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Dissolution and diffuse reflectance characteristics of coated theophylline particles

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Abstract

The aim of the present study was to investigate how the dissolution and diffuse reflectance characteristics of theophylline microcapsules were influenced by the changes in the thickness and by the plasticizer content of coating. Microencapsulation was carried out in laboratory fluidized-bed system using water dispersable Eudragit-type film coating polymer. United States Pharmacopeia rotating paddle method was applied for the in vitro dissolution study. The dissolution profile of the produced microcapsules was evaluated by Weibull distribution. The effect of the thickness of coating and that of the plasticizer content on the dissolution kinetics was modelled by a second-order polynomial equation fitted to the data gathered by a face-centered central composite statistical design. It was found that both of the examined coating parameters influenced the drug release kinetics. The diffuse reflectance spectra of the coated particles indicated the changes in coating parameters without destructive analysis of samples. © 1997 Elsevier Science B.V.

Keywords: Modified theophylline release; Fluidized-bed coating; Eudragit aqueous dispersion; Plasticizer; Diffuse reflectance

1. Introduction

Drug release from reservoir-type controlled release particles depends on the drug, the core, the coating characteristics, and the environment in to which the drug is released (Lu and Chen, 1995).

Multiparticulate dosage forms are commonly coated in fluidized-bed granulators but the possible agglomeration of beads during coating could put an end to the whole process. Therefore, a polymer which provide an efficient and predictable drug release without agglomeration should be applied (Singh et al., 1995). For the coating of solid dosage forms aqueous colloidal dispersions (latexes or pseudolatexes) have been developed from water insoluble polymers without toxic organic solvents (Lehmann and Dreher, 1981). The mechanism of the film formation from

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aqueous polymer dispersions is a complex process. The polymer dispersion is sprayed onto the solid particles in a suitable equipment meanwhile water evaporates, thus forcing the colloidal particles together (Bodmeier and Paeratakul, 1994). Plasticizers are added to film forming polymers to modify physical properties of the polymers and to improve their film forming characteristics as well as their permeability, hence controlling the drug release (Guo, 1993; Saettone et al., 1995).

In recent years, near-infrared spectroscopy (NIRS) has become an important analytical technique in the pharmaceutical industry. The measurement of diffuse light reflectance has been shown to be a rapid and effective qualitative and quantitative analytical method without the destruction of intact samples (Morisseau and Rhodes, 1995).

The main objectives of the present work were to study the dissolution and diffuse reflectance characteristics of coated theophylline particles by changing the thickness of coating (amount of the polymer) and that of the plasticizer concentration which both function as independent variables.

2. Materials and methods

2.1. Materials

Anhydrous theophylline (Ph.Hg. VII., Hungaropharma, Budapest, Batch No. B-16263.95), Lactose EP (De Melkindustrie Veghel bv, Holland, Batch No. 640937/5), polyvinylpyrrolidone (Kollidon 30, BASF, Ludwigshafen, Germany, Batch No. 107653), Eudragit L30D aqueous dispersion (Röhm Pharma, Weiterstadt, Germany, Batch No. 1240614138), polyethylene glycol 6000 (Ferax, Berlin, Germany, Batch No. 51359).

Table 1
Experimental design with factors and their levels

Levels	x_1 coating polymer (%)	x_2 plasticizer (%)
Lower (−)	5	0
Base (0)	10	1
Higher (+)	15	2

2.2. Preparation of the cores

Theophylline (200 g) and lactose (200 g) were granulated with 10% (w/w) Kollidon 30 solution (ethanol:water = 1:1) in AEROMATIC STREA-1 (Aeromatic AG, Bubendorf, Switzerland) laboratory fluidization equipment. The process parameters were the following:

The quantity of the base material: 400 g
Atomising method: top, middle spray
Atomising pressure: 1 bar
Atomising period: 10 s
Feeding rate of the granulation liquid: 12.5 ml/min
Inlet air temperature: 50°C
Drying time: 50 s after each atomising periods

Table 2
Randomized matrix of the two-factor, three-level face-centered central composite factorial design (average of three paralels ± S.D.)

Trial	Controlled factors		Response parameters		
	x_1	x_2	y_1 τ_d (min)	y_2 β	y_3 R(%)
1	+	0	18.9 ± 1.71	0.72 ± 0.036	69.6 ± 0.64
2	−	−	11.7 ± 0.97	1.18 ± 0.078	74.6 ± 0.68
3	0	−	17.6 ± 1.67	1.09 ± 0.057	71.9 ± 0.58
4	−	+	7.6 ± 0.69	0.62 ± 0.042	73.2 ± 0.67
5	0	0	12.9 ± 1.03	1.03 ± 0.061	71.9 ± 0.41
6	+	−	21.5 ± 1.95	0.99 ± 0.053	69.8 ± 0.57
7	0	+	40.2 ± 2.88	0.78 ± 0.041	71.7 ± 0.62
8	+	+	49.8 ± 3.56	0.85 ± 0.047	70.5 ± 0.83
9	−	0	4.6 ± 0.43	0.54 ± 0.035	74.0 ± 0.67

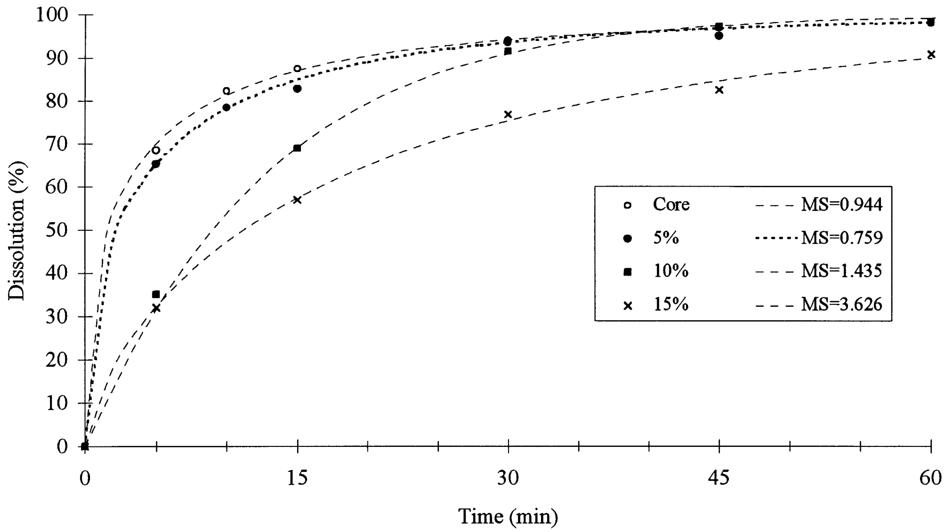

Fig. 1. Dissolution profile of theophylline cores coated with various amounts of polymer containing 1% plasticizer (observed values and predicted curves with the values of mean squares due to residuals).

2.3. Coating procedure

Before the coating procedure, the prepared theophylline granules were fractionated. Only the fractions of 250–1000 μm were used for coating. The process parameters were the following:
The quantity of the granules: 200 g
Atomising method: bottom spray
Atomising pressure: 1 bar
Atomising period: 10 s
Feeding rate of the coating dispersion: 8.3 ml/min
Coating temperature: 60°C
Drying time: 90 s after each atomising periods

2.4. Dissolution studies

Dissolution was undertaken by the USP paddle method at a stirring rate of 100 rpm in 900 ml of pH 1.2 HCl solution. Dissolution tests were repeated six times for all formulations with 150 mg of theophylline particles from the sieve fraction of 250–500 μm. The samples (2 ml) collected were analyzed by UV-Vis spectrophotometry (Unicam UV-Vis spectrophotometer type UV2-030102, ATI Unicam, Cambridge, UK) measuring the absorbance at 272 nm.

2.5. Recording diffuse reflectance spectra

The sample fractions of 250–500 μm particle size were put into a 5 mm layered cell with 4 × 5 cm sides and then placed into the sample container of the UV/VIS/NIR spectrophotometer (Hitachi U-3501, Japan) equipped with integrating sphere (diameter = 60 mm) and PbS detector. The reflectance (R%) was measured between 200–2500 nm (Eq. (1)):

$$R\% = \frac{I_R}{I_0} \times 100 \qquad (1)$$

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; Rácz et al., 1996).

2.6. Statistical experimental design

A two-factor, three-level face-centered central composite design (Franz et al., 1988) was applied to construct a second-order polynomial model describing the effect of formulation factors on the product characteristics. The two factors as well as their levels are shown in Table 1. The levels for

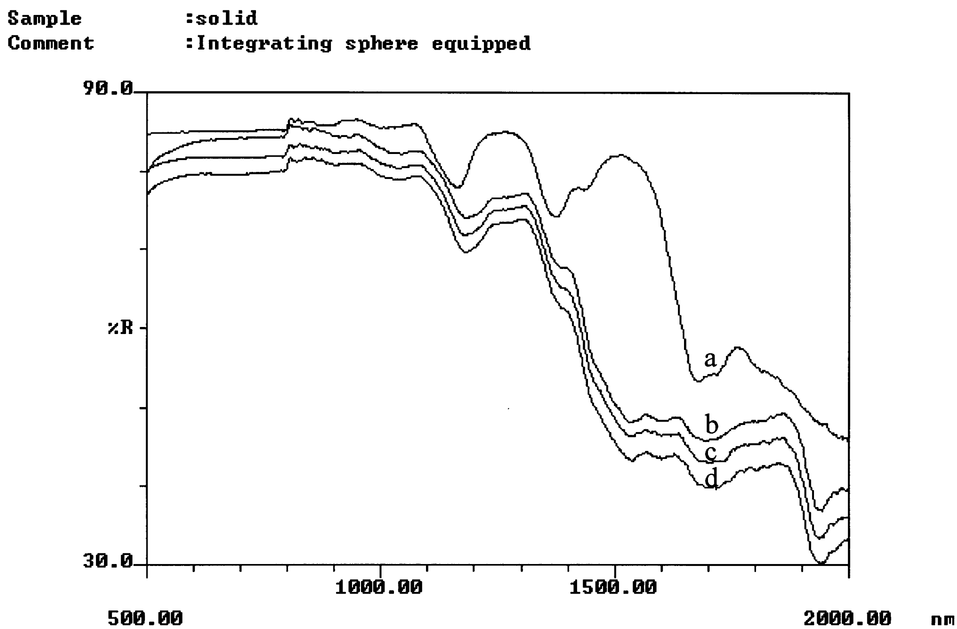

Fig. 2. Diffuse reflectance spectra of theophylline cores coated with various amounts of polymer containing 1% plasticizer ($a = 0\%$, $b = 5\%$, $c = 10\%$, $d = 15\%$).

each parameter are represented by a (−) sign for the lower level, a (+) 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 the multiple regression analysis. The expected form of the polynomial equation is as follows in Eq. (2):

$$y = b_0 + b_1x_1 + b_2x_2 + b_{11}x_1^2 + b_{22}x_2^2 + b_{12}x_1x_2 \quad (2)$$

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

3. Results and discussion

To characterize the dissolution profile of coated particles the Weibull distribution was applied in the following form in Eq. (3) (Langenbucher, 1976):

$$M_t = M_\infty\left[1 - \exp - \left(\frac{t - t_0}{\tau_d}\right)^\beta\right] \quad (3)$$

where

M_t = the dissolution (%) at time 't' (min),
M_∞ = the dissolution (%) at infinite time,
t_0 = the lag-time (min) of the dissolution,
β = shape parameter of the curve,
τ_d = time (min) when 63.2% of M_∞ has been dissolved.

A BASIC language computer program was developed for the parameter estimation using nonlinear least-squares data fitting by simplex optimization method (Jurs, 1986) to minimize the sum of squared residuals.

In order to indicate the influence of factors on the dissolution kinetics the τ_d and the shape factor were selected. No lag-time ($t_0 = 0$) values were detected in the case of the samples examined. Table 2 summarizes the estimated dissolution kinetic parameters and the diffuse reflectance values.

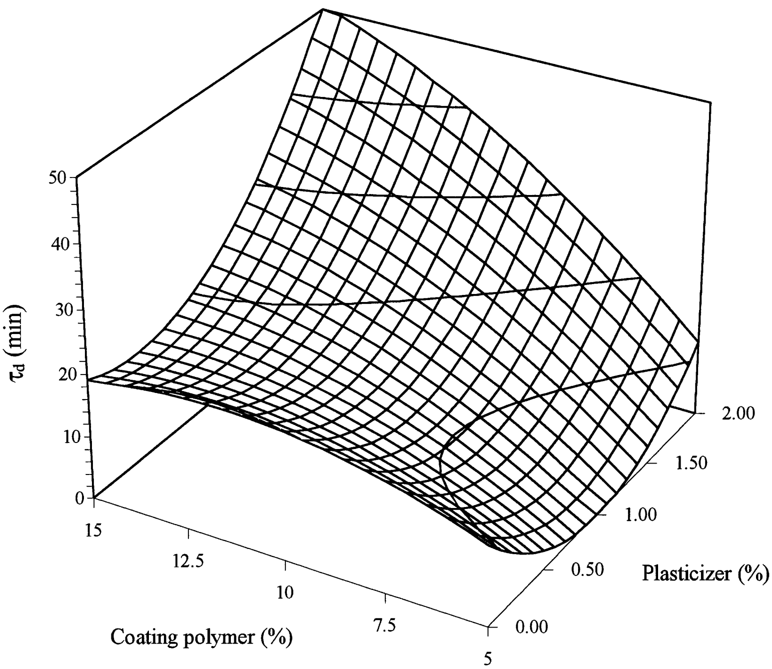

Fig. 3. The effect of independent variables of coating on the τ_d value.

Fig. 1 shows the effect of the amount of coating polymer on the theophylline release.

Fig. 2 demonstrates the difference in diffuse reflectance spectra according to the extent of coating. With increasing amount of coating polymer the reflectance values proportionally decreased.

The resultant equations (Eqs. (4)–(6)) obtained after significance test at 95% confidence level represent the effect of formulation factors (x_1, x_2) on the τ_d value (y_1), the shape parameter (y_2), and the diffuse reflectance (y_3) measured at the characteristic wavelength of coating polymer (1184 nm).

$$y_1 = -4.12 + 4.24x_1 - 33.77x_2 - 0.18x_1^2 + 12.68x_2^2 + 1.62x_1x_2 \quad (4)$$

$$y_2 = 0.70 + 0.11x_1 - 0.67x_2 + 0.15x_2^2 + 0.02x_1x_2 \quad (5)$$

$$y_3 = 77.54 - 0.60x_1 - 1.46x_2 + 0.11x_1x_2 \quad (6)$$

The positive sign of the coefficients refers to an increasing effect while the negative sign indicates a decreasing effect on the corresponding response.

Fig. 3 shows the effect of plasticizer content on the τ_d values (y_1). The applied water-soluble plasticizer (PEG 6000) dissolves while in contact with water and forms microporous channels in the polymer network. In the range of 0–1% plasticizer content, the τ_d values refer to the main effect ($b_2 = -33.77$) which facilitates the drug release. In the range of 1–2% plasticizer content this main effect is less dominant due to the quadratic effect ($b_{22} = 12.68$) of the same factor. The latter effect can be explained by the presence of pores, which increase the solvated surface area available for binding of theophylline. At 1–2% plasticizer content, the drug polymer interactions for theophylline and Eudragit polymer influenced the drug release characteristics much more than did permeability.

The possible structural modification of the film coating polymer could effect the β shape parameter (y_2) of the drug release (Fig. 4). With increasing plasticizer content the shape factor decreased. On the other hand, the raised amount of coating

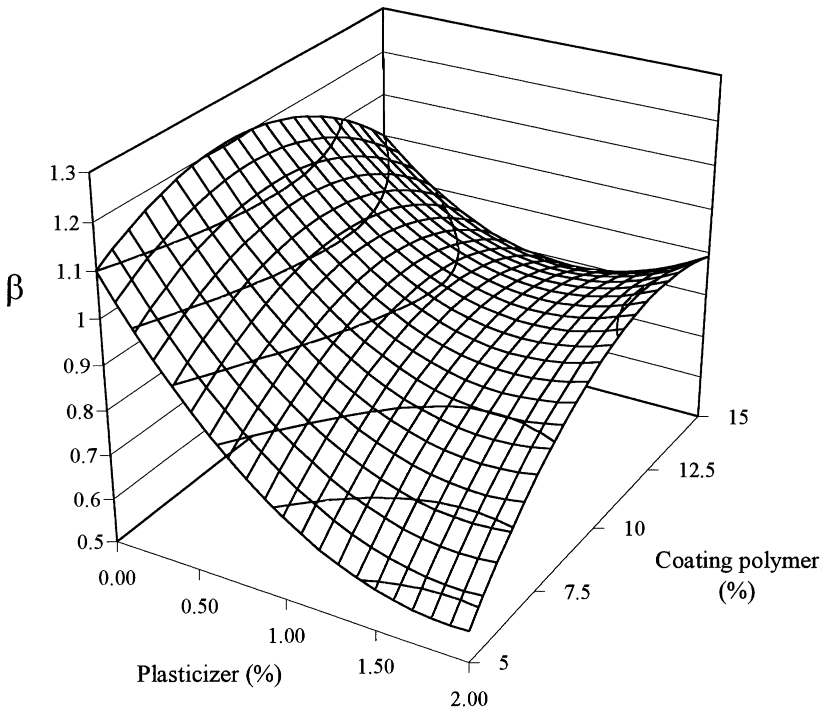

Fig. 4. The effect of independent variables of coating on the shape parameter.

polymer increases not only the τ_d value, but the value of shape parameter as well. This higher β value demonstrates that mainly the initial period of the release process slows down.

Fig. 5 indicates the effect of factors on the diffuse reflectance characteristics (y_3) of coated particles. It was found that at higher levels of coating polymer, the intensity of the reflected light decreased ($b_1 = -0.60$) at a given plasticizer content. This relationship can be described by a linear equation (Eq. (6)). The increased porosity of the coating layer—created by the pore forming effect of the PEG—caused a reduction in the effective thickness of the polymer, consequently decreased the reflectance values ($b_2 = -1.46$). The value of the coefficient b_{12} refers to the possible interaction between the coating polymer and plasticizer, which slightly increases the intensity of the reflected light.

4. Conclusions

A non-linear model was found to describe the effect of the amount of coating polymer and that of the plasticizer on the dissolution and diffuse reflectance characteristics of theophylline containing microcapsules. The dissolution profile can be controlled by modifying the thickness of coating layer and by applying various amounts of plasticizer.

Since it was found a linear relationship between the reflectance and the extent of coating at a certain plasticizer content, the diffuse reflectance of the coated particles indicates the changes in the coating parameters. On the basis of our results, the application of diffuse reflectance measurements can be recommended as a useful means during the in-process control.

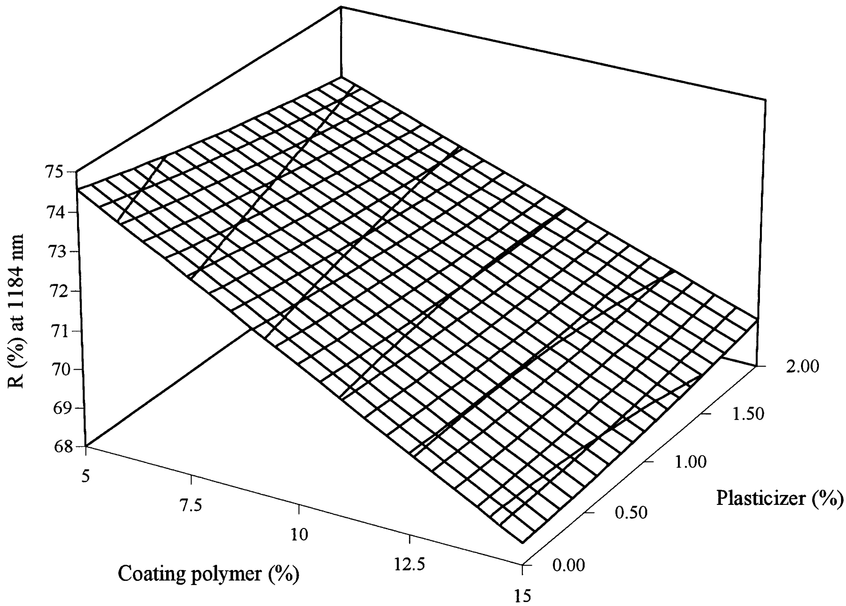

Fig. 5. The effect of independent variables of coating on the diffuse reflectance (R%) at 1184 nm.

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