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Aqueous ethyl cellulose dispersions containing plasticizers of different water solubility and hydroxypropyl methylcellulose as coating material for diffusion pellets I. Drug release rates from coated pellets

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Abstract

The present work investigates release mechanisms of theophylline pellets coated with an aqueous ethyl cellulose (EC) dispersion containing plasticizers and hydroxypropyl methylcellulose (HPMC) as a water soluble pore former. Three different drug release mechanisms from coated pellets can be determined as a function of the water solubility of the plasticizers and the ionic strength of the release medium. Coated pellets with the addition of more hydrophilic plasticizers such as triethyl citrate (TEC) or diethyl phthalate (DEP) show an approximate zero-order-release rate. In contrast, two-phase release profiles can be observed from pellets coated with dispersions containing hardly soluble plasticizers such as dibutyl phthalate (DBP) or dibutyl sebacate (DBS). Only in a release medium of high ionic strength the water soluble pore former will remain in the coating. Thus the drug diffuses through a hydrated swollen membrane containing EC, HPMC and insoluble plasticizer. The release mechanisms depend on the glass transition temperature of the ethyl cellulose and therefore on the migration of the plasticizers and the pore former. This was shown by investigation of the migration of the additives and the influence of the temperature of the release medium on the release. Additionally, the study investigates the effect of curing and storage conditions of coated pellets on the drug release rate.

Keywords: Aqueous ethyl cellulose dispersion; Hydroxypropyl methylcellulose; Plasticizers of different water solubility; Release mechanism; Curing; Release stability

1. Introduction

Since 1958 ethyl cellulose has been used as coating material for oral sustained release dosage

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forms. Aquacoat® ECD-30, an aqueous ethyl cellulose dispersion, is an alternative to respective organic solution. The film forming process of aqueous polymer dispersions is different in comparison to organic solutions. Stable films are formed after concentration of the aqueous dispersion, deformation of the latex particles and interdiffusion of the polymer chains (Vanderhoff, 1970; Chevalier et al., 1992). Therefore, the bed temperature of the coating process has to be set above the minimum film forming temperature (Lehman, 1989; Lippold et al., 1989; Fukumori, 1994) and afterwards the coated pellets have to be cured above the glass transition temperature (Hahn et al., 1986, 1988; Lippold et al., 1989). Added plasticizers reduce the glass transition temperature of ethyl cellulose and enable the formation of tough, flexible films without cracks (Harris and Ghebre-Sellassie, 1989; Steuernagel, 1989; Iyer et al., 1990; Arwidsson et al., 1991). However, the release rate of pellets coated with Aquacoat® ECD-30 containing only a plasticizing agent is extremely slow (Lippold et al., 1989; Gunder et al., 1995). The rate of release can be increased by the addition of a water soluble pore former (Bodmeier and Paeratakul, 1990; Li et al., 1990; Nesbitt et al., 1994; Gunder et al., 1995). Theophylline pellets coated with the aqueous ethyl cellulose dispersion Aquacoat® ECD-30, dibutyl sebacate as plasticizer and hydroxypropyl methylcellulose (HPMC) as pore former astonishingly show not a zero-order release rate but a two-phase release profile. The migration of the water soluble pore former creates water-filled pores, which gradually 'close' inducing the second slower phase of release (Gunder et al., 1995).

The main objective of this study is to clarify the drug release mechanisms from pellets coated with a mixture of Aquacoat® ECD-30, HPMC and plasticizers of different water solubility. Under the assumption that the decrease of the membrane permeability is only possible in the rubbery state of the ethyl cellulose, the following investigations are focused on the glass transition temperature of the water-swollen ethyl cellulose. Release rates from pellets coated with Aquacoat® ECD-30, hydroxypropyl methylcellulose and triethyl citrate (TEC), diethyl phthalate (DEP), dibutyl phthalate (DBP) and dibutyl sebacate (DBS), respectively, should reflect the influence of the water solubility of plasticizers on the release mechanism, supposing that water soluble plasticizers such as TEC migrate from the coating after contact with water (Bodmeier and Paeratakul, 1993) and that water can also act as a plasticizer (Fuzek, 1980). As the glass transition temperature of the swollen polymer coatings varies with the amount of plasticizer, it seems interesting to examine the release rate of the coated pellets at different temperatures.

A further subject of this publication is to clarify the influence of the ionic strength of the dissolution medium on the release rate of coated pellets. The water soluble pore former HPMC is very sensitive to electrolytes (Alderman, 1984; Doelker, 1990; Mitchell et al., 1990; Veiga et al., 1994). A reduced hydration of HPMC might reduce its migration. Another interesting point is the stability of the coating. For this reason the drug release rates of the coated pellets are measured after storage at ambient temperature and stress conditions.

2. Materials and methods

2.1. Materials

2.1.1. Pellets

Not coated theophylline pellets (Boehringer–Ingelheim, Ingelheim, Germany) containing 80% theophylline anhydrous with a particle size rang-

Table 1
Correlation between the water solubility of the plasticizers and the necessary standing time of plasticized Aquacoat® ECD-30

Plasticizer 10%	Solubility (H_2O; 20°C) (%)	Standing time (h)
DBS	0.01	7.00
DBP	0.04	3.00
DEP	0.15	0.25
TEC	6.90	0.03

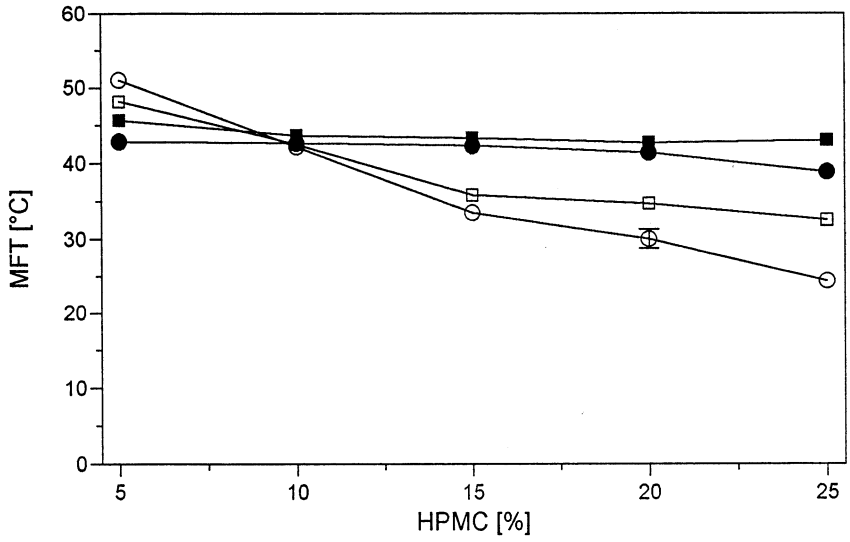

Fig. 1. Effect of the pore former HPMC on the MFT of the plasticized ethyl cellulose dispersions (mean ± S.D.; $n = 6$). ○ 12.5% DBS; □ 12.5% DBP; ● 11.0% DEP; ■ 11.0% TEC.

ing from 1250 to 1400 μm, were used as starting material.

2.1.2. Pellet coating

2.1.2.1. Film former. Aquacoat® ECD-30 (FMC Corporation, Philadelphia, USA). Aquacoat® ECD-30 is an aqueous ethyl cellulose dispersion with a solid content of 29–32%. It contains 24.5–29.5% ethyl cellulose, 0.9–1.7% sodium lauryl sulfate, 1.7–3.3% cetylalcohol and small quantities of dimethyl polysiloxane (FMC Corporation, 1985).

2.1.2.2. Pore former. Hydroxypropyl methylcellulose (HPMC, Pharmacoat® 603, ShinEtsu, Tokyo, Japan). The viscosity of a 2% aqueous solution at 20°C amounts up to 3 mPa/s.

2.1.2.3. Plasticizers. Triethyl citrate (TEC; Boehringer Ingelheim, Ingelheim; Germany, solubility at the relevant temperature (c_s) = 6.9%); diethyl phthalate (DEP, Rhône Poulenc, Frankfurt, Germany; $c_s = 0.15\%$); dibutyl phthalate (DBP, Fluka Chemie AG, Buchs, Switzerland; $c_s = 0.04\%$) and dibutyl sebacate (DBS, Henkel KGaA, Düsseldorf, Germany; $c_s = 0.01\%$). The chemicals were used as received.

2.2. Methods

2.2.1. Minimum film forming temperature (MFT)

The measuring of the MFT was performed with the Thermostair BL–MFT 'D' gradient test device (Coesfeld GmbH, Dortmund, Germany) with 20 test stations according to DIN 53787 'Determination of the minimum temperature of film formation and the white point temperature'. Three films can be made at the same time on the metal block of the device. An average film thickness of about 100 μm is reached after drying of the dispersion.

2.2.2. Manufacturing of coated pellets

2.2.2.1. Dispersion. Appropriate quantities of aqueous ethyl cellulose dispersion, plasticizer and HPMC solution are combined and mixed with a glass blade stirrer for 30 min before and after the standing time of 23 h. The pore former HPMC was added as a solution of a maximum concentration of 10% to the aqueous dispersion. The percent of plasticizers refers to the film without HPMC. The maximum concentration was not higher than 20% in order to prevent sticking (Lippold et al., 1989). The percent of pore former refers to the entire film.

2.2.2.2. Coating. Known weights of pellets (260 g) were transferred into a fluidized bed coating apparatus (Strea I Aeromatic, Muttenz, Switzerland), equipped with a bottom-spray nozzel. The bed temperature (± 2°C) was adjusted to 10°C above the MFT, but to a minimum of at least 40°C. Coating dispersions were pumped with a flow rate of 1–2 g/min and the spraying pressure was 0.06 MPa. The total spraying time was 1.5–2.5 h. The coated pellets were then dried in the same apparatus for 5 min at the above mentioned temperature. The film coating consisting of ethyl cellulose and plasticizer amounts to about 12% of the weight of the diffusion pellets. The coating level was calculated by weight of the sprayed dispersion without the amount of HPMC.

2.2.2.3. Curing. After the coating process the pellets were cured in an oven for 1 h at 70, 80, 90 or 100°C.

2.2.3. Release of drug

The paddle apparatus Ph. Eur. 1997 was used with 1000 ml of release medium, mostly 0.1 N-HCl at 15, 20, 26, 32, 37, 42 and 48°C release temperature and a stirring speed of 170 rpm. The drug concentration was determined by UV-spectroscopy (UV/VIS Spektralphotometer Lambda 2, Perkin Elmer, Überlingen, Germany) every 3 min at the minimum of the absorption spectrum at 243.4 nm. The very low amounts of DEP and DBP released from the pellet coats do not interfere with the UV-spectroscopy assay. Zero order release rate constants k_f^0 were determined from

Table 2
Release rate constants (k_f^0) of pellets coated with Aquacoat® ECD-30, HPMC and plasticizers influenced by curing conditions[a]

Coating: ECD		Release constant k_f^0 (%/h)			
Plasticizer	HPMC (%)	70°C 1 h	80°C 1 h	90°C 1 h	100°C 1 h
9.0% DBS	10	24.0[f]	**1.44**	1.46	1.45
	20	88.9[c]	**6.82**	6.11	6.00
	30	138[b]	**11.0**	10.1	10.9
12.5% DBS	10	1.26	**0.97**	1.06	1.25
	20	5.93	**5.34**	5.49	6.42
	30	10.2	**9.39**	9.23	10.0
20.0% DBS	30	**1.41**	1.39		
12.5% DBP	10	6.46	**1.57**	1.52	
	20	9.60	**7.24**	7.95	
	30	31.2[e]	**10.9**	11.0	
20.0% DBP	30	**6.98**	7.71		
11.0% DEP	10	38.6[b]	6.33	4.60	**3.34**
	20	275[b]	9.39	9.40	**8.74**
	30	464[b]	45.6[d]	12.4	**13.3**
20.0% DEP	10	**1.90**	2.70	2.92	2.52
11.0% TEC	10	59.4[b]	1.73	**1.52**	1.39
	20	196[b]	10.8	**8.83**	8.54
	30	451[b]	20.8[f]	**13.4**	13.4
20.0% TEC	10	**1.69**	1.82	1.73	2.07

[a] The numbers in bold types indicate the curing conditions to reach constant low release rates. Release conditions: 1 l; 0.1 N-HCl; 20°C; ($n = 1$); k_f^0: 2–5 h.
[b] k_f^0: 15–30 min.
[c] k_f^0: 15–45 min.
[d] k_f^0: 15–60 min.
[e] k_f^0: 1–1.5 h.
[f] k_f^0: 1–2 h.

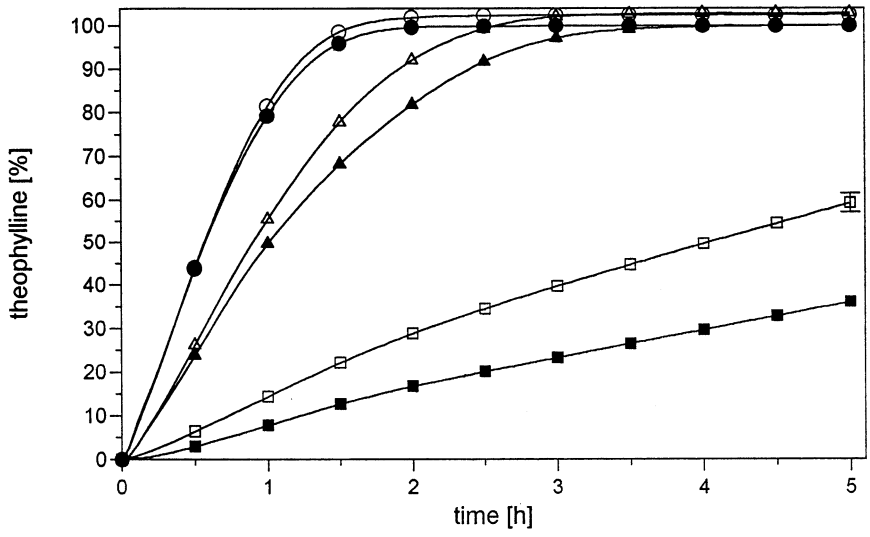

Fig. 2. Effect of the pore former content in combination with water soluble and fairly water soluble plasticizers in the coatings on the release of theophylline. Film: 90, 80, 70% ECD (11.0% TEC, DEP); 10, 20, 30% HPMC. Curing: TEC: 1 h, 90°C, DEP: 1 h, 100°C. Release conditions: 1 l; 0.1 N-HCl; 37°C; (mean ± S.D.; $n = 2$). 11.0% TEC: ■ 10% HPMC; ▲ 20% HPMC; ● 30% HPMC. 11.0% DEP: □ 10% HPMC; △ 20% HPMC; ○ 30% HPMC.

the linear parts of the release curves, generally during the second and the fifth hour of release.

2.2.4. Content of plasticizer in the coating

A newly developed HPLC assay was used for the analysis of the plasticizers in the diffusion pellets before exposure to the aqueous medium and in the release medium after exposure to the aqueous medium. The samples were measured with the HPLC model LC-6A (Shimadzu, Duisburg, Germany) with an automatic sample injector (model SIL-6B), system controler (model SCL-6B), UV spectrophotometric detector (model SPD-6AV), an integrator (model C-R4AX Chromatopac) and an analytical column (LiChrospher® 100 RP-18, 5 μm particle size, 125 mm length and 4 mm internal diameter, E. Merck, Darmstadt, Germany). The mobile phase consisted of methanol:distilled water 50:50% (v/v) for DEP and acetonitril:distilled water 70:30% (v/v) for DBP. The volume of injection varied between 20 and 150 μl. The flow rate was 2 ml/min and the UV absorption was measured at 230 nm for both plasticizers. Validation was performed with an external standard of three concentrations between 0.1 and 0.4 mg/l (Frohoff-Hülsmann, 1997).

In order to measure the amount of plasticizer in the coatings, the coated pellets were crushed, mixed with methanol (DEP) or acetonitril (DBP) and stirred for 24 h.

2.2.5. Storage conditions

After coating and curing the pellets were stored in brown airtight bottles of glass at ambient temperature for a maximum of 31 months. To evaluate the influence of higher temperature and higher relative humidity these pellets were stored after a minimum of 23 months at ambient temperature for 4 months at 40°C and 75% RH. The samples of about 1.5 g were transferred into open petridishes and kept in a hygrostate containing a saturated solution of NaCl.

3. Results and discussion

3.1. Minimum film forming temperature (MFT)

The MFT, defined as the temperature at which a continuous film without cracks is formed, is an important parameter to determine the appropriate bed temperature of the fluidized bed apparatus. In

the literature it is known that MFT values decrease with increasing level of added plasticizers (Amighi and Moes, 1996), with increasing standing time of the aqueous plasticized polymer dispersion (Lippold et al., 1990; Monells Pagés and Lippold, 1995) and in some cases with increasing amount of pore former (Gunder et al., 1995).

The standing time is defined as the minimum time period which is necessary for the plasticized aqueous polymer dispersion to reach a constant MFT value. The distribution of plasticizers between the aqueous and the polymer phase is time dependent. Table 1 shows the influence of the water solubility of the plasticizers on the standing time of the plasticized EC dispersion. The water insoluble plasticizers DBS and DBP need 7 and 3 h, respectively, to reach the maximum of concentration in the ethyl cellulose. DEP and TEC, the more water soluble plasticizers, distribute between polymer and aqueous phase during the stirring time of 30 min. The water solubility of the plasticizers effects the concentration gradient between the aqueous and the polymer phase and thus the standing time of the polymer dispersion. For all further experiments a standing time of 23 h is used.

Experiments with Aquacoat® ECD-30 containing increasing amounts of DBS, DBP, DEP, TEC or HPMC show a decrease of MFT values (Frohoff-Hülsmann, 1997). Fig. 1 illustrates the influence of the increasing amounts of the pore former HPMC on the MFT values of the plasticized aqueous polymer dispersion. The MFT values of the ethyl cellulose dispersion containing DBS and DBP decrease with increasing amounts of HPMC as expected. In contrast, the effect of HPMC on the aqueous polymer dispersion containing DEP and TEC seems to disappear. The MFT varies between 46 and 43°C. These unexpected results underline the importance of evaluating the interactions of all additives.

3.2. Release rates of theophylline diffusion pellets

3.2.1. Curing of the coated pellets

The bed temperature of 40°C or 10°C above the MFT, respectively, during the coating of the pellets in the fluidized bed apparatus is not sufficient to reach a release rate of coated pellets which is independent of curing conditions. Curing of coated pellets in an oven can cause a decrease of

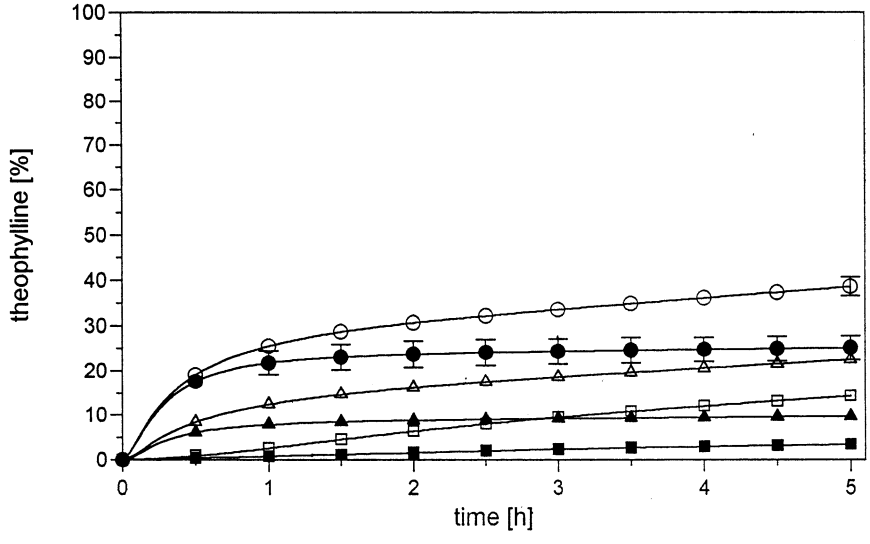

Fig. 3. Effect of the pore former content in combination with very fairly water soluble and water insoluble plasticizers in the coatings on the release of theophylline. Film: 90, 80, 70% ECD (12.5% DBP, DBS); 10, 20, 30% HPMC. Curing: DBP: 1 h, 80°C, DBS: 1 h, 80°C. Release conditions: 1 l; 0.1 N-HCl; 37°C; (mean ± S.D.; $n = 2$). 12.5% DBP: □ 10% HPMC; △ 20% HPMC; ○ 30% HPMC. 12.5% DBS: ■ 10% HPMC; ▲ 20% HPMC; ● 30% HPMC.

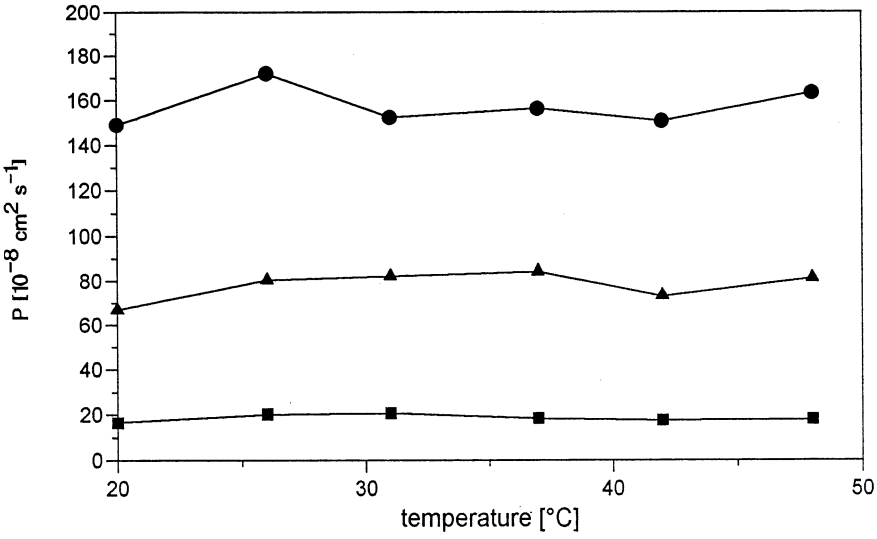

Fig. 4. Permeability coefficients of theophylline (starting phase) for coatings with the addition of DEP in dependence on the temperature of the release medium. Film: 90, 80, 70% ECD (11.0% DEP); 10, 20, 30% HPMC. Curing: 1 h, 100°C; Release conditions: 1 l; 0.1 N-HCl; (mean; $n = 2$). ■ 10% HPMC; ▲ 20% HPMC; ● 30% HPMC.

the drug release rates to an endpoint (Lippold et al., 1989; Gilligan and Li Wan, 1991; Schmidt and Niemann, 1993; Bodmeier and Paeratakul, 1994a; Hutchings et al., 1994b; Keshikawa and Nakagami, 1994; Amighi and Moes, 1996; Guma et al., 1997). In this case, the interdiffusion of the (pseudo-) latex particles is not completed without the curing process.

Table 2 demonstrates that the curing temperature which is necessary to reach a constant and low release rate decreases with increasing amount of plasticizer. For example coated pellets containing 9.0 and 20.0% DBS show constant release rates after curing 1 h at 80 and 70°C, respectively. The amount of plasticizer as well as the type of plasticizer influence the film formation and therefore the adequate curing temperature and time period. Pellets coated with 11.0% DEP and TEC need curing conditions from 1 h at 100°C and 1 h at 90°C to reach stable coatings (Table 2). The content of pore former in the coating hardly effects the curing conditions which are necessary to reach a constant release rate (Table 2). Another possibility to lower the relatively high curing temperatures to reach a constant and low release rate is the curing at higher relative humidities (Amighi and Moes, 1996).

3.2.2. Pore former content and type of plasticizer

Pellets coated with an aqueous ethyl cellulose dispersion, containing DBS and HPMC, show a two-phase release profile (Gunder et al., 1995). The comparison of release rates from pellets coated with plasticizers of different water solubility should clarify the reason for the two-phase release profile. Figs. 2 and 3 illustrate the release of theophylline from coated pellets as a function of the HPMC content as well as the type of plasticizer.

As expected the release rates of diffusion pellets plasticized with TEC and DEP increase with increasing amount of pore former from 10 to 30% in the coatings (Fig. 2; Donbrow and Friedman, 1975; Steuernagel, 1989; Li et al., 1990). After a short lag-time an approximate zero-order release rate can be observed (Lippold et al., 1980; Lippold and Förster, 1981; Lippold et al., 1981; Li and Peck, 1989; Lippold et al., 1989). The pore former migrates after exposure to the aqueous medium and the drug diffuses through water-filled pores (Lippold et al., 1989; Sheen et al., 1992). Swelling studies with ethyl cellulose films confirm the complete migration of the pore former (Frohoff-Hülsmann, 1997). The reason for the differ-

ent release profiles of TEC and DEP containing pellets may be the different content of plasticizer after coating and curing process of the pellets due to the evaporation of the plasticizer (Frohoff-Hülsmann, 1997).

Pellets coated with Aquacoat® ECD-30, 12.5% DBP or DBS and HPMC also show increasing release rates with increasing amount of HPMC from 10 to 30% (Fig. 3). However, the release curves do not take a linear course, but show a two-phase profile. During the first phase (almost 1 h) the release is fast and characterized by drug diffusion through water-filled pores after the migration of the water soluble pore former comparable to the release mechanism of pellets coated with TEC and DEP (Fig. 2). During the second phase the free volume between the polymer chains is dramatically reduced and therefore the permeability of the coatings obviously decreases. The remaining film containing ethyl cellulose and plasticizer is able to shrink (Frohoff-Hülsmann, 1997). The drug is supposed to diffuse mainly through the plasticized ethyl cellulose coatings (Lippold et al., 1998). The release rates are independent of the HPMC content. The curves of coated pellets with 10, 20 and 30% HPMC content run parallel towards each other. The requirement for the reduction of the free volume between the polymer chains is the exceeding of the glass transition temperature (T_g) of the swollen ethyl cellulose. The T_g is influenced by the amount of plasticizer and water. The extent of shrinking differs between coated pellets plasticized with DBP and DBS. DBS probably retains almost completely in the coating whereas DBP distributes partially out of the coating into the aqueous medium according to their different water solubility and partition coefficient, respectively.

3.2.3. Temperature of the release medium

The following Figs. 4 and 5 present the influence of the temperature of the release medium on the permeability coefficients (P). They are calculated according to the following equation

$$P = \frac{d_M \cdot k_f^0}{A_{ges} \cdot c_s}$$

with $d_M = 32$, 39.5 and 47 μm for coatings with 10, 20 and 30% HPMC. Where, d_M is the film thickness of the coating; k_f^0 is the zero-order release rate constant; A_{ges} is the area of the coated pellets; and c_s is the solubility of theophylline at the relevant temperature.

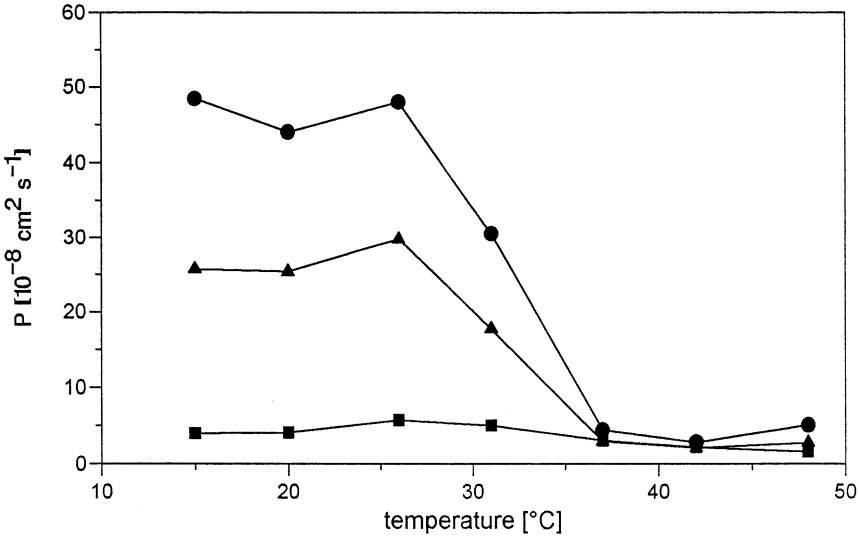

Fig. 5. Permeability coefficients of theophylline (terminal phase) for coatings with the addition of DBP in dependence on the temperature of the release medium. Film: 90, 80, 70% ECD (12.5% DBP); 10, 20, 30% HPMC. Curing: 1 h, 80°C; Release conditions: 1 l; 0.1 N-HCl; (mean; $n = 2$). ■ 10% HPMC; ▲ 20% HPMC; ● 30% HPMC.

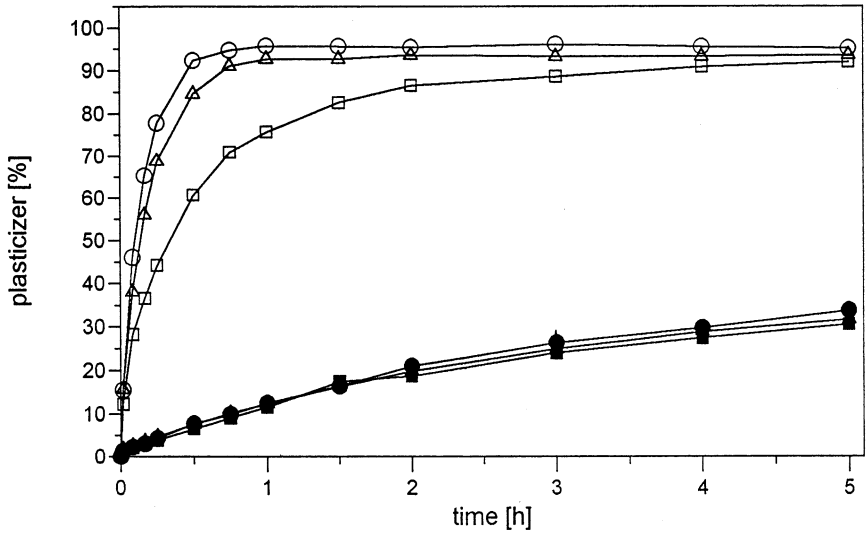

Fig. 6. Migration of the plasticizers DEP and DBP in dependence on the HPMC content of pellet coatings. Film: 90, 80, 70% ECD (11.0% DEP and 12.5% DBP); 10, 20, 30% HPMC. Curing: DEP: 1 h, 100°C, DBP: 1 h, 80°C. Release conditions: 1 l; 0.1 N-HCl; 37°C; ($n = 1$). 11.0% DEP: □ 10% HPMC; △ 20% HPMC; ○ 30% HPMC. 12.5% DBP: ■ 10% HPMC; ▲ 20% HPMC; ● 30% HPMC.

In this way it is possible to compare release properties, because the temperature dependent solubility of theophylline as well as the differences of the film thickness are considered in this calculation.

Coated pellets with the addition of fairly water soluble plasticizers such as DEP and water soluble plasticizers such as TEC show a permeability which is nearly independent of the temperature of the release medium (Fig. 4, with DEP as example) but increases with increasing amount of HPMC in the coating. The investigated temperatures between 20 and 48°C are not able to change the drug release mechanism. The glass transition temperature (T_g) of the coatings is apparently not exceeded. The plasticizer content of those swollen coatings decreases very fast to a minimum (Fig. 6). Interestingly, EC dispersions containing 11.0% DEP and 10–30% HPMC show MFT values of about 45°C (Fig. 1). The MFT value of Aquacoat® ECD-30 without further additives is 77°C and the T_g is 95°C (Frohoff-Hülsmann, 1997).

In contrast, the temperature dependence of the permeability coefficients of pellet coatings with more or less water insoluble plasticizers is characterized by curves which show an upper plateau, a sharp decrease and a lower plateau (Fig. 5, with DBP as example). At lower temperatures from 15 to 26°C the permeability coefficients are nearly independent of the temperature, but increase with

Table 3
Influence of the ionic strength of the release medium on the permeability coefficients of theophylline for pellet coatings[a]

Coating		$P\ 10^{-8}$ cm$^2 \times$ s	
Plasticizer	HPMC	Distilled water	1.5 N-NaCl
11.0% TEC	10%	11.9	3.27
11.0% DEP	10%	19.6	9.48
12.5% DBP	10%	4.21	3.36
12.5% DBS	10%	0.51	3.02
11.0% TEC	30%	n. m.[b]	37.7
11.0% DEP	30%	202[c]	45.4
12.5% DBP	30%	10.3	43.8
12.5% DBS	30%	1.60	32.3

[a] 90 or 70% ECD plus plasticizer; 10, 30% HPMC; Release conditions: 1 l; distilled water or 1.5 N-NaCl solution; 37°C; (mean; $n = 2$); k_f^0: 2–5 h.
[b] Not measured.
[c] k_f^0: 0.5–1 h.

increasing amount of HPMC. The sharp decrease begins at 26°C and ends at 37°C. From 37 to 48°C the P values build up the lower plateau. The decrease as well as the lower plateau are independent of the HPMC content. The temperature of 37°C is apparently sufficient to exceed the T_g of the swollen ethyl cellulose plasticized with 12.5% DBP. The very slightly water soluble plasticizer DBP is still present in the coatings after 5 h of drug release (Fig. 6). The two-phase release mechanism might be explained by the physical condition of the swollen ethyl cellulose during the drug release period. Only a polymer in the rubbery state is able to shrink (Fuzek, 1980; Frohoff-Hülsmann, 1997) and to close pores and channels (Bodmeier and Paeratakul, 1989; Gunder et al., 1995). The temperature of the release medium can influence the release of coated pellets. It is important to distinguish if the temperature of the release medium exceeds or does not exceed the glass transition temperature of the swollen film forming polymer.

3.2.4. Ionic strength of the release medium

The release mechanism of pellets coated with a plasticized aqueous EC dispersion in combination with HPMC as a water soluble pore former may change when the cellulose ether remains in the coating of the pellets. A strongly reduced hydration of HPMC, enforced by a high ionic strength of the release medium, can prevent the pore former from migration out of the coating.

In the release medium of distilled water the permeability coefficients of theophylline vary according to the added plasticizers (Table 3). At high ionic strength of the release medium the P values adjust more or less to each other. Coated pellets with the addition of 30% HPMC in the coatings show P values between 32.3 and 45.4×10^{-8} cm^2/s which are independent of the water solubility of the plasticizers. According to these values the drug does not diffuse mainly through water-filled pores or the plasticized ethyl cellulose membrane but through a swollen EC/HPMC membrane. The high ionic strength of the release medium apparently prevents the complete migration of the pore former (Frohoff-Hülsmann, 1997). Thus, the differentiating influence of the plasticizers disappears. The release mechanism is characterized by the remaining content of HPMC in the coating instead of the physical state of the ethyl cellulose. This type of release mechanism for EC/HPMC films was already described in the literature (Shah and Sheth, 1972; Rowe, 1986).

3.3. Plasticizer content

3.3.1. Volatility of plasticizers

The knowledge of the plasticizer content of the coated pellets before their exposure to the aqueous medium is a requirement to measure the migration of the plasticizer during drug release. Loss of plasticizer can occur after coating, curing (Bindschaedler et al., 1987; Bodmeier and Paeratakul, 1994b) and/or after storage at stress conditions of coated pellets (Gutiérrez-Rocca and McGinity, 1994; Hutchings et al., 1994a).

Dibutyl phthalate does not tend to volatize. The residual amount of DBP varies between $82 \pm 5\%$ and $93 \pm 3\%$ after curing at 80°C for 1 h. In contrast to DBP, DEP has a high tendency to volatize during the coating and curing process of the pellets. The content of diethyl phthalate decreases after coating at 53 ± 2°C and curing 1 h at 100°C to 28–21%. These results are in accordance with direct volatility measurements (Frohoff-Hülsmann, 1997). They show low values for DBP and DBS, an intermediate value for TEC and a high value for DEP. The high volatility of DEP probably explains the high curing temperature which is necessary to reach a constant release rate.

3.3.2. Migration of plasticizers

Plasticizers leach out of the polymer according to their physical and chemical properties (Hennig and Kala, 1986; Lippold et al., 1990; Bodmeier and Paeratakul, 1992, 1993, 1994b).

As expected, the rates of migration of the plasticizers differ between DEP and DBP (Fig. 6). The relatively water soluble plasticizer DEP migrates almost completely from the pellet coatings within 0.5–5 h in 0.1 N HCl solution at 37°C. The rate of migration increases with increasing amount of pore former. In the same period of time DBP is recovered between 30.5 and 38.0% in the release medium. The migration of DBP is independent of

Table 4
Influence of the storage conditions on the release of theophylline[a]

Film	k_r^0-interval (h)	k_r^0 (%/h) ambient conditions		k_r^0 (%/h) amb. + stress
11.0% TEC		1 m	31 m	27 + 4 m
10% HPMC	(2–5)	6.37 ± 0.16	6.69 ± 0.16	4.77 ± 0.35
20% HPMC	(0.5–1)	52.1 ± 0.74	54.7 ± 0.84	40.9 ± 0.25
30% HPMC	(0.25–0.75)	87.2 ± 1.3	88.4 ± 1.2	85.7 ± 2.2
20.0% TEC		3 m	30 m	26 + 4 m
10% HPMC	(3–5)	4.81 ± 0.11	4.50 ± 0.13	2.98 ± 0.41
11.0% DEP		1 m	31 m	27 + 4 m
10% HPMC	(3–5)	9.79 ± 0.42	9.69 ± 0.12	10.1 ± 0.21
20% HPMC	(0.5–1)	58.9 ± 0.93	57.5 ± 0.84	46.2 ± 1.2
30% HPMC	(0.25–0.75)	90.5 ± 1.3	91.9 ± 2.4	80.4 ± 1.6
20.0% DEP		3 m	30 m	26 + 4 m
10% HPMC	(3–5)	8.01 ± 0.29	7.72 ± 0.15	7.84 ± 0.16
12.5% DBP		1 m	30 m	26 + 4 m
10% HPMC	(2–5)	2.60 ± 0.10	3.05 ± 0.10	1.81 ± 0.06
20% HPMC	(2–5)	2.05 ± 0.02	4.61 ± 0.20	6.14 ± 0.59
30% HPMC	(2–5)	2.48 ± 0.30	6.90 ± 0.16	9.75 ± 0.21[b]
20.0% DBP		1 m	27 m	23 + 4 m
30% HPMC	(2–5)	1.47 ± 0.34	1.90 ± 0.49	1.61 ± 0.06
12.5% DBS		7 m	31 m	27 + 4 m
10% HPMC	(2–5)	0.60 ± 0.01	0.61 ± 0.13	0.56 ± 0.01
20% HPMC	(2–5)	0.28 ± 0.01	0.30 ± 0.07	0.52 ± 0.03
30% HPMC	(2–5)	0.44 ± 0.08	0.70 ± 0.20	1.96 ± 0.07[c]
20.0% DBS		1 m	27 m	23 + 4 m
30% HPMC	(2–5)	1.05 ± 0.10	0.87 ± 0.12	0.95 ± 0.16

[a] Film: 90, 80, 70% ECD plus plasticizer; 10, 20, 30% HPMC; Curing: 11.0% TEC: 1 h, 90°C, 11.0% DEP: 1 h, 100°C, 12.5 and 9% DBP and DBS: 1 h, 80°C, 20.0% plasticizer: 1 h, 70°C. Storage conditions: ambient conditions and stress (40°C/75% RH). Release conditions: 1 l; 0.1 N-HCl; 37°C; (mean ± S.D.; $n = 2–3$).
[b] k_r^0: 3–4 h.
[c] k_r^0: 3–5 h.

the pore former content. TEC and DBS have not been investigated.

The fast loss of plasticizer during the drug release from coated pellets plasticized with the fairly water soluble DEP causes a zero-order release rate. A two-phase release profile is determined by coated pellets with a high content of plasticizer during the drug release period. The different amount of plasticizer influences the glass transition temperature of the swollen ethyl cellulose and thus the physical state of the polymer and its ability to shrink at 37°C. If the T_g of the swollen EC lies above or below the temperature of the release medium can only be shown by measuring the T_g of swollen EC films. The respective method and the results will be reported in another publication.

3.4. Release stability of coated pellets

Several groups reported a decrease of drug release rates from pellets coated with aqueous dispersions during the storage at ambient conditions as well as at higher temperatures and relative humidities (Li and Peck, 1989; Niemann, 1991; Bianchini et al., 1993; Oshlack, 1993; Amighi and Moes, 1996). These authors explain this phenomenon with a further coalescence of the latex particles. High relative humidities reduce the glass transition temperature and increase the mo-

bility of polymer chains at a given temperature (Amighi and Moes, 1996).

Table 4 shows all zero-order release constants of coated pellets after storage at ambient conditions and after 4 months storage at 40°C/75% RH. In the case of two-phase release curves, the long persistent second phase is characterized by a zero-order rate constant. The release of theophylline from pellets coated with aqueous EC dispersion, HPMC and TEC or DEP, is independent of the storage at ambient conditions over 31 months. Only the 4 months' storage at stress conditions causes a partial decrease of the theophylline release rate. For example, the release rate constant from coated pellets containing 11.0% TEC and 10% HPMC decreases during the 4 months' stress storage from $6.69 \pm 0.16\%$ to $4.77 \pm 0.35\%$ [%/h]. One can assume that the coalescence of the latex particles is completely achieved according to the constant release rate of these coated pellets during the storage at ambient conditions. The influence of the higher temperature and relative humidity is possibly based on structural modifications of the film which only arise under these conditions.

In contrast, the release rates of coated pellets containing 12.5% DBP and 20 or 30% HPMC increase with increasing storage time at ambient conditions as well as at stress conditions. The curves approach a zero-order release behavior, the two-phase release mechanism gradually disappears. This effect may indicate a loss of plasticizer during the storage because the amount of remaining plasticizer in the coatings during the drug release is responsible for the two-phase release profile (Figs. 3 and 6). The effect of storage diminishes in the case of 12.5% DBS. Coated pellets with 20.0% DBP or DBS do not show any influence of storage on the release rate.

4. Conclusions

Three different release mechanisms of pellets coated with aqueous ethyl cellulose dispersion, hydroxypropyl methylcellulose and triethyl citrate, diethyl phthalate, dibutyl phthalate or dibutyl sebacate are determined. The drug release is dependent on the physical state of the swollen ethyl cellulose and on the migration of the water soluble pore former, respectively. If the pore former mostly migrates from the coating, the type and amount of plasticizer in the swollen coating and the temperature of the release medium influence the release rate to a large extent. If the film forming polymer is present in the glassy state as it is after the migration of the water soluble plasticizer and pore former at temperatures above T_g, the drug diffuses through water filled pores (first mechanism). If the ethyl cellulose is in the rubbery state as it is the case with the water insoluble plasticizer at temperatures below T_g, the drug release rate is characterized by a two-phase release profile as a result of pore shrinking (second mechanism). The third mechanism occurs if the migration of the pore former is incomplete. A high ionic strength of the release medium causes a reduced hydration of the pore former. The drug diffuses through a swollen heterogeneous membrane containing EC, HPMC and insoluble plasticizer.

The evaluation of the respective free films is described in a forthcoming paper to back up the discussed release mechanisms.

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