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THE MiniWiD-COATER: II. COMPARISON OF ACID RESISTANCE OF ENTERIC-COATED BISACODYL PELLETS COATED WITH DIFFERENT POLYMERS

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ABSTRACT

Neutral pellets were loaded with bisacodyl and enteric-coated with hydroxypropyl methylcellulose acetate succinate (HPMCAS), carboxymethyl ethylcellulose (CMEC), cellulose acetate trimellitate (CAT), and poly(ethylacrylate, methacrylic acid) (Eudragit L 30 D) in a miniature fluid-bed pan coater called MiniWiD. Gastric juice resistance was tested by dissolution using USP Apparatus 2 (paddle) in 0.1 N hydrochloric acid under sink conditions over 6 hours. As a measure of enteric coating quality the USP specifications were used meaning that no more than 10 % of the drug should be released within 2 hours.

Organic-solvent based films of HPMCAS, CMEC and CAT at a coating level of 18 to 25 % provided gastroresistance for more than 6 hours. Aqueous suspensions of HPMCAS and CMEC as well as the ammonium salt aqueous solutions of CAT produced films with a

short gastroresistance of below 0.6 hours. By doubling the coating level of water-based HPMCAS films the protection was prolonged to 3.4 h.

Enteric coatings were obtained from all aqueous latex dispersions of Eudragit L 30 D at a coating level of 24 %. The alteration of coating temperature between 25 and 45 °C had no significant effect on the release rates, whereas the variation of type and amount of plasticizer led to a different release rate after 2 hours. Best protection was obtained using films plasticized with 20 % of dibutyl phthalate (DBP) allowing a release of only 4 % of the drug in 6 hours although the application temperature was 15 °C below the minimum film-forming temperature (MFT). All coatings dissolved in artificial intestinal fluid within 15 minutes.

INTRODUCTION

Since extensive efforts were made to replace organic solvents, different aqueous application systems have been developed. Water-insoluble enteric polymers can be applied either as aqueous ammonium salt solution, colloidal latex or pseudolatex dispersion or as a micronized particle suspension. The properties of films produced using ammonium salts are discussed differently, and there is no evidence whether all these films provide gastric juice resistance[1,2] or not[3]. A recent study indicated that some of the ammonium salt preparations produced coatings that are less gastroresistant than their corresponding organic-solvent based films[4]. Similar results were obtained using suspensions of micronized polymer particles in which it was mentioned that a higher film thickness was necessary to provide gastroresistance[3]. Latex dispersions, on the other hand, showed excellent enteric coating qualities[4].

To produce homogeneous coatings with latex dispersions, it is very important to reach the minimum film-forming temperature (MFT) during the process or even exceeding it by 10 to 20 °C[5]. Depending on the type and the amount of plasticizer used, the MFT can be decreased. Lipophilic plasticizers such as dibutyl phthalate (DBP) seemed to be less suitable for Eudragit L 30 D films than the more hydrophilic triethyl citrate (TEC) because the MFT raised from 27 °C to 35 resp. 41 °C (Table 1).

In this article enteric properties of water-based coatings were compared with organic-solvent based films, and the effect of coating temperature on the release rate was studied for different Eudragit formulations.

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

Plasticizer	0 %	10 %	20 %
Triethyl citrate (TEC)	27 °C	< 0 °C	< 0 °C
Dibutyl phthalate (DBP) + 2.7 % Polysorbate 80	27 °C	35 °C	41 °C
The level of plasticizer is related to film former.			

EXPERIMENTAL

Materials

Neutral pellets (90 % between 710 and 850 μm in diameter, Hanns G. Werner, D-W-2082 Tornesch); bisacodyl (Dr. K. Thomae GmbH, D-W-7950 Biberach); carboxymethyl ethylcellulose (CMEC, Duodcel AQ, Freund Industrial Comp., Ltd., Tokyo, Japan); poly-(ethylacrylate, methacrylic acid) 1:1 (Eudragit L 30 D, 30 % aqueous dispersion, Röhm-Pharma GmbH, D-W-6108 Weiterstadt); hydroxypropyl methylcellulose acetate succinate (HPMCAS, AQOAT AS-MF, Shin-Etsu Chemical Co., Ltd, Tokyo, Japan); cellulose acetate trimellitate (CAT), acetylated monoglycerides (Myvacet 9-40, Eastman Kodak Comp., Ltd., Kingsport, Tennessee, USA); dibutyl phthalate (DBP), triethyl citrate (TEC, Dr. T. Schuchardt & Co., D-W-8011 Hohenbrunn); glycerol monocaprylate (Dynamit Nobel AG, D-W-5810-Witten); polysorbate 80 (Tween 80, Atlas Chemie, D-W-4300 Essen); microfine talc (Norwegian Talc Deutschland GmbH, D-W-6483 Bad Soden-Salmünster); hydroxyethyl cellulose (Tylose H 300, Hoechst AG, D-W-6230 Frankfurt 80); trisodium citrate dihydrate, ammonia 25 % (w/w), hydrochloric acid 32 % (w/w) p.A. (E. Merck, D-W-6100 Darmstadt); acetone, ethanol 96 % (v/v) and destilled water were used.

Preparation of pellets

Neutral pellets were loaded with bisacodyl up to a level of 4 % (w/w) and subsequently enteric-coated with various formulations of different film-forming polymers using the MiniWiD-Coater[6], a miniature fluid-bed pan coater. The formulations shown in Table 2 were recommended by the manufacturer. Due to the high viscosity, the solids content had to

TABLE 2
Formulas of Aqueous and Organic-Solvent Based Film Coatings

Formula	HPMCAS		CMEC		CAT	
	I	II	I	II	I	II
HPMCAS	10.0	5.0	-	-	-	-
CMEC	-	-	8.00	8.0	-	-
CAT	-	-	-	-	6.0	5.0
Triethyl citrate (TEC)	3.0	-	-	-	-	-
Acetyl. monoglycerides	-	0.5	-	1.0	1.2	1.0
Glycerol monocaprylate	-	-	2.40	-	-	-
Polysorbate 80	-	-	0.04	-	-	-
Sodium citrate	-	-	0.70	-	-	-
Hydroxyethyl cellulose	0.1	-	-	-	-	-
Ammonia 25 %	-	-	-	-	2.0	-
Talc	3.0	2.5	-	-	2.4	2.0
Acetone	-	-	-	-	-	92.0
Ethanol	-	73.6	-	72.5	-	-
Water	83.9	18.4	88.86	18.5	88.4	-
Solids content [% (w/w)]	16.1	8.0	11.14	9.0	10.1	8.0
Density [g/ml]	1.05	0.86	1.02	0.86	1.03	0.82

Formula	L 30 D		
	I	II	III
Eudragit L 30 D	37.50	50.00	50.00
Dibutyl phthalate (DBP)	-	1.50	3.00
Triethyl citrate (TEC)	2.25	-	-
Polysorbate 80	-	0.40	0.40
Talc	4.50	7.50	6.00
Water	55.75	40.60	40.60
Solids content [% (w/w)]	18.0	24.4	24.4
Density [g/ml]	1.06	1.08	1.07

be varied between 8 and 24.4 % (w/w). All aqueous 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. Generally, core bed temperatures of 30 to 40 °C were suggested and hence 35 °C should be sufficient to provide film formation. To study the effect of temperature on the quality of Eudragit films, the core bed temperature was varied between 25 and 45 °C. Further experimental details are given elsewhere[6].

Drug content

A sample of 0.5 g of pellets was withdrawn just before the addition of the enteric coat and assayed spectrophotometrically at 264 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 increase in pellet weight (coating level) and was expressed as a percentage of the coating quantity. Due to the spherical shape of the pellets and the narrow size distribution, it was possible to calculate a mean specific surface area of 40.7 cm^2/g of pellets. Therefore, a coating level of 4 % (w/w) is equivalent to 1 mg/cm^2. Based on the manufacturers recommendations of 4 to 8 mg/cm^2, a coating level of about 25 % (w/w) should be sufficient to provide gastric juice resistance.

Agglomerates

After the film coating process the pellets were passed through a sieve with a mesh size of 1.0 mm. The remaining agglomerates were weighed and the amount was expressed as percentage of the final pellet weight.

Dissolution testing

The acid resistance of the pellets was determined in a six-station dissolution tester (PTW, Pharmatest GmbH, D-W-6452 Hainburg) using Apparatus 2 (paddle), USP XXII. Taking in consideration the sink conditions, 2.5 g of pellets containing about 70 mg of bisacodyl, were placed in 500 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. All batches were tested together in each run using two or three samples per batch. After each time interval the average value and the standard deviation were computed and finally a mean releasing curve and a mean standard deviation[7] were calculated. Since no problems occured with the dissolution in buffer medium of pH 6.8, testing was continued in the acid phase only.

TABLE 3
Coating Conditions

Formula	Bed temperature [°C]	Processing time [min]	Mean spray rate [ml/min]	Coating level [%]	Loss of coating [%]	Agglomerates [%]
HPMCAS I	35	177	0.531	25.3	16.5	-
I	35	328	0.573	57.6	5.6	1.9
(org.) II	35	419	0.504	25.1	9.0	4.6
CMEC I	35	271	0.380	21.3	5.7	-
I	35	437	0.480	42.5	7.4	1.8
(org.) II	35	385	0.393	17.9	19.2	13.8
CAT I	35	323	0.409	23.1	10.9	10.0
I	35	508	0.532	48.6	5.0	11.0
(org.) II	35	201	1.007	22.9	7.3	0.5
L30D I	25	146	0.429	23.7	-	-
	35	140	0.446	23.6	0.6	1.2
(20 % TEC)	45	144	0.426	23.3	2.0	12.9
L30D II	25	114	0.417	23.7	0.3	-
	35	114	0.415	23.6	0.9	0.1
(10 % DBP)	45	112	0.426	23.2	2.4	2.2
L30D III	25	116	0.406	23.8	-	-
	35	111	0.425	23.5	0.3	0.3
(20 % DBP)	45	111	0.429	22.9	2.9	3.1

RESULTS AND DISCUSSION

Coating procedure

As shown in Table 3, aqueous latex dispersions were the most effective application systems characterized by short processing times, minimal agglomeration and negligible loss of coating. Best results were obtained at bed temperatures of 25 °C. Higher temperatures led to spray-drying effects represented by an increase in loss of coating and agglomeration of pellets due to the higher tackiness of the film.

The comparatively bad results of the aqueous systems of HPMCAS, CAT and the organic system of CMEC were caused by reduced adhesion to the pellet surface at the

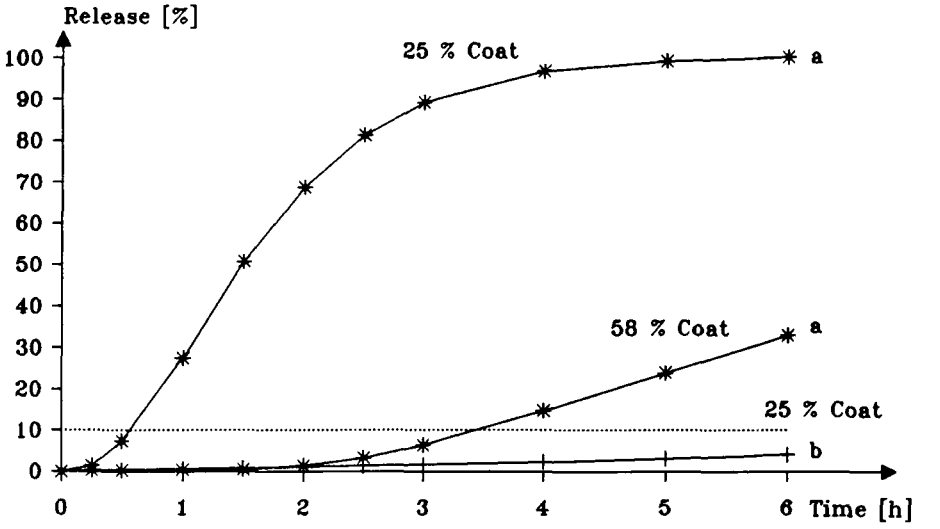

FIGURE 1
HPMCAS: Release of bisacodyl from pellets enteric-coated with aqueous suspensions (a) and organic solutions (b)

beginning of the coating process. Repeated nozzle blockage which appeared with aqueous suspensions of HPMCAS was overcome by an extended stirring time of 17 h before use.

Aqueous suspensions

At coating levels ranging from 21 to 25 % gastric juice resistance (USP XXII) was not achieved with aqueous suspensions of HPMCAS and CMEC although the corresponding organic-solvent based films provided a drug release of less than 10 % within 6 h. Doubling the coating level showed a remarkable effect, prolonging the gastroresistance to 3.4 hours using water-based HPMCAS films (Figure 1) and thus fulfilling the USP specifications. With CMEC films on the other hand, a slight improvement was achieved in prolonging the gastroresistance to only 1 h (Figure 2) which is still not in accordance with the USP specifications. A close examination of the pellets by scanning electron microscopy showed a rough surface caused by partially coalesced particles[6]. This explains the high permeability of these coatings. To improve film formation, a size reduction of the polymer particles might be successful.

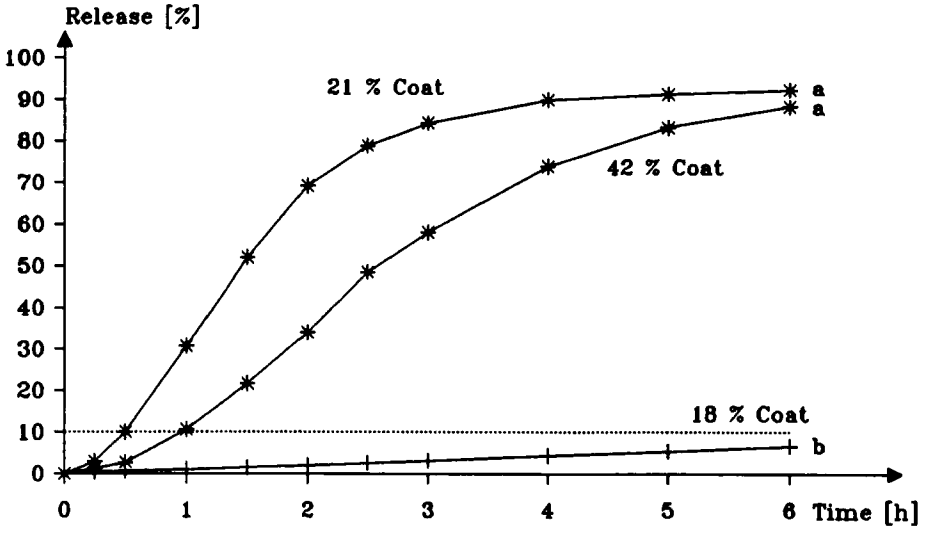

FIGURE 2
CMEC: Release of bisacodyl from pellets enteric-coated with aqueous suspensions (a) and organic solutions (b)

Aqueous ammonium salt solutions

In contrast to aqueous suspensions, aqueous ammonium salt solutions of CAT produced smooth and homogeneous films but the gastroresistant properties were achieved only with the organic system (Figure 3). Increasing the coating level from 23 % to 49 % had a little effect on the drug release. Obviously the ammonium salt was not transformed into free carboxylic acid when placed in acidic medium as presumed earlier[2]. Even a storage at 50 °C for 24 hours to remove the ammonia from the coat[8] had no effect on the release rates.

Aqueous latex dispersions

Homogeneous films were obtained from aqueous latex dispersions of Eudragit L 30 D and gastroresistance was achieved at a coating level of 24 % (3.6 mg/cm^2). The coating temperature was altered between 25 and 45 °C but nearly no effect on the dissolution profile was detected. In contrast, the influence of the type of plasticizer was evident. As shown in Figure 4, films plasticized with 20 % of dibutyl phthalate (DBP) remained gastroresistant for more than 6 hours showing a maximum drug release of 4 %, whereas films containing the same amount of triethyl citrate (TEC) passed the 10%-limit after 2.5 hours and more than

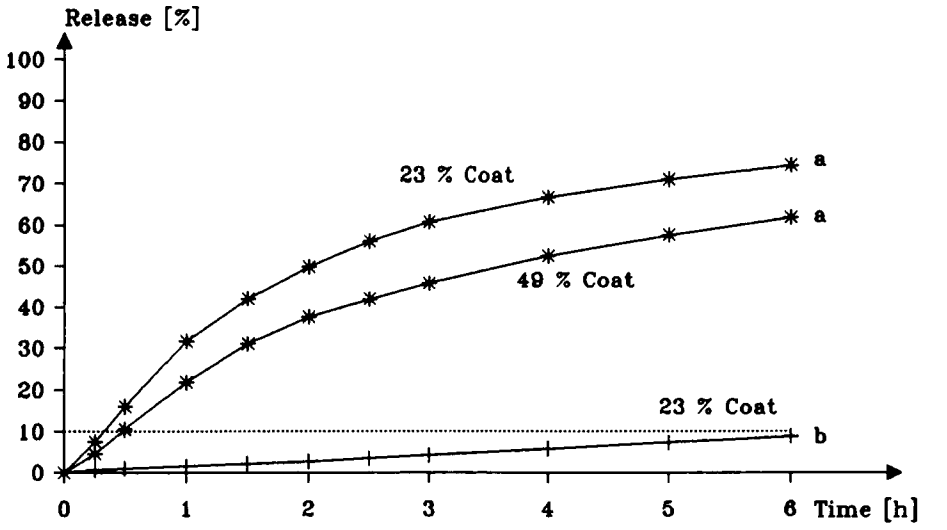

FIGURE 3

CAT: Release of bisacodyl from pellets enteric-coated with aqueous ammonium salt (a) and organic solutions (b)

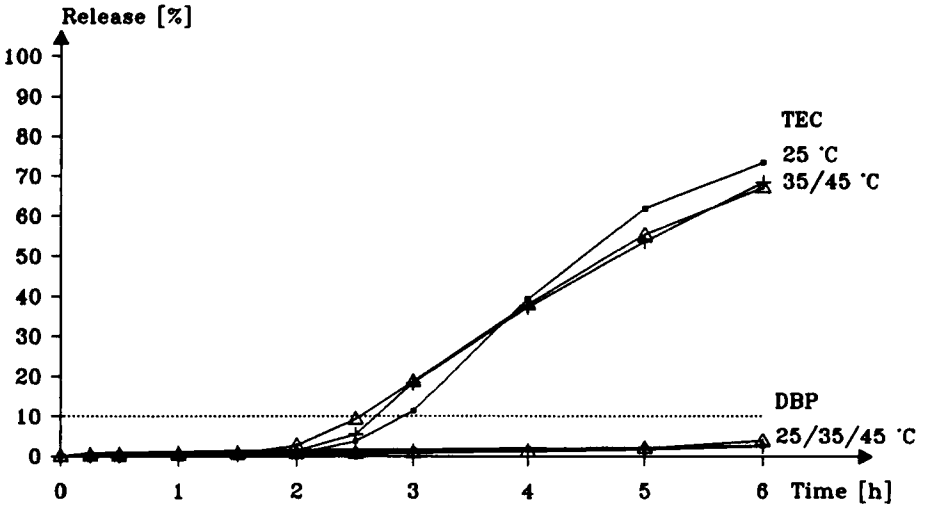

FIGURE 4

Eudragit L 30 D: Effect of coating temperature on the release of bisacodyl from pellets enteric-coated with aqueous dispersions containing different plasticizers

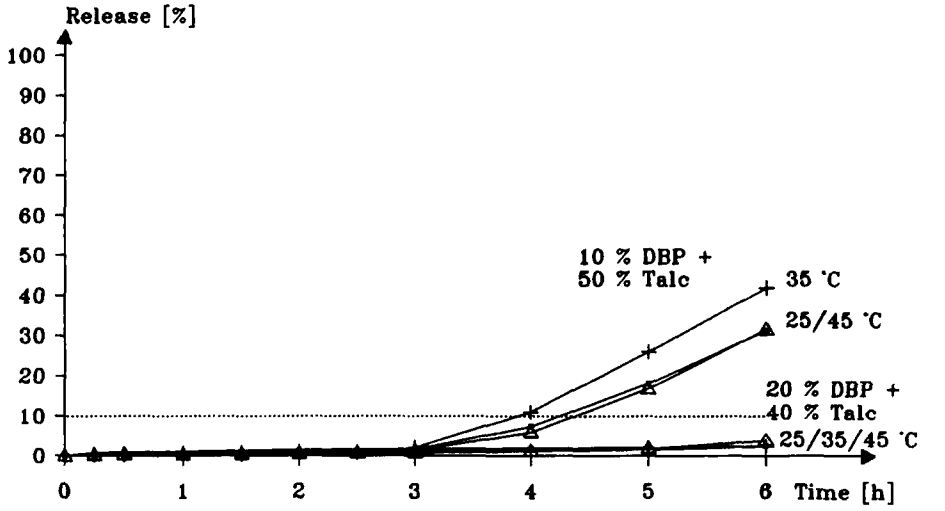

FIGURE 5

Eudragit L 30 D: Effect of coating temperature on the release of bisacodyl from pellets enteric-coated with aqueous dispersions containing different amounts of dibutyl phthalate

65 % of the drug released within 6 hours. This is surprising because increasing MFT proved that DBP is an ineffective plasticizer. The low release rates may be explained by the more hydrophobic properties of DBP remaining undissolved in the film whereas the more hydrophilic TEC was eluted from the coating after 2 hours.

Finally, the amount of plasticizer had a marked effect on the dissolution profile (Figure 5). An increase from 10 to 20 % of DBP led to an excellent enteric coating and the maximum drug release was reduced from 40 to 4 %.

CONCLUSIONS

Compared with the aqueous suspensions and ammonium salt solutions, aqueous latex dispersions of Eudragit L 30 D are the most effective application systems in aqueous enteric coating. The MFT do not represent the plasticizing qualities of DBP in Eudragit L 30 D films when sprayed onto pellets. Therefore the choice of the best plasticizer should be confirmed by experimental data.

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