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Effect of Particle Size and Coating Level on the Diffuse Reflectance of Wax Matrices

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Abstract

The aim of this study was to examine the influence of particle size and extent of coating on the diffuse-reflectance spectra of wax matrices containing embedded potassium chloride.

Near-infrared spectroscopy was used to analyse the diffuse-reflectance characteristics of the prepared multi-particulate matrices without destructive sample preparation. A 2-factor, 3-level face-centred central composite design was selected to construct a second-order polynomial model which described the effect of particle size and amount of coating on the intensity of the diffusely reflected light. A non-linear model was used to demonstrate the effect of the selected parameters on the intensity of the reflected light; good correlation was obtained between experimental and predicted results. The results indicated that the extent of coating and the particle size of the examined systems in the selected particle size-range modified the intensity of the reflected light.

It can be concluded that near-infrared spectroscopy is a sensitive means of measuring not only the particle size of powders (substrates and their mixtures), but also that of coated multi-particulate systems.

Highly water-soluble drugs are often embedded in a lipophilic coating to prepare sustained- or slow-release formulations. Waxy excipients have been successfully used as release-controlling agents (Huang et al 1994; Giannola et al 1995). Release of drug from these systems can be controlled by the nature and quantity of coating material (Khan 1995).

Near-infrared spectroscopy furnishes useful information for qualitative and quantitative analysis of multi-particulate systems without invasive sample preparation (Morisseau & Rhodes 1995). Differences between the core-wall proportions of lipophilic matrices (Rácz et al 1997) and between the particle sizes of powders and their mixtures (Otsuka & Matsuda 1996) are apparent from differences in the spectra.

The main objectives of our work were to study and compare the influence of the particle size of the prepared matrix particles and of the amount of lipophilic matrices applied on the diffuse reflectance spectra of the particles.

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Materials and Methods

Materials

USP 23 grade potassium chloride was selected as model drug. The 400–630-μm fraction was embedded in white beeswax (melting range 62–65°C; Fluka Chemie, Buchs, Switzerland).

Preparation of the samples

The thermosoftening coating material was heated to 70°C ($\pm$ 1°C) in a double-jacketed vessel mixer (SG 3/W; Erweka, Germany). The material was stirred constantly (30 rev min^{-1}) until the wax was completely molten (approximately 15 min).

Crystals of the model drug were mixed with the molten mass in the proportions 85 : 15, 90 : 10 and 95 : 5. Stirring was continued during cooling and resulted in drug particles individually coated with a layer of the congealed, thermosoftening waxy material.

Recording diffuse-reflectance spectra

Diffuse reflectance was measured by means of a Hitachi (Japan) U-2501 UV/Vis/NIR spectrophotometer equipped with integrating sphere (d = 60 mm) and PbS detector. The reflectance, R%, of samples was determined in the wavelength

range 200–2500 nm by use of a 5-mm layered cell.

$$R\% = (I_R/I_0) \times 100 \quad (1)$$

where I_R is the intensity of the diffusely reflected light collected by the integrating sphere and I_0 is the intensity of the incident light (Weyer 1985; Rãcz et al 1996).

The intensity of the reflected light in the presence of an absorbing material can be characterized by the Kubelka–Munk equation (Morisseau & Rhodes 1995):

$$K/S = (1 - R_\infty)^2/2R_\infty \quad (2)$$

where R_∞ is the intensity of totally reflected light, K is the absorption coefficient and S is the scattering coefficient. S depends on the number, size, shape and refractivity of particles, and K depends on the absorbing material and the wavelength.

Statistical experimental design

A 2-factor, 3-level face-centred central composite design (Franz et al 1988) was used to construct a second-order polynomial model to describe the effect of particle size and the coating level on the diffuse reflectance values of wax matrix particles. The two factors and their levels are shown in Table 1. The levels for each parameter are represented by a minus (−) sign for the lower level, a plus (+) sign for the higher level and by (0) for the base level.

A BASIC (Microsoft Visual Basic Professional Edition 3.0) language computer program was developed for multiple regression analysis. The expected form of the polynomial equation is:

$$y = b_0 + b_1x_1 + b_2x_2 + b_{11}x_{12} + b_{22}x_{22} + b_{12}x_1x_2 \quad (3)$$

where y is the response, x are the factors, and the b parameters denote the coefficients characterizing the main (b_1, b_2), quadratic (b_{11}, b_{22}) and interaction (b_{12}) effects.

Results and Discussion

Our earlier work (Dredán et al 1996) showed that increasing the quantity of coating material modified not only drug liberation but also the diffuse reflectance spectra of embedded particles. Figure 1 illustrates how the extent of coating affected the spectra. The greater the amount of embedding material used, the less was the intensity of the reflected light. Figure 2 shows that reflectance values decreased with increasing particle size at a fixed coating level.

Table 1. Experimental design with factors and coded levels.

Levels	Coded levels	Particle size (mm; x_1)	Coating level (% w/w; x_2)
Lower	−1	0·75	5
Base	0	1·00	10
Higher	+1	1·25	15

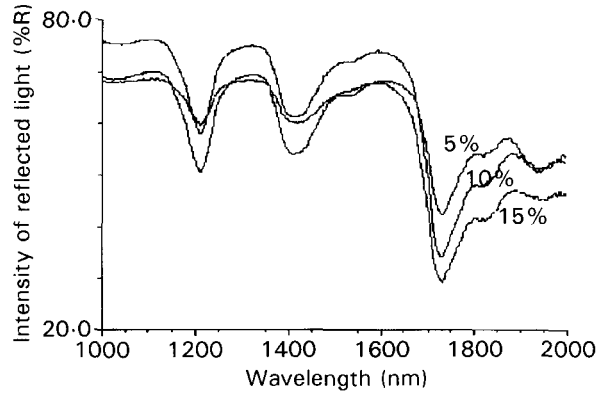

Figure 1. Effect of the coating level (% w/w) on reflected light intensity (%R). Particle size: 1·00 mm.

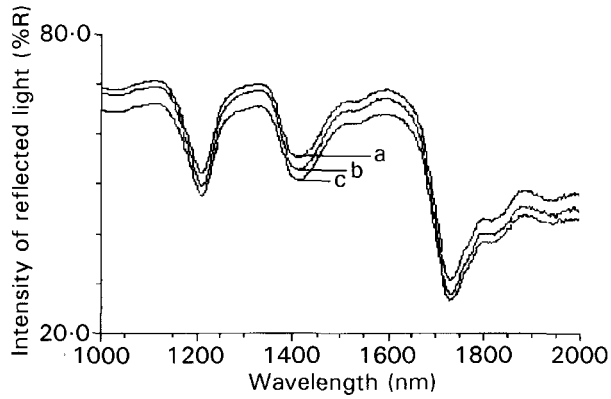

Figure 2. Influence of particle size on the diffuse reflectance spectra of samples of 90 : 10 core/wall ratio. Mean particle sizes: a, 0·75 mm; b, 1·00 mm; c, 1·25 mm.

Table 2 summarizes the diffuse reflectance (%R) measured at the characteristic wavelengths of 1210, 1414 and 1730 nm and the area under the plot of reflectance against wavelength (AUC; %R·nm) for different particle sizes and coating levels.

There were no remarkable differences in peak intensity at the characteristic wavelengths of particles of various sizes for the 95 : 5 core/wall ratio. As a result of the increasing wax content of the samples the peak intensity changed significantly with particle size.

Figure 3 shows the effect of particle size and coating level on the reflectance values. The equations obtained after significance testing at the 95% confidence level, using coded levels of independent

Table 2. Diffuse reflectance values of samples of different particle size measured at characteristic wavelengths, and the calculated AUC values for three coating levels.

Coating level (%)	Mean particle size (mm)	Area under plot of reflectance against wavelength (1300–1850 nm) (%R·nm)	Diffuse reflectance (%)		
			1210 nm	1414 nm	1730 nm
5	0·75	35432·95	59·55	59·42	41·81
5	1·00	35312·43	59·65	60·04	41·38
5	1·25	35060·86	60·10	60·74	41·32
10	0·75	36808·09	58·99	62·24	37·31
10	1·00	35851·54	57·95	61·04	34·05
10	1·25	34587·79	55·67	58·80	32·31
15	0·75	32565·95	51·81	54·95	33·03
15	1·00	32154·06	50·75	54·01	29·33
15	1·25	29986·78	49·59	53·06	27·96

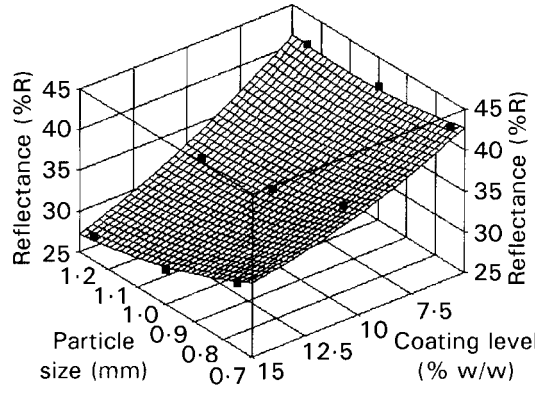

Figure 3. Surface plot for the influence of particle size and coating level on diffuse reflectance.

variables (−1, 0, +1):

$$y_1 = 34{\cdot}09 - 1{\cdot}76\,x_1 - 5{\cdot}70\,x_2 + 0{\cdot}70\,x_1^2 + 1{\cdot}25\,x_2^2 - 1{\cdot}15\,x_1x_2 \quad (4)$$

represent the effect of the selected factors (particle size, x_1, coating level, x_2) on the diffuse reflectance (y) measured at the characteristic wavelength of the wax-matrix base (1730 nm).

A positive sign for the coefficient indicates an increasing effect on the corresponding response whereas a negative sign indicates a decreasing effect. Increasing the particle size and the wax coating level reduced the intensity of the reflected light ($b_1 = -1{\cdot}76$; $b_2 = -5{\cdot}70$). Because of the higher negative main coefficient value ($b_2 = -5{\cdot}70$), the decreasing effect of the coating level on the response parameter is more dominant. The value of the interaction coefficient b_{12} (−1·15) indicates the close connection between particle size and coating level. Table 3 summarizes the measured and the estimated diffuse reflectance values.

Conclusions

The non-linear model developed describes the effects of particle size and amount of embedding material on the intensity of the reflected light. It was found that both the particle size and the amount of coating significantly modified the

Table 3. Randomized matrix of the 2-factor, 3-level face-centred central composite factorial design in the case of coded levels (average of six parallels).

Trial	Controlled factors		Response parameter, y (%R)		
	Particle size	Coating level	Measured	Predicted	● s.d.
1	+1	0	32·31	33·03	0·72
2	−1	−1	41·81	43·35	0·54
3	0	−1	41·38	41·03	0·35
4	−1	+1	33·03	33·25	0·22
5	0	0	34·05	34·09	0·04
6	+1	−1	41·32	41·12	0·20
7	0	+1	29·33	29·64	0·31
8	+1	+1	27·96	27·44	0·52
9	−1	0	37·31	36·55	0·76

intensity of the reflected light. Because the particle size and the amount of coating determine the drug-release characteristics, it is possible to apply near-infrared spectroscopy as a method for rapid in-process control during the formulation of modified-release multi-particulate systems, without destructive sample analysis.

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