (1988).
21. J. N. Israelachvili. Intermolecular and surface forces. In *Intermolecular and surface forces,* London: Academic Press, 1995, pp. 326-334.
22. J. Barra, F. Lescure, and E. Doelker. Influence of surface free energies and cohesion parameters on pharmaceutical material interaction parameters—Theoretical simulations. *Pharm. Res.* **13**:1746–1751 (1996).
23. J. N. Staniforth, J. E. Rees, J. B. Kayes, R. C. Priest and N. J. Cotterill. The design of a direct compression tableting excipient. *Drug Dev. Ind. Pharm.* **7**:179–190 (1981).
24. J. N. Staniforth. Advances in excipient technology. Powder and tableting characteristics. *S. T. P Pharma*, **6**:162–168 (1990).
25. H. Y. Xie. The role of interparticle forces in the fluidization of fine particles. *Powder Technol.* **94**:99–108 (1997).
26. C. W. Yip and J. A. Hersey. Perfect powder mixtures. *Powder Technol.* **16**:189–192 (1977).
27. H. Egermann. Effects of adhesion on mixing homogeneity. Part I: ordered adhesion-random adhesion. *Powder Technol.* **27**:203–206 (1980).
28. N. M. Ahfat, G. Buckton, R. Burrows, and M. Ticehurst. Predicting mixing performance using surface energy measurements. *Int. J. Pharm.* **156**:89–95 (1997).
29. N. M. Ahfat, G. Buckton, R. Burrows, and M. Ticehurst. Predicting the interaction of powders in binary mixes from their surface energy components. *Unpublished communication* (1996).
30. R. C. Rowe. Interaction of lubricants with microcrystalline cellulose and anhydrous lactose—a solubility parameter approach. *Int. J. Pharm.* **41**:223–226 (1988).