STUDY OF PARTICLE INTERACTIONS IN A PHYSICAL MIXTURE OF Mg STEARATE AND METHYL ORANGE

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Abstract

It is of great interest to pharmaceutical technologists to be able to predict interactions between particles in mixtures in order to predict their behaviour during technological processes and to control the pharmacokinetic and pharmacodynamic properties of the resulting dosage forms. In our study we used Mg stearate and methyl orange as model compounds to study the mixing behaviour. As expected, the mixture prepared with mortar and pestle in mass proportion 1:1 was slightly coloured since Mg stearate particles (white) are covering the methyl orange. Our results show that Mg stearate has a lower surface free energy than methyl orange so, theoretically, particles of Mg stearate are expected to spread over the methyl orange particles. This was confirmed by calculation of spreading coefficients that gave positive spreading coefficients of Mg stearate over methyl orange. FT IR measurements for physical mixtures of Mg stearate and methyl orange in different proportions substantiate the spreading coefficient calculation. The results suggest that Mg stearate has a higher covering capacity at lower weight ratios in mixtures with methyl orange.

Introduction

Mixing powders is an essential operation in pharmaceutical industry during the manufacture of different pharmaceutical preparations *e.g.* granulates, tablets and powder blends. Great interest exists among pharmaceutical technologists to be able to predict interactions between particles in mixtures. These physical properties of mixtures are very important for the technological processes used in drug manufacturing and can influence pharmacokinetics and pharmacodynamic of the resulting drug formulation. In order to characterize the interactions that exist in a mixture we can calculate an interaction parameter which is determined by the strength of interaction between the lubricant and the powder.[1] Other attempts, based on surface free energy data of the components, have been made to predict the organization of binary powder mixtures, and have been widely used as a powerful prediction tool.[2,3] The results obtained in these studies show that mixing of powders can be modelled in a crude fashion by predictions based on the relative magnitude of the adhesive and cohesive interactions.[4] The results indicate that modelling powder mixtures on the basis of surface free energy is possible, but particle size should be also taken into consideration.[3]

Mg stearate is a lubricant widely used in tabletting mixtures because of its low surface free energy and therefore its ability to cover various compounds. For this reason we used it in preparations of physical mixtures with methyl orange as a model of the active component. Changes in colour of physical mixtures of Mg stearate ($(CH_3(CH_2)_{16}COO)_2Mg$) and methyl orange have been correlated with surface free energy parameters and FT IR spectroscopy measurements. We have shown that Mg stearate covers methyl orange and, interestingly, we found that Mg stearate at lower weight ratios spreads effectively over methyl orange particles.

Solid surface free energy and spreading coefficient

Surface free energy as an important physicochemical property of a solid can be assessed indirectly from wettability measurements. According to the method of Wu [6], surface free energy is the sum of polar (p) and dispersion (d) components. Solid surface free energy can be determined by contact angle measurement of two liquids of known polarity and assessed by solving two equations with two unknowns (Equation 1).

$$(1+\cos\theta)\gamma_l = \frac{4(\gamma_s^d \times \gamma_l^d)}{\gamma_s^d + \gamma_l^d} + \frac{4(\gamma_s^p \times \gamma_l^p)}{\gamma_s^p + \gamma_l^p} \qquad [1]$$

θ=liquid contact angle on a solid plate

γ_l=liquid surface tension

γ_s^d=dispersion component of solid surface free energy

γ_s^p=polar component of solid surface free energy

γ_l^d=dispersion component of liquid surface tension

γ_l^p=polar component of liquid surface tension

When solid surface free energy parameters are known, the spreading coefficient (S) may be calculated to predict the interactions between two powders (1 and 2). The spreading coefficient is a measure of the spreading degree of one substance over another, and is calculated as the difference between work of adhesion (W_a, equation 2)

and work of cohesion (W_c, equation 3). The spreading coefficient of a binder over the substrate (S_{12}) or substrate over binder (S_{21}) can be calculated according to Equations 4 and 5 (Wu[6]).

$$W_a = 4\left[\frac{\gamma_1^d \gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p \gamma_2^p}{\gamma_1^p + \gamma_2^p}\right] \qquad [2]$$

$$W_c = 2\gamma_i \qquad [3]$$

$$S_{12} = 4\left[\frac{\gamma_1^d \gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p \gamma_2^p}{\gamma_1^p + \gamma_2^p} - \frac{\gamma_1}{2}\right] \qquad [4]$$

$$S_{21} = 4\left[\frac{\gamma_1^d \gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p \gamma_2^p}{\gamma_1^p + \gamma_2^p} - \frac{\gamma_2}{2}\right] \qquad [5]$$

Results and discussion

The organization of particles in binary mixtures can be predicted from surface free energy parameters of the components that can be calculated from wettability measurements. Because the methods used for determining wettability have many drawbacks,[7,8] it is important to confirm these predictions based on surface energy parameters with an alternative method. This can be easily done when one of the component in the mixture is coloured.[9,10] We used Mg stearate as a lubricant and white model powder in tabletting mixtures. As the second model powder, the intensely coloured methyl orange was used to make physical mixtures. Because of its complex chemical structure and its diverse chemical behaviour methyl orange can be treated as a model for an active drug compound.

Mg stearate is a lubricant which possesses low surface free energy. A mixture prepared with mortar and pestle in mass proportion 1:1 resulted, as expected, in an only

lightly coloured product, since Mg stearate particles (white powder) covered the methyl orange.

The results in Table 1, which show the surface free energy difference between methyl orange and Mg stearate, are consistent with the observed change of colour. Theoretically, particles with low work of cohesion that is twice the surface free energy will cover particles with high surface free energy.

Table 1: Contact angle of liquids on solid samples and surface free energy parameters of Mg stearate and methyl orange.

	Contact angle		Surface free energy			
	H_2O[°]	CH_2I_2[°]	γ_s^d[mN/m]	γ_s^p [mN/m]	γ_s[mN/m]	W_c[mN/m]
Mg stearate	108	76	22.9	1.1	24.0	48.0
Methyl orange	50	61	30.0	25.7	55.7	111.4

The higher work of adhesion (Table 2) than work of cohesion of Mg stearate also predicts that Mg stearate will spread over methyl orange particles. This was confirmed by the positive spreading coefficient of Mg stearate over methyl orange (Table 2).

Measured absorption of methyl orange in mixture with Mg stearate obtained with FT IR plotted against concentration of methyl orange clearly show non-linear behaviour of the mixture, indicating that the covering capacity of Mg stearate is higher at lower proportions in the mixture. (Chart 1) These measurements substantiate the conclusions drawn from spreading coefficients.

Table 2: Spreading coefficients, S_{12}, of Mg stearate over methyl orange and S_{21} of methyl orange over Mg stearate and work of adhesion between the two powders.

S_{12}	S_{21}	W_a[mN/m]
8.0	-55.2	56.2

Table 3: Absorbance measurements of mixtures and methyl orange concentration calculated with principal component regression (PCR).

Weight % (exp.)	Absorbance	Weight % (calc.)
25	0,104	23,7
30	0,189	27,2
40	0,25	44,6
60	0,424	61,3
65	0,476	66
70	0,524	69,4
75	0,507	76,7
80	0,444	77,7
90	0,427	91,4
92,5	0,577	91
95	0,686	93,4

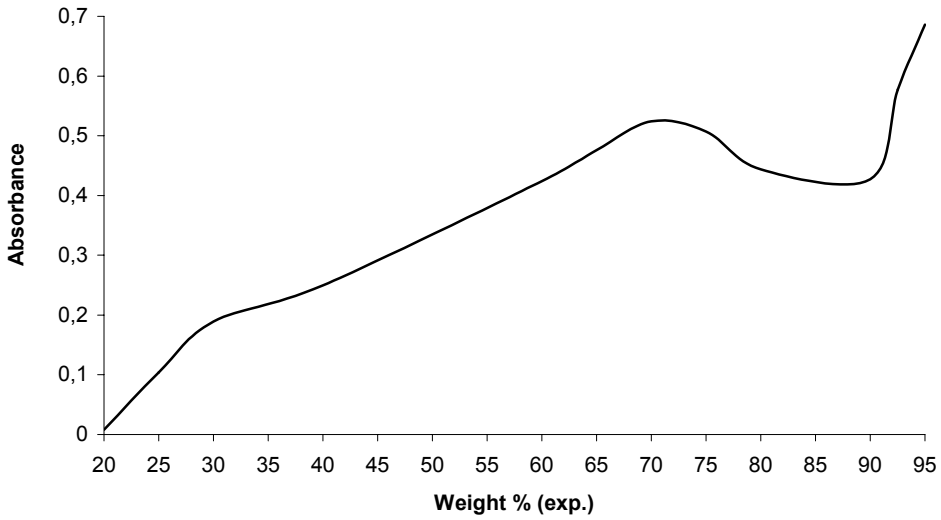

Figure 1: Non-linear behaviour of methyl orange/Mg stearate mixtures. The chart represents the DR FT IR measurements of absorbance as a function of concentration.

Additionally we were able to develop a quantitative analysis method, based on FTIR, for determining methyl orange concentrations in mixtures with Mg stearate.

Principal component regression analysis showed the calculated values to be in agreement with actual concentration. The Pearson coefficient of correlation, 0,992, was good .

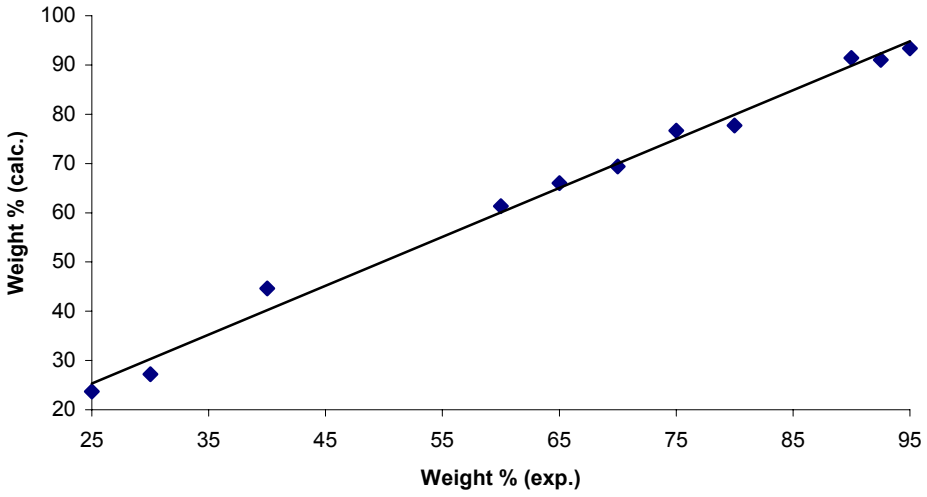

Figure 2: Calculated concentration of methyl orange obtained with the principal component regression method as function of concentration represented with dots and the regression trendline (R^2=0,992) shown as full line.

Conclusions

We have shown that Mg stearate, which is commonly used in tabletting mixtures, has a high covering capacity even when used in lower weight ratios. Surface free energy parameters, calculated from wettability measurements, were shown to correlate with FT IR measurements of absorbance. As second powder we used methyl orange, which is coloured and therefore could be used to relate measured absorption to covering capacity of Mg stearate. Moreover we were able to develop a relation that can be used for quantitative analysis of this type of mixture that exhibits non-linear behaviour for FTIR vs. concentration.

Experimental

Materials

The powders used in the study were Mg stearate (Carlo Erba, Italy) and methyl orange (Sigma Aldrich, Germany). Liquids used were bidistilled water and diiodomethane (Sigma Aldrich, Germany).

Wetting measurements

Compacts of the powder (200 mg) were prepared in a highly polished stainless steel punch and die assembly (2,5 × 10 mm) in a Specac (England) hydraulic press with a 10 seconds dwell time and at a pressure of 2×10^8 Pa. The exact perimeter of the plates (25x10 mm) was measured using a micrometer. Contact angle of the liquids was determined by means of the Wilhelmy plate technique using a Krűss Tensiometer K12 (Germany). Temperature was controlled at 20 ± 0.5°C, by flowing water from a circulator (Haake, Germany). The test liquid (water or diiodomethane) was placed in a clean glass dish and raised by means of a motorized platform to contact the powder plate. The platform was raised with the speed of 1,2 mm/min. From the force measurements, the contact angle was obtained using Krüss tensiometer software (Krűss GmbH, 1996). The experimental technique is described elsewhere.[5]

IR measurements

All IR measurements were performed on a Nicolet FT IR spectrometer using Nexus Smart Collector accessory. Spectra were processed with Omnic [ver. 5.2] software and analyzed with TQ Analyst [ver. 6.0.0.289].

Mixtures of methyl orange and Mg stearate were diluted with KBr and mixed to give samples containing 5% [w/w] of mixture.

Principal component regression which we used as a model for methyl orange behaviour is a quantitative analysis technique which is based on the principal component regression algorithm. First the spectral data from calibration standards is examined to determine the spectral variation and then the specified regions which vary statistically are used to build a model to correlate the spectral variation with concentration. The data

were processed with different statistical methods but the best fit was obtained with principal component regression method as shown in Chart 2 and Table 3.

References and Notes

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Povzetek

Poznavanje sil med posameznimi delci sestavin praškov in tabletirnih zmesi je zaradi vodenja tehnoloških procesov in vpliva na farmakokinetske in farmakodinamske lastnosti različnih zdravilnih oblik za farmacevtske tehnologe odločilnega pomena. Pri študiji smo uporabili metiloranž in magnezijev stearat kot modelni substanci in smo ugotovili, da magnezijev stearat dobro prekriva metiloranž. Rezultati kažejo, da ima magnezijev stearat nižjo prosto površinsko energijo kot metiloranž, prav tako pa je koeficient razširjanja za magnezijev stearat in metiloranž pozitiven. Meritve absorpcije dobljene z metodo difuzne refleksije potrjujejo, da magnezijev stearat prekriva metiloranž, dodatno pa je iz rezultatov razvidno, da magnezijev stearat v nizkih koncentracijah nepričakovano dobro prekriva metiloranž.