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Interactions in coloured powders and tablet formulations: a theoretical approach based on solubility parameters

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Summary

Based on a simple but crude model for calculating the relative intensity of the adhesive and cohesive interactions in two-component systems using partial solubility parameters, it has been possible to predict the properties of binary mixes of a number of components commonly used in tablet formulation with the insoluble colouring agents red iron oxide and carbon black. Three general cases have been identified, one where the adhesive interaction within the system is lower than either of the cohesive interactions, one where the adhesive interaction within the system is lower than the cohesive interaction within the colour but higher than that within the other component and one where the adhesive interaction within the system is higher than the cohesive interaction within the colour but lower than that within the other component. While the first will result in a stable uniformly coloured mix the others will result in enrobement of either the colour by the added component or the added component by the colour, leading to mottling in the powder mix These trends have been confirmed using real systems

Introduction

Colourants are widely used in the manufacture of oral dosage forms, both for aesthetic reasons and ease of identification. Despite the widespread use of coloured film coatings, many compressed tablets are still produced self-coloured using either dyes dissolved in the binding solution prior to granulation or insoluble colouring agents (e.g. aluminium lakes of soluble dyes, iron oxides) added to the initial powder blend. In both cases, uneven distribution of the colourant, due either to migration of the dye during the drying process or just poor blending, can result in mottling on the final tablet (Armstrong and March, 1976).

Since the distribution of an insoluble colouring agent amongst the various ingredients of the final formulation will depend on the relative magnitudes of its adhesive and cohesive interactions, it would appear logical to apply to this system the solubility parameter approach used so successfully to predict the properties of both binary mixtures of microcrystalline cellulose or lactose with lubricants (Rowe, 1988a) and ternary mixtures of microcrystalline cellulose, magnesium stearate and silica (Rowe, 1988b). In this study, calculations have been made on binary mixtures of various ingredients of tablet formulations with two colouring agents, red iron oxide and carbon black, partial solubility parameters which have been reported in the literature (Hansen, 1967).

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Materials and Methods

Implicit in the equation used to predict the adhesive and cohesive interactions in the systems assuming ideality in that the properties of a single material and the results of the interaction of two materials are based on the integration of the Leonard–Jones pair potential function, is a knowledge of the molar volume, solubility parameter, dispersion component of the solubility parameter and fractional polarity (Rowe, 1988a).

The literature data used in this study are given in Table 1. In order to test some of the predictions, specific binary mixtures were prepared by tumbling the components in a 100 ml glass jar with glass beads using a laboratory ball mill. These mixes were examined for uniformity of colour by visual inspection and photographed.

Results and Discussion

Calculations of both the adhesive and cohesive interactions for mixtures of red iron oxide or carbon black with each of the other ingredients found in a tablet/powder formulation are shown in Table 2. Inspection of the data reveals 3 general cases.

Case 1. Here, the adhesive interaction within the mix is lower than either of the cohesive interactions within the individual components. This is applicable to the colours mixed with the majority of the drugs and fillers and should result in a stable, uniformly coloured mix easily produced by simple tumbling.

Fig. 1 shows the results for one such mix of red iron oxide (mean size 0.3 μm) with microcrystalline cellulose (mean size 18 μm) where it can be seen that a uniformly coloured mix is indeed formed.

Case 2. Here, the adhesive interaction within the mix is higher than the cohesive interaction within the ingredient but lower than that within the colour. This is applicable to the colours mixed with the lubricants and binders and should result in the enrobement of the colour by the ingredient. For a mix of colour and lubricant this should initially result in the formation of a white mix

TABLE 1

Molar volumes, solubility parameters and fractional polarities of materials used in this study

Material	Molar volume (cm^3/mol)	δ MPa$^{1/2}$	δ_d MPa$^{1/2}$	x_p	Reference
Drugs					
Caffeine (anhydrous)	144.0	26.6	16.8	0.60	Phuoc et al. (1987a)
Theophylline (anhydrous)	124.0	28.6	21.3	0.45	Phuoc et al. (1987a)
Testosterone propionate	294.0	19.4	14.9	0.41	James et al. (1976)
Fillers					
Microcrystalline cellulose	216.0	39.3	19.4	0.76	Phuoc et al. (1987b)
Lactose (anhydrous)	236.8	39.9	19.6	0.76	Phuoc et al. (1986)
Binders					
Hydroxypropylmethylcellulose	185.7	22.8	14.4	0.60	Rowe (1988c)
Methylcellulose	150.9	21.3	14.1	0.56	Rowe (1988c)
Polyvinyl pyrrolidone	95.0	21.2	15.5	0.47	Rowe (1988c)
Colours/opacifiers					
Titanium dioxide	20.8	34.4	24.1	0.51	Hansen (1967)
Red iron oxide	29.6	28.0	20.7	0.45	Hansen (1967)
Carbon black	6.0	27.8	21.1	0.42	Hansen (1967)
Lubricants					
Magnesium stearate	542.0	18.2	15.7	0.26	Panzer (1973), Rowe (1988a)
Stearic acid	326.0	17.6	16.4	0.13	Hansen and Beerbower (1967)

TABLE 2

Calculated strength of adhesive and cohesive interactions for red iron oxide and carbon black mixed with various tablet ingredients

Material	Strength of Interaction (MPa)		
	Adhesive		Cohesive
	Red iron oxide	Carbon black	
Drugs			
Caffeine (anhydrous)	167.4	120.7	176.9
Theophylline (anhydrous)	175.9	122.3	204.5
Testosterone propionate	135.5	115.1	94.0
Fillers			
Microcrystalline cellulose	130.9	99.9	386.1
Lactose	126.3	76.6	398.0
Binders			
Hydroxypropylmethyl-cellulose	153.1	120.2	130.0
Methylcellulose	147.3	126.8	113.4
Polyvinyl pyrrolidone	146.3	137.2	112.4
Opacifiers			
Titanium dioxide	230.1	173.3	295.8
Lubricants			
Magnesium stearate	121.3	101.2	82.3
Stearic acid	107.7	100.6	77.4

Cohesive interactions in red iron oxide = 196.0 MPa.
Cohesive interactions in carbon black = 193.0 MPa.

with specks of colour which, on further mixing, will result in the development of a highly coloured mix with a high degree of mottling. Shearing of the mix should result in the formation of intensely coloured streaks. This is indeed the case for both colours mixed with magnesium stearate and Fig. 2 shows a photograph of the mix of red iron oxide (mean size 0.3 μm) and magnesium stearate (mean size 5 μm). Shearing of the mix by, for instance, rubbing a sample between the fingers, results in the formation of red streaks.

Case 3. Here, the adhesive interaction within the mix is lower than the cohesive interaction within the ingredient but higher than that within the colour. This is applicable to mixes of the colours with titanium dioxide and should result in the enrobement of the titanium dioxide by the colour and the formation of a coloured mix with white specks. This is indeed the case as can be seen in Fig. 3 for a mix of red iron oxide (mean size 0.3 μm) and titanium dioxide (mean size 0.3 μm).

It is important to relate these findings to the practical application of minimising mottling in self-coloured tablet formulations. It is obvious from the data given in Table 2 that it is important to prevent the colours and lubricants from coming into contact, especially if the local concentrations of lubricants are in excess of those of the colours. In direct compression formulations this can only be achieved by initially forming a premix of the colour with a filler and then adding the lubricants in such a way that they are spread evenly through the mix rather than added as a bolus. Even with these precautions mottling on compression is likely to occur. In the case of wet granulation with a polymeric binder it would still be appropriate to form a premix before granulation but this does not appear to be essential since the data in Table

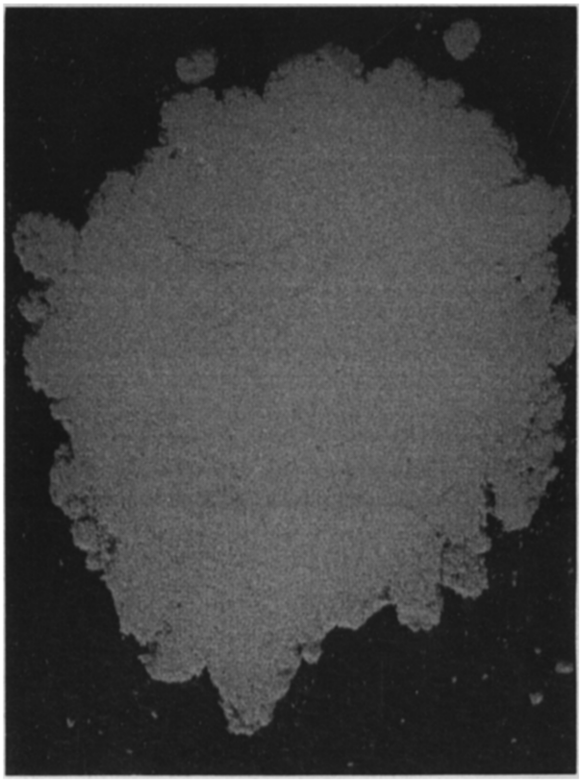

Fig 1 Photograph of a mix consisting of red iron oxide (mean size 0.3 μm) with microcrystalline cellulose (mean size 18 μm) showing uniformity of colour

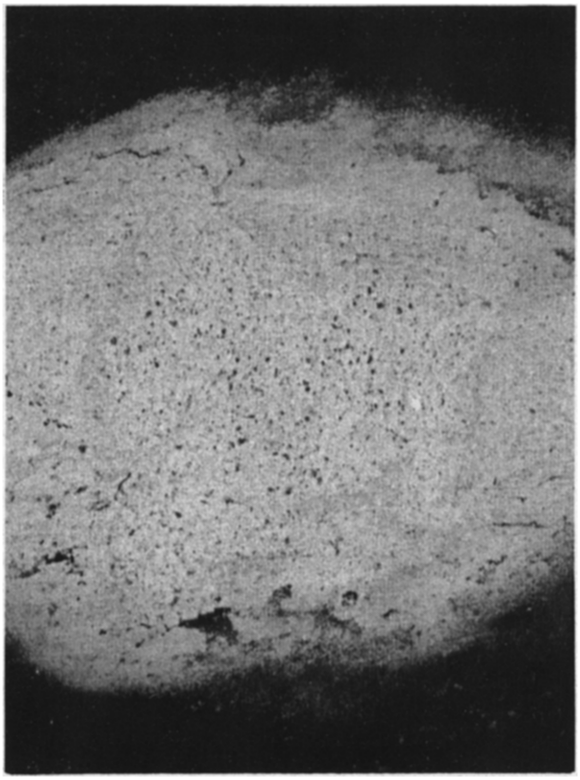

Fig 2 Photograph of a mix consisting of red iron oxide (mean size 0.3 μm) with magnesium stearate (mean size 5 μm) showing specks of colour

2 show that, at least for the two colours studied here, both will be coated by the binder during granulation (Rowe, 1988c). Hence, when lubricants are added at the final stage before tableting, direct contact between the colour and lubricant will be minimised, if not totally eliminated.

Although the conclusions have been found to be consistent with data generated in our laboratory with a formulation coloured with red iron oxide, the question arises as to how generally applicable the predictions are. The answer would appear to depend, at least in part, on the magnitude of the fractional polarity of the colour with respect to the other ingredients. It would appear that for cases 1 and 2 to be valid, the colour should have a fractional polarity greater than 0.4. Unfortunately, no data exist on colours such as the aluminium lakes commonly used.

However, data for both a vast number of organic pigments (some very similar in structure to the dyes used to make these lakes) and alumina used as the base would suggest that although the organic dyes will have fractional polarities in the range 0.1–0.5 (Hansen, 1967; Wu and Brzozowski, 1971) the alumina will have a fractional polarity in the region of 0.8 (calculated from the liquid–solid chromatography data of Keller and Snyder, 1971) and hence the lake so formed will probably have a fractional polarity within the range for Cases 1 and 2 to be valid.

As stated in previous publications on the application of the solubility parameter approach to the prediction of the properties of powder blends (Rowe, 1988a and b) the assumptions made in the derivation of the original equations (Gardon, 1977) do not take into account the existence of cracks and flaws at the interface and hence the calculated

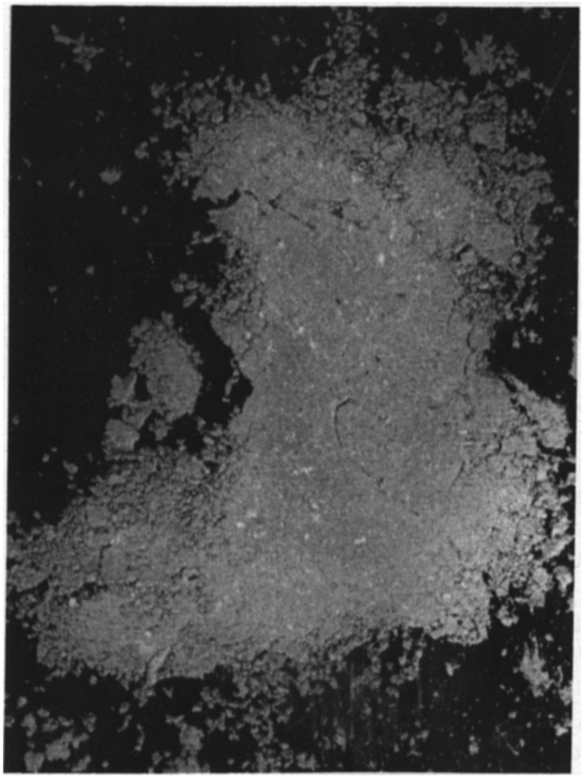

Fig 3. Photograph of a mix consisting of red iron oxide (mean size 0.3 μm) with titanium dioxide (mean size 0 3 μm) showing white specks.

values of cohesive and adhesive interactions will certainly differ in magnitude from experimental values. However, if the theory is not used to predict absolute quantities but rather the relationship between two or three independent quantities the effect of the deficiencies in the theory are minimised (Gardon, 1977) and trends or rank orders can be predicted as has been done in this case.

The ability to predict trends in mixes simply from independent measurements of solubility parameter and fractional polarity clearly has potential use in the optimisation of both formulation and processing in product development.

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