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THE MiniWiD-COATER. III. EFFECT OF APPLICATION TEMPERATURE ON THE DISSOLUTION PROFILE OF SUSTAINED-RELEASE THEOPHYLLINE PELLETS COATED WITH EUDRAGIT RS 30 D

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ABSTRACT

Theophylline pellets were coated with Eudragit RS 30 D in a miniature fluid-bed pan coater called MiniWiD developed recently. The dispersions were plasticized with varying amounts of triethyl citrate (TEC), dibutyl phthalate (DBP), and polyethylene glycol 6000 (PEG) and applied at different temperatures ranging from 25 to 45 °C. Theophylline release was tested by dissolution using the USP Apparatus 2 (paddle) in 0.1 N hydrochloric acid under sink conditions over 6 hours.

At a coating level of 4 % (0.7 mg/cm^2) sustained-release profiles were obtained from dispersions plasticized with TEC or DBP. By reducing the amount of plasticizer from 20 to 10 %, films with higher permeabilities were obtained. This effect was compensated by temp-

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TABLE 1
Minimum Film-Forming Temperatures (MFT) of Eudragit RS 30 D Formulations According to DIN 53787 (Deutsche Industrie-Norm)

Plasticizer	0 %	10 %	20 %
Polyethylene glycol 6000 (PEG)	47 °C	46 °C	45 °C
Triethyl citrate (TEC)	47 °C	20 °C	5 °C
Dibutyl phthalate (DBP) + 2.7 % Polysorbate 80	47 °C	24 °C	10 °C
The level of plasticizer is related to film former.			

ering the pellets at 50 °C for 24 hours. The coating temperature had little effect on the dissolution profiles of TEC-plasticized films and no effect on films with DBP.

Coatings plasticized with 20 % PEG were applied at temperatures ranging from 25 to 45 °C. These films required a coating level of about 18 % (3.3 mg/cm^2) to provide comparable sustained-release properties. In contrast to DBP and TEC, a strong influence of the coating temperature on the release rates was observed in which higher temperatures led to slower release rates. This behavior can be explained by the minimum film-forming temperature (MFT). Since PEG does not lower the MFT of Eudragit RS 30 D, the application of these films below the MFT of 45 °C is associated with a lower degree of film formation.

INTRODUCTION

In aqueous film coating, the application temperature should exceed the minimum film-forming temperature (MFT) specified in DIN 53787 (Deutsche Industrie-Norm) by 10 to 20 °C[1], otherwise cracking will be observed on free films. Depending on the hardness of the film-forming polymer, a plasticizer is required to reduce the MFT. Effective plasticizers will decrease the MFT even at low levels. According to this definition the best plasticizer for Eudragit RS 30 D is TEC whereas PEG appears to be unsuitable (Table 1).

Furthermore, it is known that film formation in latex coatings can occur within a few minutes or even several days depending on the hardness of the polymer under coating conditions[1]. However, this can be accelerated if it is followed by heat treatment[2,3,4]. To examine the importance of the MFT for the bed temperature of a coating process, 3 different plasticizers with different hydrophilic properties were selected. Their solubilities in water are

TABLE 2
Formulas of Eudragit RS 30 D films

Formula	DBP		TEC		PEG
	10 %	20 %	10 %	20 %	20 %
Eudragit RS 30 D	26.7	26.7	26.7	26.7	50.0
Dibutyl phthalate (DBP)	0.8	1.6	-	-	-
Triethyl citrate (TEC)	-	-	0.8	1.6	-
Polyethylenglycol 6000 (PEG)	-	-	-	-	3.0
Polysorbate 80	0.4	0.4	-	-	-
Talc	3.2	2.4	3.2	2.4	6.0
Water	68.9	68.9	69.3	69.3	41.0
Solids content [% (w/w)]	12.4	12.4	12.0	12.0	24.0
Density [g/ml]	1.04	1.04	1.03	1.03	1.06

as follows[5]: PEG 55 g/dl, TEC 6.5 g/dl, and DBP 0.04 g/dl. Varying temperatures ranging from 25 to 45 °C provided an application above and below the MFT.

EXPERIMENTAL

Materials

Spherical theophylline pellets (30 % between 710 and 1000 μm, 70 % between 100 and 1400 μm in diameter, drug content 93.9 %, Klinge Pharma GmbH, D-W-8000 München 80); theophylline (Boehringer Ingelheim KG, D-W-6507 Ingelheim); poly(ethylacrylate, methylmethacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1 (Eudragit RS 30 D, 30 % aqueous dispersion, Röhm-Pharma GmbH, D-W-6108 Weiterstadt); dibutyl phthalate (DBP), triethyl citrate (TEC, Dr. T. Schuchardt & Co., D-W-8011 Hohenbrunn); polyethylene glycol 6000 (PEG, Polyglykol 6000 P, Hoechst AG, D-W-6230 Frankfurt 80); - polysorbate 80 (Tween 80, Atlas Chemie, D-W-4300 Essen); microfine talc (Norwegian Talc Deutschland GmbH, D-W-6483 Bad Soden-Salmünster); hydrochloric acid 32 % (w/w) p.A. (E. Merck, D-W-6100 Darmstadt) and destilled water were used.

Preparation of coated pellets

Theophylline pellets were coated with Eudragit RS 30 D using the MiniWiD-Coater[6], a miniature fluid-bed pan coater. The formulations are shown in Table 2. All dispersions had

to be stirred continously to prevent sedimentation. During the coating process the core bed temperature was monitored every 2 seconds and kept constant with a standard deviation of ± 0.3 °C. To study its effect on the coating quality, the core bed temperature was varied between 25 and 45 °C.

Drug content

A sample of 0.5 g of pellets was withdrawn just before the coat was applied and assayed spectrophotometrically at 270 nm in 0.1 N hydrochloric acid against a blank. The drug content was expressed as percentage of the final pellet weight.

Coating quantity

Before and after each coating process, the exchange unit of the dosing pump was weighed to determine the amount of liquid sprayed onto the pellets. Afterwards the solids content was examined by drying an aliquot of 20 g of the spray liquid and the amount of dry substance applied (coating quantity) was calculated. The loss of coating was calculated as the difference between coating quantity and the increase in pellet weight (coating level) and was expressed as percentage of the coating quantity. Due to their spherical shape and the narrow size distribution, it was possible to calculate a mean specific surface area of 55 cm^2/g of pellets. Therefore a coating level of 5.5 % (w/w) is equal to 1 mg/cm^2.

Dissolution testing

Theophylline release determined in a six-station dissolution tester (PTW, Pharmatest GmbH, D-W-6452 Hainburg) using the USP Apparatus 2 (paddle). Taking in consideration the sink conditions, 150 mg of pellets, containing about 130 mg of theophylline, were placed in 800 ml of 0.1 N hydrochloric acid at 37 °C and 100 rpm. Samples of 10 ml were withdrawn and replaced by dissolution medium at 10 different times over a period of 6 hours and assayed spectrophotometrically as described under drug content. Two or three replicates of each batch were analysed together. After each time interval the average value and the standard deviation and finally a mean releasing curve and a mean standard deviation[7] were calculated.

RESULTS AND DISCUSSION

Coating procedure

The application of aqueous latex dispersions was very effective. No agglomeration was detected and the loss of coating was negligible (Table 3). At higher temperatures spray drying

TABLE 3
Coating Conditions

Plasticizer		Bed temperature [°C]	Processing time [min]	Mean spray rate [ml/min]	Coating level [%]	Loss of coating [%]
DBP	10 %	25	34	0.448	3.8	-
		35	20	0.765	3.8	-
		40	18	0.932	3.8	-
	20 %	25	45	0.349	3.8	0.9
		35	23	0.680	3.7	4.4
		40	17	0.969	3.7	2.9
TEC	10 %	25	37	0.422	3.7	-
		35	20	0.764	3.7	-
		45	15	1.109	3.7	0.5
	20 %	25	48	0.326	3.6	-
		35	26	0.598	3.5	2.7
		45	17	0.973	3.6	2.7
PEG	20 %	25	112	0.342	17.6	-
		30	113	0.328	18.0	-
		35	113	0.325	17.8	-
		40	114	0.326	17.8	0.7
		45	108	0.347	17.6	1.4

effects occured leading to an increase in loss of coating. Problems were caused by electrostatic charges on films containing TEC and DBP. This effect was reduced by increasing the spraying rates at higher temperatures. Nevertheless, DBP-plasticized films could not be applied at 45 °C due to the sticking of pellets. On the other hand, films plasticized with PEG required a coating level 5 times higher than the levels of DBP- or TEC-plasticized films so as to provide comparable sustained-release properties. Obviously the application at temperatures below the MFT led to deteriorated film formation.

Application above MFT

The effect of coating temperature on the release rates of TEC- and DBP-plasticized films was small compared with the effect of plasticizer concentration (Figures 1 and 2). Nevertheless there is a tendency that higher coating temperatures cause lower permeabilities

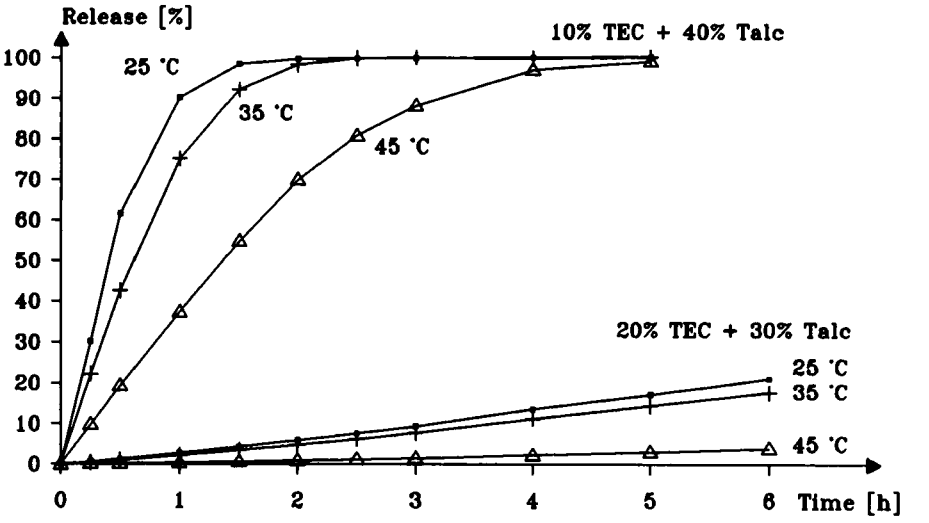

FIGURE 1

Eudragit RS 30 D with 10 and 20 % TEC: Effect of coating temperature on the release of theophylline from sustained-release pellets. Coating level 4 %.

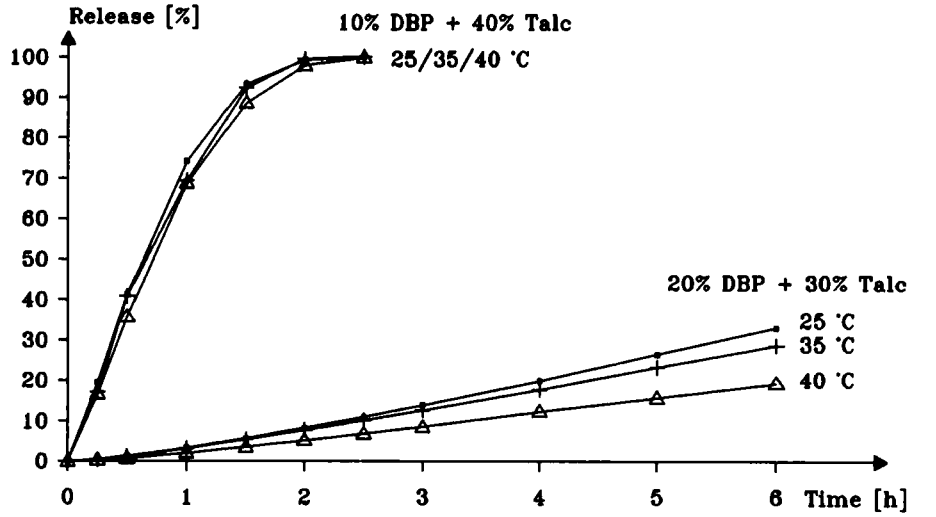

FIGURE 2

Eudragit RS 30 D with 10 and 20 % DBP: Effect of coating temperature on the release of theophylline from sustained-release pellets. Coating level 4 %.

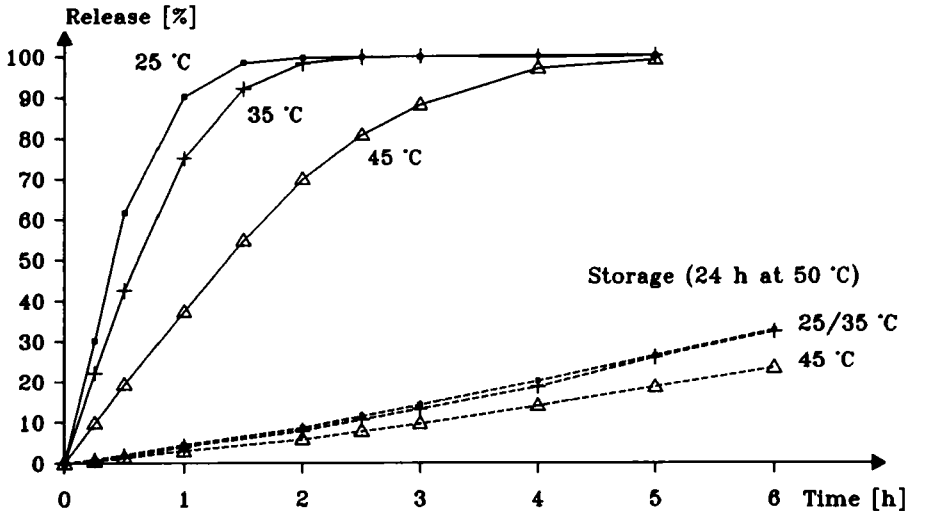

FIGURE 3
Eudragit RS 30 D with 10 % TEC: Effect of tempering and coating temperature on the release of theophylline from sustained-release pellets. Coating level 4 %.

and prolonged releasing rates. This effect is pronounced by films plasticized with TEC rather than those with DBP.

Surprisingly, the permeability of films with 10 % plasticizer was reduced by tempering the pellets at 50 °C for 24 hours. As shown in Figure 3 and 4 the dissolution profiles of films with 10 % plasticizer nearly reached those obtained from coatings with 20 % plasticizer without heat treatment. Adverse effects occured when films with high plasticizer concentrations were tempered at 50 °C. After 24 hours the pellets stuck together and could not be separated without damaging the coat[6].

The results imply that the level of the plasticizer had an accelerating effect on the speed of film formation. Although low concentrations may cause incomplete coatings, a heat treatment after the coating process can complete the film formation.

Application below MFT

In contrast to the formulations of TEC and DBP, PEG had nearly no effect on the MFT. Therefore application temperatures were always below the MFT. As expected, these films were highly permeable and therefore the level of coating had to be increased. Sustained-release characteristics were achieved at a level of 18 % compared with 4 % of DBP

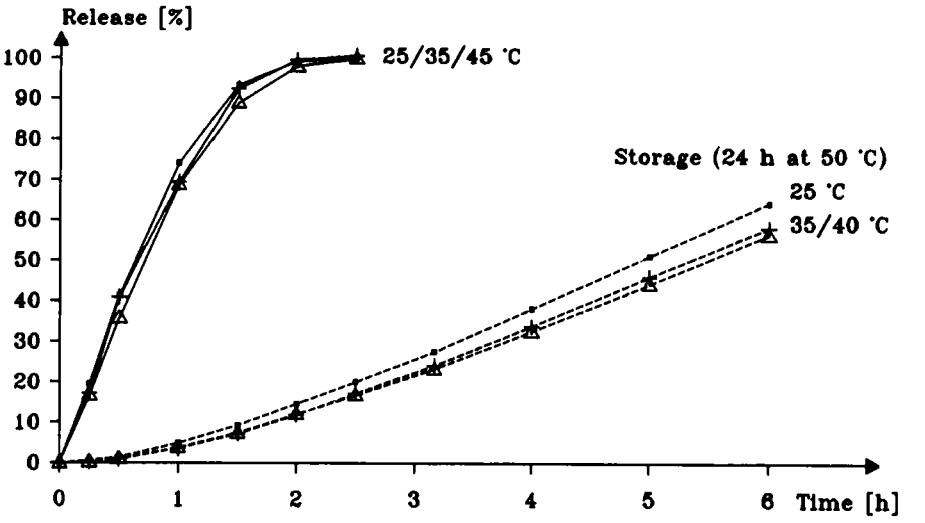

FIGURE 4

Eudragit RS 30 D with 10 % DBP: Effect of tempering and coating temperature on the release of theophylline from sustained-release pellets. Coating level 4 %.

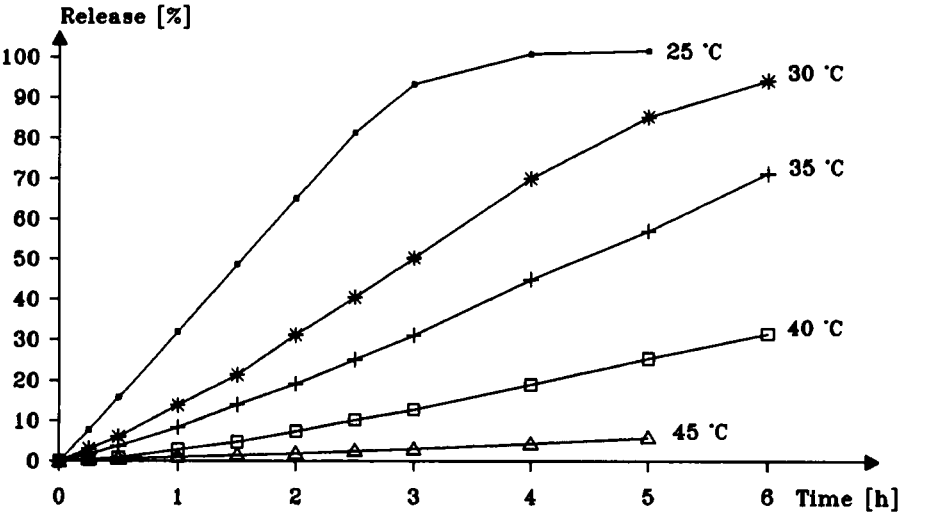

FIGURE 5

Eudragit RS 30 D with 20 % PEG: Effect of coating temperature on the release of theophylline from sustained-release pellets.
Coating level 18 %.

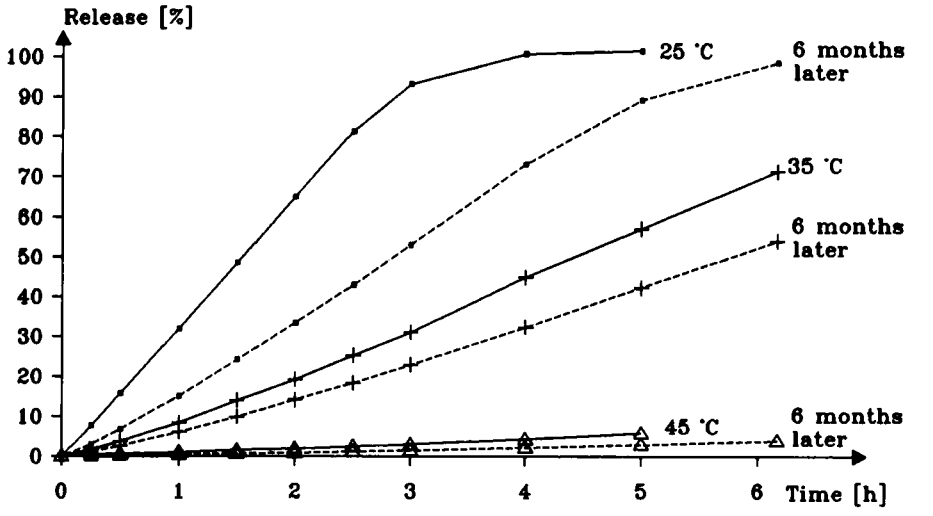

FIGURE 6

Eudragit RS 30 D with 20 % PEG: Effect of storing temperature and coating temperature on the release of theophylline from sustained-release pellets. Coating level 18 %.

and TEC. By increasing the coating temperature by 5 °C, the permeability of the film was remarkably reduced and theophylline release was dropped of more than 90 % when the temperature was changed from 25 to 45 °C (Figure 5). A slight decrease in the permeability was observed after storage at room temperature for 6 months (Figure 6). An examination of the pellets by scanning electron microscopy showed minute cracking of the film surface especially at lower application temperatures[6].

CONCLUSIONS

Aqueous latex dispersions of Eudragit RS 30 D should be plasticized with DBP rather than with TEC or PEG because the resulting films showed that the sustained-release properties were independant on the application temperature. Low release rates were easily obtained from films with 20 % plasticizer at 25 °C and a coating level of 4 % corresponding to 0.7 mg/cm^2.

REFERENCES

1. K.O.R. Lehmann, " Chemistry and Application Properties of Polymethacrylate Coating Systems" in "Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms", J.W. McGinity (ed.), Marcel Dekker Inc., New York/Basel 1989, p. 153-245

2. F.W. Goodhart, M.R. Harris, K.S. Murthy, R.U. Nesbitt, "An evaluation of aqueous film-forming dispersions for controlled release", Pharm. Technol. 8 (4), 64-71 (1984)

3. R.-K. Chang, C.H. Hsiao, J.R. Robinson, " A review of aqueous coating techniques and preliminary data on release from a theophylline product", Pharm. Technol. 11 (3), 56-68 (1987)

4. R.-K. Chang, J.C. Price, C.H. Hsiao, "Preparation and preliminary evaluation of Eudragit RL and RS pseudolatices for controlled drug release", Drug Dev. Ind. Pharm. 15 (3), 361-372 (1989)

5. D. Hennig, H. Kala, "Einfluß von von Weichmachern auf die Permeabilität von Poly(meth)acrylatüberzügen (Eudragit RS)", Pharmazie 41 (5), 335-338 (1986)

6. F. Niemann, "Untersuchung des Temperatur- und Weichmachereinflusses beim Überziehen von Wirkstoffpellets mit dem computergesteuerten Miniatur-Wirbelschicht-Dragierkessel (MiniWiD)", Dissertation, Universität Marburg 1991

7. E. Renner, "Mathematisch-statistische Methoden in der praktischen Anwendung", Verlag Paul Parey, Berlin/Hamburg 1981, p. 79