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Correlation between predicted binder spreading coefficients and measured granule and tablet properties in the granulation of paracetamol

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Summary

The interfacial works of cohesion, adhesion, interaction parameters and spreading coefficients have been calculated for paracetamol granulated with hydroxypropyl methylcellulose, acacia, polyvinyl pyrrolidone and starch using literature values of surface free energies. In general, the predictions made regarding film formation, granule morphology and failure processes are consistent with literature data. Correlations have been found between the spreading coefficient of the binder over the substrate and actual experimental measurements of granule friability, tablet strength and tablet capping. The shape and complexity of the relationships can be further explained on the basis of the relative changes in binder cohesion.

Introduction

Pharmaceutical powders are often formulated as granules with polymer binding agents to enhance flow and compaction characteristics. Considerable research has been conducted in an attempt to correlate subsequent granule and tablet properties with the constituent binder properties often with limited success (Krycer et al., 1983a,b; Reading and Spring, 1984, 1985; Cutt et al., 1986, 1987.). Krycer et al. (1983a) concluded that significant determinants for optimum granulation are the wetting of the substrate by the binder, binder-substrate adhesion and binder cohesion. Recent work by Rowe (1988, 1989a–c) 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) of a number of substrates and binders leading to statements regarding film formation, granule morphology, fracture processes and granule strength (Rowe, 1989b). Indeed, if data from all the calculations are expressed in terms of the common dimensionless parameters of fractional polarity of the substrate and reduced spreading coefficient of the binder over the substrate, it is possible to show a parabolic relationship between the two parameters independent of the method used to calculate them but specific to each polymer binder (Rowe, 1989c). It is possible,

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using the relationship, not only to predict the optimum binder for any particular substrate of known fractional polarity, but also to explain the apparently anomalous results in the literature regarding the rank ordering of polymeric binders. (Krycer et al., 1983a; Agrawal and Prakasam, 1988). Unfortunately it has not been possible to correlate experimental measurements of granule friability and tablet strength with predicted spreading coefficients due to lack of data. This has been attempted in this study where the surface free energy approach has been applied to the system consisting of paracetamol granulated with a variety of polymeric binders as originally used by Krycer et al. (1983a), using literature data on the surface free energy of paracetamol measured by Von Ohm and Lippold (1986).

Theoretical Considerations

If γ_1 and γ_2 are the surface free energies of the binder and the substrate respectively, then it is possible to calculate not only the work of cohesion (W_c) of each of the two components, but also the interaction parameter ($\varnothing$) and the work of adhesion between the two components (W_a) and the spreading coefficients λ_{12} (binder over substrate), λ_{21} (substrate over binder) and λ_R (reduced) (Wu, 1973; Rowe, 1989b,c); i.e.

$$W_{c_1} = 2\gamma_1 \tag{1}$$

$$W_{c_2} = 2\gamma_2 \tag{2}$$

$$W_a = 4\left[\frac{\gamma_1^d\gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p\gamma_2^p}{\gamma_1^p + \gamma_2^p}\right] \tag{3}$$

$$\lambda_{12} = W_a - W_{c_1} \tag{4}$$

$$\lambda_{21} = W_a - W_{c_2} \tag{5}$$

$$\lambda_R = \frac{W_a}{W_{c_1}} \tag{6}$$

$$\varnothing = 2\left[\frac{x_1^d x_2^d}{x_1^d g_1 + x_2^d g_2} + \frac{x_1^p x_2^p}{x_1^p g_1 + x_2^p g_2}\right] \tag{7}$$

where γ^d and γ^p denote the non-polar and polar contributions of the surface free energy and x^d and x^p are the fractional non-polarity and polarity, respectively, of each component, i.e.

$$x_1^d = \frac{\gamma_1^d}{\gamma_1} \tag{8}$$

$$x_2^p = \frac{\gamma_2^p}{\gamma_2} \tag{9}$$

and g_1 and g_2 are defined by

$$g_1 = \frac{\gamma_1}{\gamma_2} \tag{10}$$

$$g_2 = \frac{\gamma_2}{\gamma_1} \tag{11}$$

Results and Discussion

Numerical values of the surface free energies of the paracetamol and the polymeric binders are given in Table 1. It is important to note that these values are representative literature data and have not been measured on the actual batches of material used by Krycer et al. (1983a) although the values for acacia and starch were calculated from surface tension and contact angle data given by Krycer et al. (1983a) – see Rowe (1989a).

The results of the calculations are listed in Table 2 and graphs of the spreading coefficient

TABLE 1

Surface free energy data on paracetamol and polymeric binders

	γ (mN m^{-1})	γ^d (mN m^{-1})	γ^p (mN m^{-1})	Reference
Paracetamol	56.5	29.2	27.3	Von Ohm and Lippold (1986)
HPMC	48.4	18.5	29.9	Rowe (1989a)
PVP	53.6	28.4	25.2	
Acacia	50.6	21.6	29.0	
Starch	58.7	29.0	29.7	

HPMC, hydroxypropyl methylcellulose; PVP, polyvinyl pyrrolidone.

TABLE 2

Calculations based on data in Table 1

	HPMC	Acacia	PVP	Starch
Work of cohesion ($mN\ m^{-1}$)	96.8	101.2	107.2	117.4
Work of adhesion ($mN\ m^{-1}$)	102.4	105.9	110.0	115.1
Spreading coefficients				
$\lambda_{12}(mN\ m^{-1})$	5.6	4.7	2.8	−2.3
$\lambda_{21}(mN\ m^{-1})$	−10.6	−7.1	−3.0	2.1
λ_R	1.06	1.05	1.03	0.98
Interaction parameter	0.97	0.99	1.00	1.00

HPMC, hydroxylpropyl methylcellulose; PVP, polyvinyl pyrrolidone.

λ_{12} plotted vs. granule friability index, tablet strength (crushing force) and tablet capping index (data from Krycer et al., 1983a) are presented in Fig. 1. The relevance of these data can be best discussed under each of the five subheadings below.

Film spreading and granule morphology

The positive values of the spreading coefficients λ_{12} for paracetamol granulated with hydroxypropyl methylcellulose acacia and polyvinyl pyrrolidone imply good film formation in the order stated. The negative value of λ_{12} together with the positive value of λ_{12} for starch implies the absence of a continuous film but the presence of patches of polymer binder. Similar conclusions can be drawn from the reduced spreading coefficient where a value in excess of unity implies good film formation and where a value less then unity implies the reverse.

Recently, Rowe (1989a) has advanced the hypothesis of two distinct granule morphologies. In the case where λ_{12} is positive and there is a strongly adhering film of binder around the substrate, a strong dense granule will be formed, since there will always be a bond formed at all points of contact between the substrate particles. However, in the case where λ_{12} is negative and λ_{21} is positive and there is no continuous film, a porous open granule will be formed since bonds will only occur through isolated patches of polymer. Unfortunately, Krycer et al. (1983a) did not publish photomicrographs of all the prepared granules to show whether or not there were any differences between the morphologies of the granules but recent data reported by Cutt et al. (1986) as analysed by Rowe (1989b) would confirm this hypothesis.

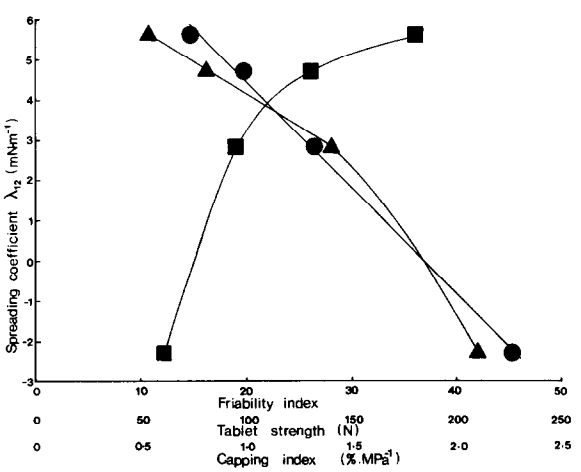

Fig. 1. Relationship between the calculated spreading coefficient λ_{12} and granule friability (●), tablet strength (crushing force) (■) and tablet capping index (▲) as measured by Krycer et al. (1983a).

Failure processes

The value of the interaction parameter, ∅, is important since it provides information on the possible mode of failure of the system, i.e., interfacial/adhesive or cohesive within the weaker component. If the interaction parameter is unity, then interfacial failure in a perfectly bonded system will not be possible because the interfacial bond strength would be greater than the tensile strength of the weaker component. If the interaction parameter is significantly less than unity then interfacial failure will always occur. The values generated in Table 2 would imply cohesive failure within the polymer binder for all systems. Evidence from the photomicrographs published by Krycer et al. (1983a) would support cohesive failure within the polymer binder at least for the hydroxypropyl methylcellulose.

Granule friability

In view of the previous discussion, it is not surprising that the higher the spreading coefficient, λ_{12}, the lower the granule friability (Fig. 1). However, what is unexpected is the linear relationship found for all systems with no deviation in the case of starch, which is thought to produce a different granule morphology. It may well be that the linear relationship is purely fortuitous and dependent on the experimental method used by Krycer et al. (1983a). The method is unique to these workers and involves vibrating a set weight of fractionated granulés with a number of large plastic balls on a 250 μm mesh sieve and recording the weight of powder passing through the sieve as a function of time. The friability index is then taken as the inverse of the half-life of the percentage weight of granules remaining on the sieve.

In tests such as those described above, the applied stresses on the granules are likely to be in shear rather than tensile and hence the relative cohesive strengths of the binder will be less important. Hence, friability will vary according to the number of points of contact between the substrate particles in the granule i.e., it is dependent on the extent of film formation and hence on the spreading coefficient. In the case of a friability test dependent on tensile stresses, a more complex relationship would be likely to occur, since the cohesive strengths of the binders will become more important and, as can be seen from table 2, the thermodynamic work of cohesion of starch is some 21% higher than that of hydroxypropyl methylcellulose.

Tablet strength

The strength of a compacted tablet is related to both the extent and magnitude of interparticulate bonding. Since paracetamol forms tabets that are very weak any increase in strength on the addition of polymeric binders will be a result of both the extent of film formation and the magnitude of the cohesive strength of the binder itself. It is not surprising, therefore, that the higher the spreading coefficient the stronger the tablet. However, the relationship is not linear as in the case of the granule friability, with the tablets prepared from granules prepared with starch being stronger than would be predicted from data on the other three binders. The exponential type of relationship is due to the fact that the work of cohesion of the binders and hence their cohesive strength increase with decreasing spreading coefficient (Table 2).

Tablet capping

The tablet capping index as used by Krycer et al. (1983a) is defined as the gradient of a plot of tablet percentage recovery vs. residual die wall pressure – the higher the value the greater the propensity of the tablet to cap. The index is stated as taking into account both the influence of plastic flow during compaction and bond disruption during elastic recovery. It is apparent from the data in Fig. 1 that the relationship between this capping index and the spreading coefficient is similar in complexity to that between the tablet strength and the same spreading coefficient. However, in this case there is a linear relationship for those binders where there is good film formation (i.e., with hydroxypropyl methylcellulose, acacia and polyvinyl pyrrolidone) and the capping index of tablets prepared using starch as binder is much lower than would be expected from the extrapolation. It would appear that the extent of film formation is the most important factor when spreading does occur but in the case where there is no continuous film the cohesive strength of the polymer binder itself is the most important factor. Of course, more data are necessary to confirm this hypothesis for other substrates.

Conclusion

It has long been recognised that significant determinants of both granule and tablet strength are the binder film formation and deformation properties. (Krycer et al., 1983a). The approach presented here allows the calculation of a spreading coefficient which can be related to actual experimental measurements of granule friability, tablet strength and tablet capping. The shape and complexity of the relationships can be further explained on the basis of the relative change in the calculated thermodynamic work of cohesion for each binder.

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