3.5. DRY POWDER COATING

3.5.1. The key role of plasticisers

In dry powder coating the plasticiser plays a key role, as it needs to soften the polymer to enable the deformation and thus the coalescence of the polymer particles (Pearnchob, 2003).

The extent of the polymer-plasticiser interaction is usually quantitated by the decrease of the glass transition temperature (Tg) of the polymer. The most effective plasticiser will thereby result in the strongest reduction of the Tg at the same plasticiser content (Rekhi and Jambhekar, 1995). The rank order of plasticiser efficiency for ethylcellulose is TEC > AMG > DBS (Wheatley and Steuernagel, 1997). This was confirmed by DSC-measurements (Table 20). The Tg correlated with the required temperature for film formation during the coating process and curing (Pearnchob and Bodmeier, 2003b), and is associated with further decisive parameters as the mechanical properties and viscosity of the polymer at a given temperature.

Table 20 Effect of plasticiser type on the Tg of ethylcellulose (plasticiser concentration: 20 % w/w based on the formulation)

Plasticiser type	Tg, °C
none	132 ± 1.5
MCT	68.1 ± 0.0
DBS	65.7 ± 0.6
AMG	65.4 ± 2.0
ATBC	56.6 ± 2.7
ATEC	55.3 ± 0.3
TEC	54.3 ± 3.3
TBC	47.4 ± 0.6

With increasing plasticiser concentration the glass transition temperature of ethylcellulose was reduced (Fig. 63). In general the citrates (TBC and TEC) revealed a superior performance.

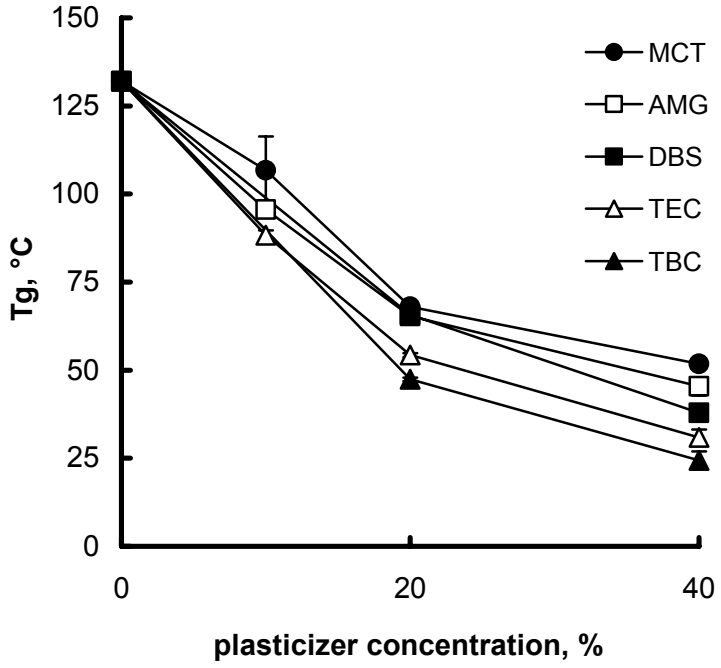

Figure 63 The effect of type and amount of plasticiser on the Tg of ethylcellulose films (plasticiser content: % w/w, based on the formulation; EC 10 cp, cast from 10 % w/w chloroform solution)

Intrinsic viscosity measurements reinforced the order of the polymer-plasticiser interaction determined by DSC. Thereby it was important to consider, that the pure plasticisers vary in their initial viscosity. Among the investigated plasticisers the lowest value (8 mPas) differed from the highest value (50.4 mPas) by a factor of more than 6 (Fig. 64A). The calculated relative viscosity is weighting the increase of the viscosity in relation to the viscosity of the pure plasticiser. The minor performance of AMG and DBS compared to the citrate esters was confirmed (Fig. 64B).

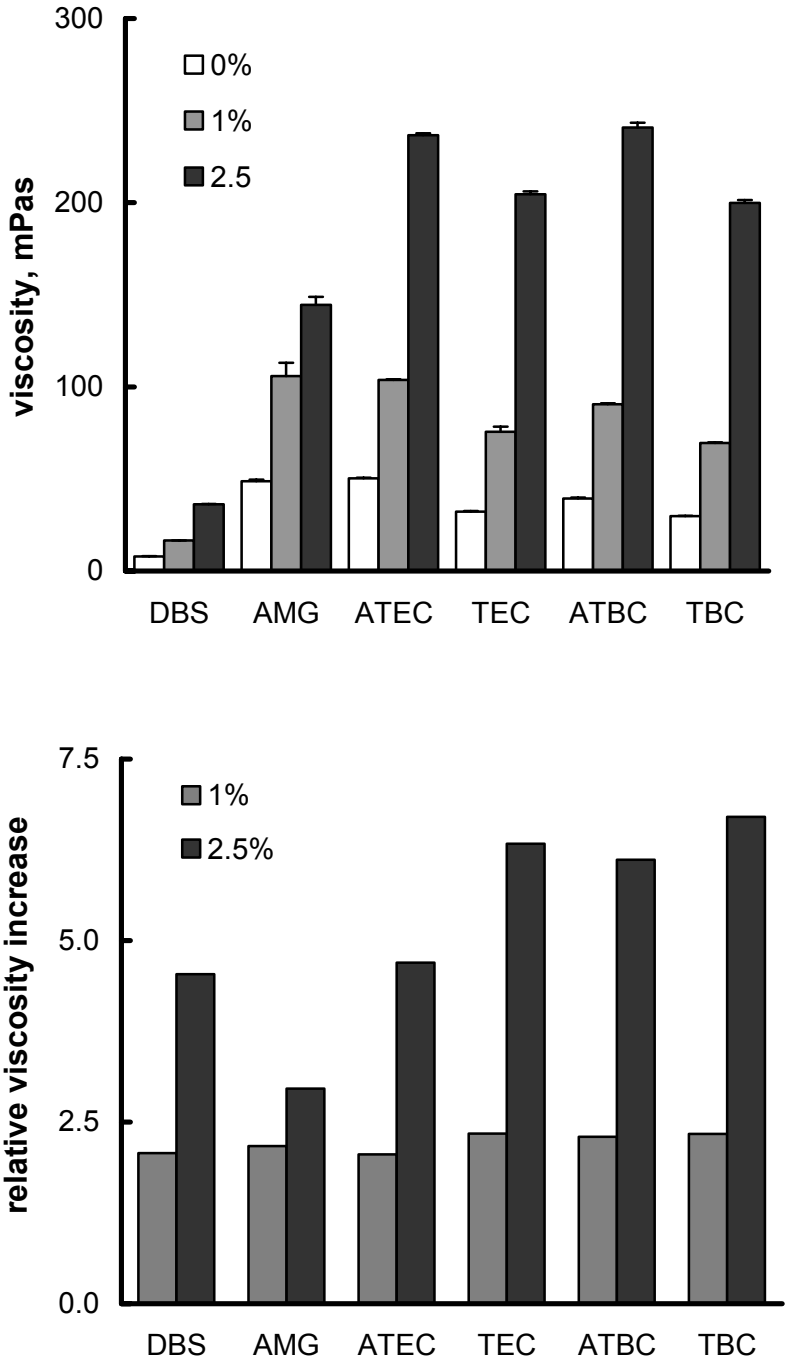

Figure 64 Polymer-plasticiser interaction quantitated by the viscosity increase of ethylcellulose dissolved in different plasticisers (polymer concentration: 0-2.5 % (w/w))

The mechanical properties of the polymer are crucial parameters affecting the deformation and hence the coalescence of the polymer particles. Plasticised ethylcellulose films exhibit lower puncture strength and modulus compared to unplasticised ethylcellulose films (Table 21). The percent elongation increased with increasing plasticiser efficiency and confirmed again the order with MCT < DBS < AMG < ATBC < ATEC < TEC < TBC.

Table 21 Mechanical properties of plasticised ethylcellulose films characterised by puncture strength, elongation an modulus at puncture (plasticiser content: 40 % (w/w) based on the formulation; EC 10 cp, cast from 10 % w/w chloroform solution)

Plasticiser	Puncture strength, MPa	Elongation, %	Modulus at puncture, MPa
none	8.6 ± 2.5	3.9 ± 1.7	219.9 ± 27
MCT	2.6 ± 0.1	16.0 ± 1.3	15.9 ± 3.6
DBS	0.8 ± 0.1	17.0 ± 2.2	4.9 ± 1.5
AMG	1.6 ± 0.1	17.8 ± 0.4	8.8 ± 1.3
ATBC	2.4 ± 0.1	18.0 ± 0.8	13.3 ± 3.5
ATEC	2.5 ± 0.0	20.0 ± 0.7	12.6 ± 1.0
TEC	1.6 ± 0.1	22.0 ± 1.5	7.1 ± 1.8
TBC	1.6 ± 0.1	24.7 ± 1.8	6.4 ± 2.1

Increasing plasticiser concentrations resulted in a decrease of the puncture strength and modulus at puncture (Fig. 65). The increase in percent elongation with increasing plasticiser concentration reflected the enhancement of flexibility of the films, which is crucial for the deformation and coalescence of the polymer particles.

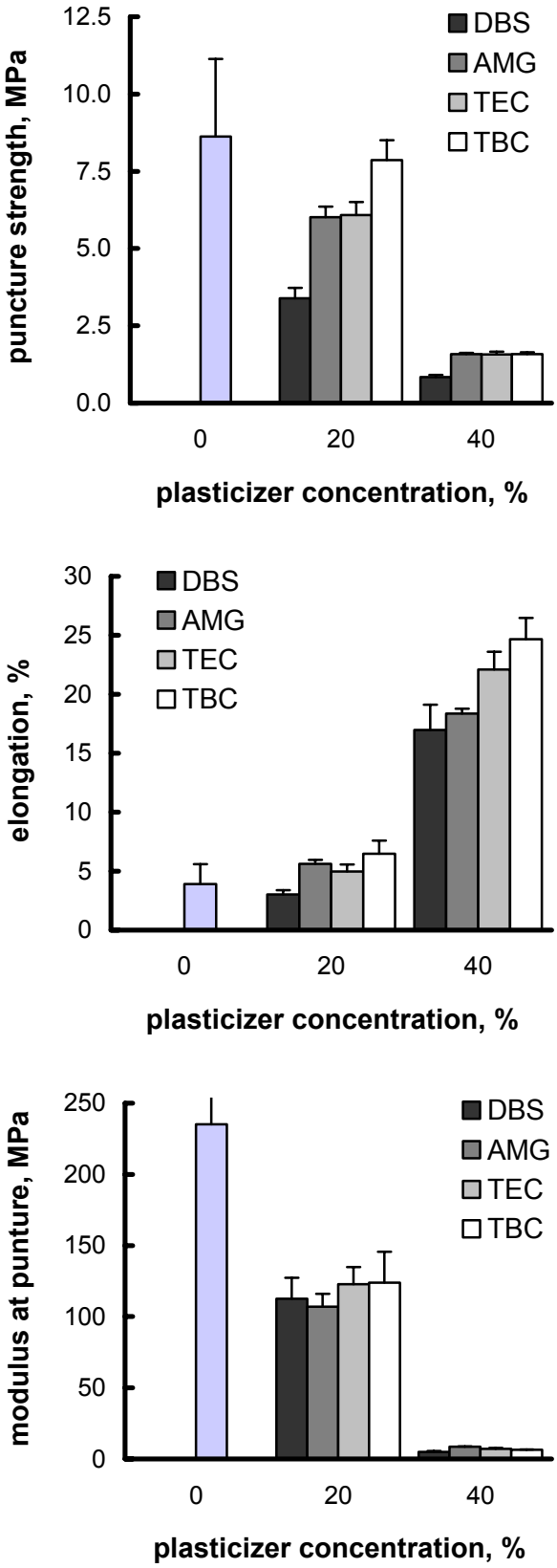

Figure 65 The effect of plasticiser concentration on the puncture strength, elongation and modulus at puncture of EC-films (plasticiser content: % w/w, based on the formulation; EC 10 cp, cast from 10 % w/w chloroform solution)

Polymers are viscoelastic materials and applied stress induces a combined response of elastic deformation and viscous flow (Eckersley and Rudin, 1990). The application of a sinusoidal stress on the films allows to resolve the response of the polymer sample into the in-phase elastic component E´ and the out-of-phase energy dissipative component E´´, which is related to the viscous property of the polymer (Lafferty et al., 2002; Rowe et al., 1984). The storage (elastic) and loss (viscous) modulus are obtained from dynamic mechanical measurements. The ratio of the loss and storage modulus, tan δ, provides crucial information about the more predominant property of the polymer. The measurements are especially useful if conducted over a temperature gradient, to reveal the thermal impact on the mechanical behaviour of the polymer.

Dynamic mechanical analysis (DMA) of plasticised ethylcellulose films proved the effect of the plasticiser on the modulus of elasticity of the polymer (Fig. 66A). The drop in the modulus of elasticity (corresponding the Tg) was shifted to lower temperature values with increased plasticiser efficiency during dynamic mechanical analysis (DMA) measurements. The plateau value of the modulus of elasticity of the polymer in the rubbery state decreased also with increasing plasticiser efficiency (Fig. 66A). AMG exhibited once more its poor plasticising property for ethylcellulose. The brittle films were already difficult to cut into the required shape and resulted in premature cracking of the film specimen during the measurement (as obvious from the tan δ curve (Fig. 66B)). AMG by virtue of its mixed composition may result in variable effects on the polymer.

The influence of the plasticisers on the modulus of elasticity and Tg of ethylcellulose films correlated well to the values determined by DSC (Table 20 vs. Fig. 66), with the exception of AMG due to the above mentioned reason.

The jump in the modulus of elasticity and thus the Tg of ethylcellulose was shifted to lower values also with increasing plasticiser concentration (Fig. 67). The modulus of the polymer in the rubbery state was further decreased. Moreover, the increased molecular mobility of the polymer resulted in a more pronounced β-transition (transition occurring at the second

highest temperature), visible in the tan δ curve, usually attributed to the motion of side chains (Lafferty et al., 2002; Menard, 1999).

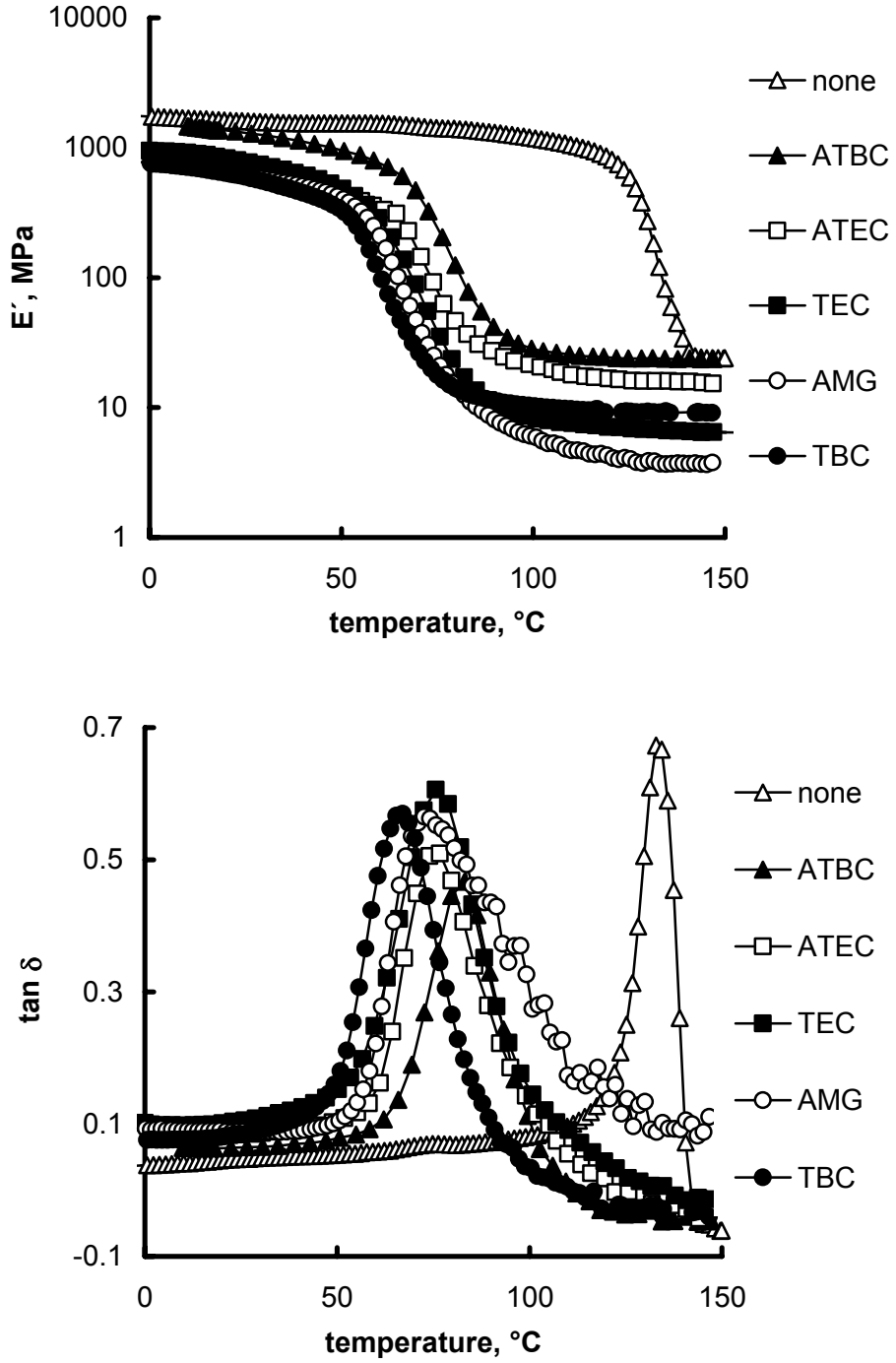

Figure 66 Effect of plasticiser type on the modulus of elasticity (E´) and tan δ of plasticised ethylcellulose films (plasticiser content: 20 % (w/w) based on the formulation; film thickness: 100-150 µm)

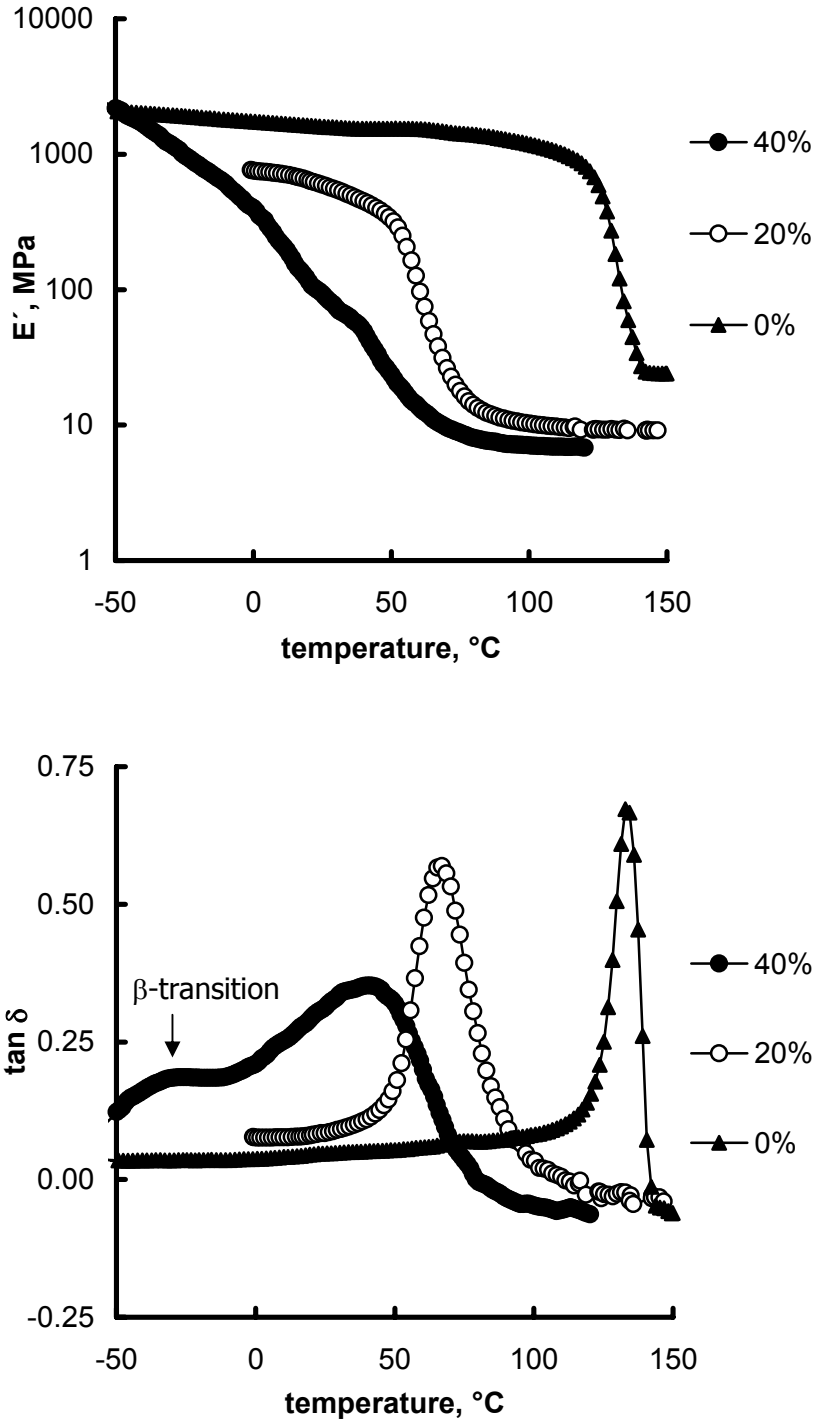

Figure 67 Effect of plasticiser concentration on the modulus of elasticity (E´) and tan δ of plasticised ethylcellulose films (plasticiser: TBC; film thickness: 100-150 µm)

The state of the polymer (e.g. glassy or rubbery) is essential for good film formation, but determines also the drug release, as the permeability of the polymer is different in the glassy and the rubbery state. DVS-measurements were conducted to estimate the state of the ethylcellulose coatings during drug release. The amount of adsorbed moisture, necessary to induce the change of the polymer from the glassy to the rubbery state was thus determined (Fig. 68). Glass transition of pure ethylcellulose happened after the uptake of 2.46 % (w/w) moisture, while in a mix of ethylcellulose with 50 % (w/w) TBC (based on the polymer amount) only 1.54 % (w/w) moisture was required. This is less than the expected value, if calculated from the moisture uptake of pure ethylcellulose. For ethylcellulose with 50 % (w/w) TBC based on the polymer, the ratio of ethylcellulose based on the total formulation is 66.7 %. Accordingly, 1.64 % (w/w) moisture uptake for the ethylcellulose part could have been expected. However, TBC was able to plasticise the polymer such, that a lower amount of moisture was sufficient to induce the glass transition. The change was observed at 79.1 % r.h. and 77.8 % r.h. for the unplasticised and plasticised ethylcellulose, respectively. Hence, the ethylcellulose coatings will undergo the same transition once they are in the release medium and the polymer will be in the rubbery state during drug release.

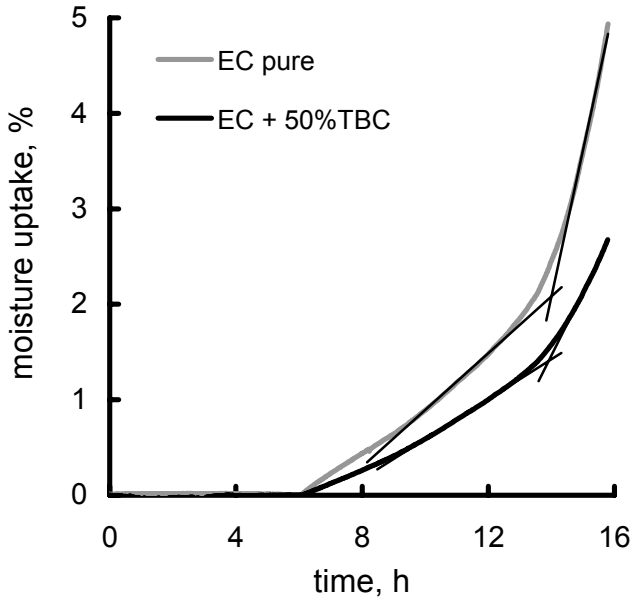

Figure 68 Moisture uptake measured by DVS of EC-films with and without 50 % TBC w/w, based on the polymer amount

The ranking of the effectiveness of the plasticisers was reflected in the drug release, too (Fig. 69). For the uncured pellets the drug release decreased with increasing plasticiser efficiency in the order of MCT > DBS > AMG > ATBC > TBC. Optimal plasticisers (e.g. TBC and ATBC) achieved extended drug release already without curing, thus confirming good film formation. Curing at 60 °C resulted in a decrease of the drug release for all formulations, even for those with non-optimal plasticisers (e.g. MCT, DBS and AMG).

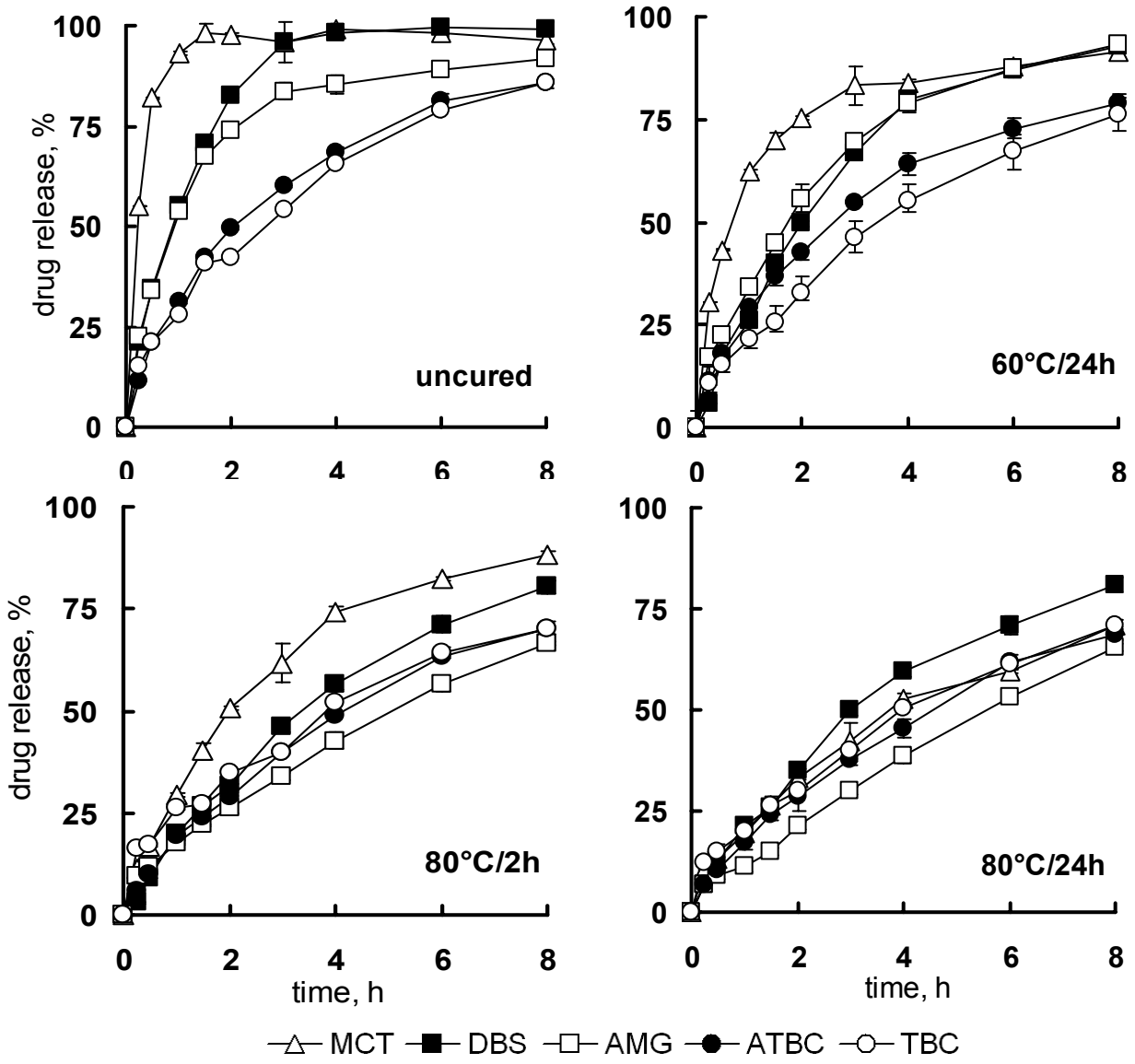

Figure 69 Effect of plasticiser type and curing condition on the drug release from DPC-coated pellets with ethylcellulose (coating level: 15 %; plasticiser: 50 % w/w, based on the polymer)

However, for TBC and ATBC no significant change in the release profile occurred compared to the uncured pellets. Curing at 80 °C for 24 h resulted in the limiting release profile for all formulations. Shorter curing time, e.g. 80 °C for only 2 h was also sufficient for most formulations (except MCT).

In general, higher plasticiser concentrations are required to achieve coalescence, if applying the coating polymer as distinct particles (e.g. aqueous dispersion or dry powders) in contrast to polymer solutions (Pearnchob et al., 2004a). The drug release of pellets coated with a plasticiser concentration of 50 % w/w based on the polymer was decreased for the uncured pellets and pellets cured at low temperature in comparison to only 40 % plasticiser concentration (Fig. 70), indicating an improved film formation.

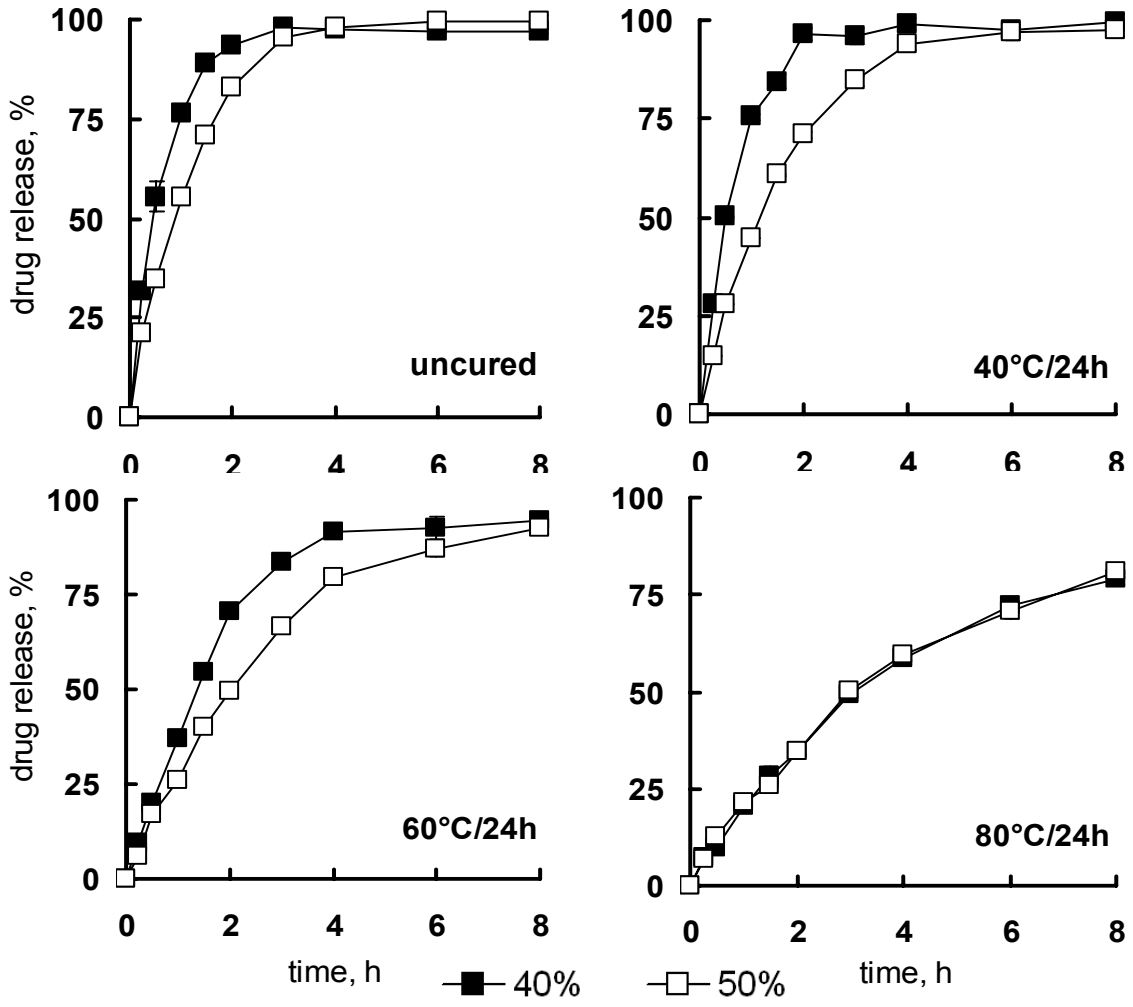

Figure 70 Effect of plasticiser concentration (w/w, based in the polymer) on the drug release from DPC-coated pellets with ethylcellulose (coating level: 15 %; plasticiser: DBS)

Curing at 80 °C for 24 h resulted in superimposing release profiles for both formulations, thus at this temperature coalescence occurred for both formulations.

Higher plasticiser content (e.g. 60 % w/w based on the polymer) resulted in sticking of the pellets during the coating process and even lump formation occurred. Thus, 50 % is the recommended plasticiser concentration.

The film formation process of dry powder coatings can be described more accurately to proceed by the following steps (Fig. 71): as the plasticiser is applied simultaneously with the polymer, the polymer is not homogeneously plasticised at the time point it hits the surface of the dosage form. However, as a solvent for the polymer, the plasticiser will be able to soften or even dissolve the surface of the particles. This facilitates the adhesion of the polymer to the surface of the substrate and the coalescence of the particles.

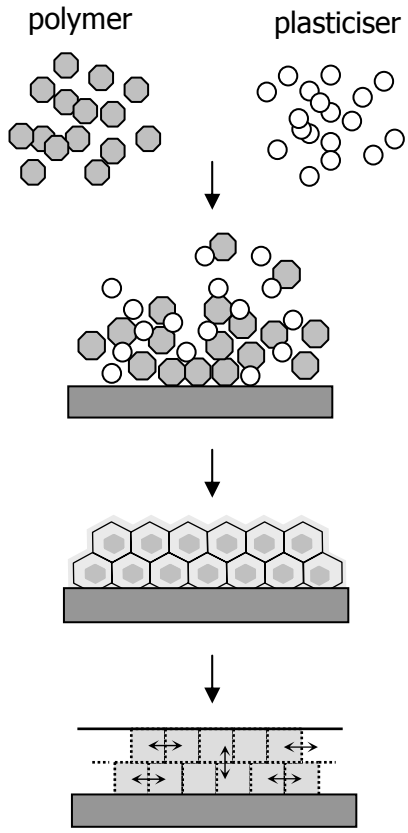

Figure 71 Mechanism proposed for the film formation by dry powder coating of solid dosage forms

A similar mechanism of film formation was described also for an aqueous dispersion of HPMCAS (AQOAT®). The particles size of the polymer in that system is around 5 µm, thus the film formation was assumed to be different from the mechanism proposed based on capillary forces (Nagai et al., 1997).

The viscosity and modulus of the polymer is also decreased by the plasticiser, enhancing the deformation and the resulting coalescence of the particles, as in general a softer polymer is able to deform and flow easier than a harder one (Keddie et al., 1995). The particles identity vanishes and the mechanical properties of the film strengthen upon the interdiffusion of polymer chains, as already described for the colloidal aqueous dispersions (Voyutsskii, 1958).

Further improvement of the film formation was expected with pre-plasticisation of the ethylcellulose powder. Different methods were investigated in comparison to the standard procedure with simultaneous application of the polymer powder and the plasticiser. Strongest improvement of the coalescence, observed by a decrease in the drug release, was achieved for the pre-plasticised ethylcellulose powders obtained by spray-drying (Fig. 72), whereas no film formation and thus no retardation of the drug release could be achieved for the hot melt extruded (HME) powder. Even after curing up to 80 °C for 24 h no retardation of the drug release occurred.

The lack in film formation was attributed to the particle size of the powder. Spray-drying of aqueous ethylcellulose dispersions, either of the pre-plasticised Surelease® or of Aquacoat® ECD after plasticisation resulted in a fine powder of a particle size comparable to the pure ethylcellulose powder, whereas the powder received after hot melt extrusion and cryogenic milling had a considerably bigger particle size (mean particle size: ethylcellulose: 2.8 µm, Surelease®: 3.1 µm, Aquacoat®: 2.0 µm, HME-powder: 27.3 µm). As the film formation from polymer particles is strongly influenced by the particle size, the deformation of the particles above a certain size may be insufficient to achieve coalescence (Dillon et al., 1951; Frenkel, 1945).

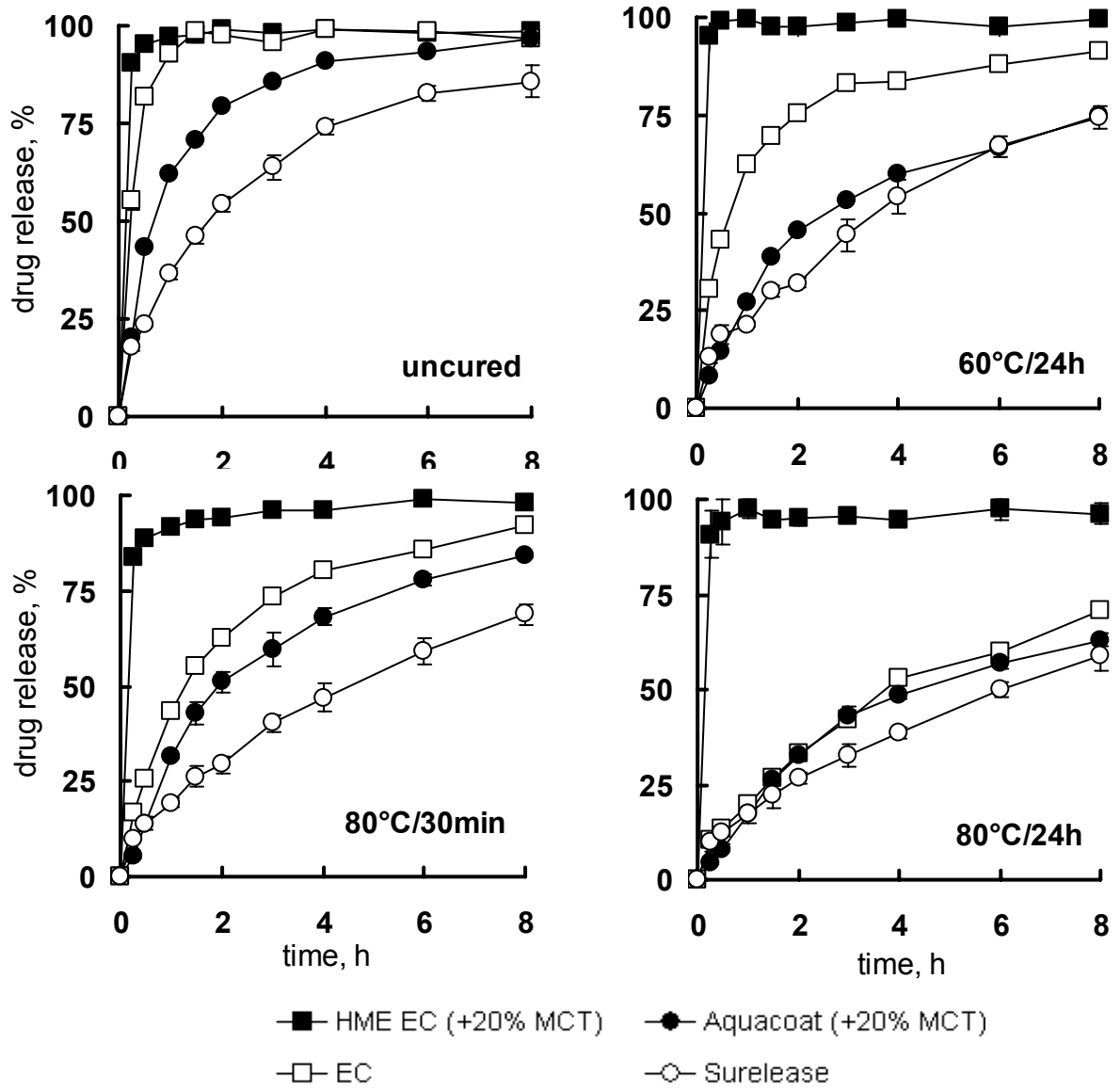

Figure 72 Effect of the preparation method of pre-plasticisation of ethylcellulose and curing conditions on the drug release of DPC-coated pellets with ethylcellulose (coating level: 15 %; plasticiser: MCT; total plasticiser content: 50 % w/w, based on the polymer)

Spray-dried Surelease® powder exhibited the best film formation already for the uncured pellets, as it showed the strongest retardation of the drug release (Fig. 72). This is in accordance to the reported fact, that Surelease® coatings are unaffected by curing (Ghebre-Sellassie et al., 1988; Porter, 1989; Shah et al., 1994).

SEM-pictures confirmed the difference in coalescence in dependence of the particles size (Fig. 73). Pellets coated with micronised ethylcellulose powder received by hot melt extrusion

exhibited a rough surface with distinct polymer particles. In contrast, the surface of the pellets coated with micronised ethylcellulose with simultaneous spraying of the plasticiser displayed a much smoother appearance, with no single polymer particles on the surface.

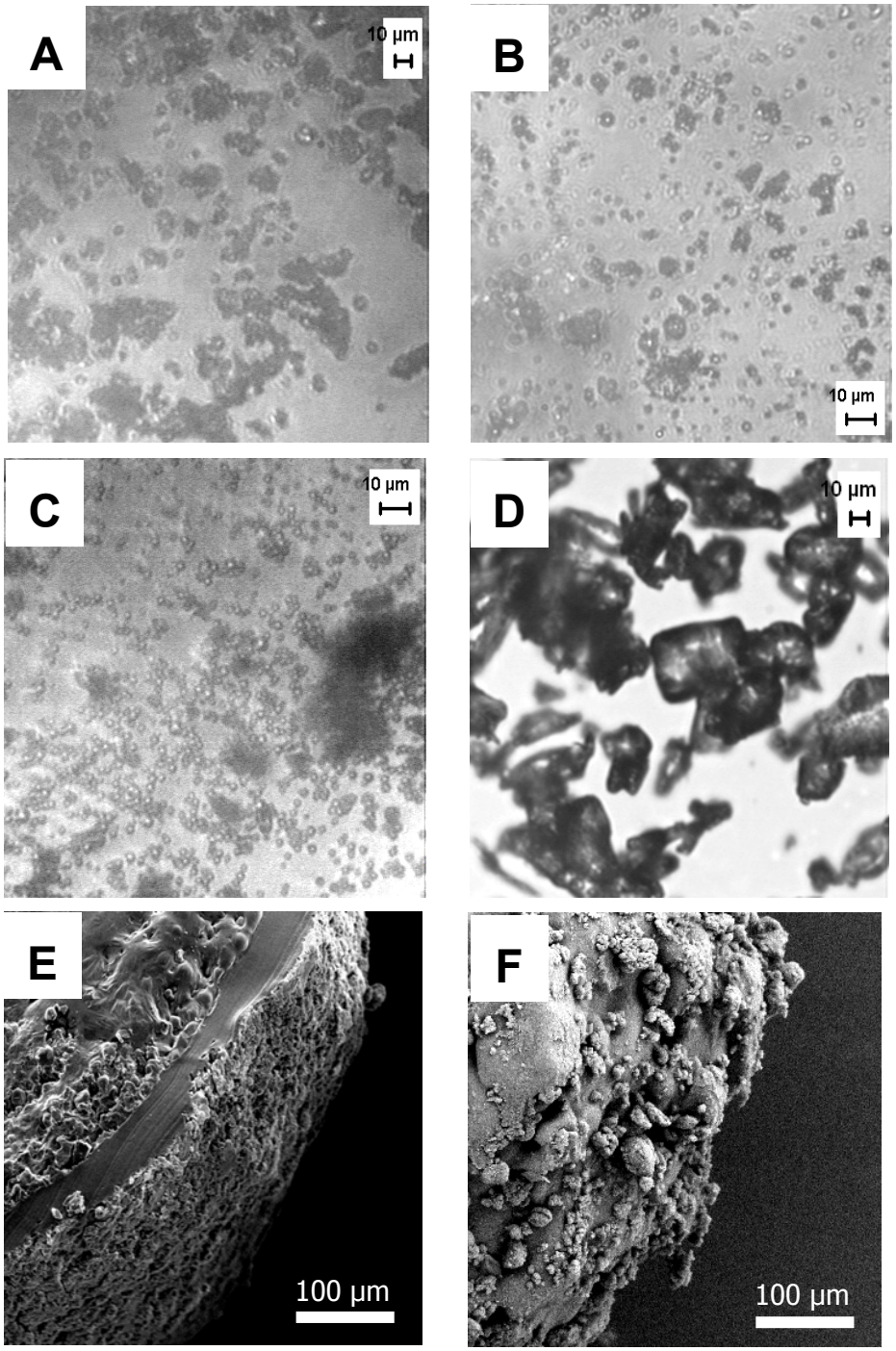

Figure 73 Optical microscopy of micronised pure EC (A), spray-dried Surelease powder (B), spray-dried Aquacoat powder containing 20 % w/w MCT (C), HME-EC after milling (D) and the appearance of DPC-coated pellets by ESEM with micronised EC (E) or micronised HME-EC (F)

3.5.2. Mechanism of film formation

a. Role of water for film formation

The most important aspect giving reason to criticism on dry powder coating was the use of water or aqueous binder solutions (Engelmann, 2004; Kablitz et al., 2006). These small amounts of water were introduced either as an emulsion with the liquid plasticiser together with a hydrophilic polymer (HPMC) as a binder in order to facilitate the adhesion of the polymer particles onto the substrate surface (Pearnchob and Bodmeier, 2003a; b; c), or it was sprayed after the coating during a curing step to induce the coalescence of the polymer particles(Obara et al., 1999). Heating alone was not sufficient to achieve film formation, especially for polymers with high glass transition temperature, such as HPMCAS or EC.

Table 22 Surface tension of water or water/plasticiser emulsions measure with a ring-tensiometer (plasticiser concentration: 50 % w/w, based on the formulation)

System	**surface tension, dyne/cm**		
H_2O	71.8 ± 0.3		
HPMC E5 – solution (10%)	45.6 ± 0.8		
Plasticizer	**pure**	**ratio 1:1**	**Δ**
TEC	35.9 ± 0.1	37.2 ± 0.2	1.3
ATEC	35.2 ± 0.1	36.0 ± 0.3	0.8
AMG	33.0 ± 0.5	34.6 ± 0.2	1.6
DBS	33.0 ± 0.1	33.5 ± 0.7	0.5
ATBC	32.0 ± 0.1	33.7 ± 1.1	1.7
TBC	31.8 ± 0.1	33.0 ± 0.1	1.2

Table 23 Contact angle of water or water/plasticiser emulsions on ethylcellulose films (plasticiser concentration: 50 % w/w, based on the formulation)

System	Contact angle, °		
H_2O	74.7 ± 1.7		
HPMC E5 – solution (10%)	67.0 ± 2.2		
Plasticizer	**pure**	**ratio 1:1**	Δ
TEC	39.7 ± 1.2	47.0 ± 2.9	7.3
ATEC	37.7 ± 1.2	41.0 ± 0.7	3.3
AMG	37.0 ± 0.8	40.3 ± 1.1	3.3
DBS	34.0 ± 1.9	39.0 ± 1.6	5.0
ATBC	32.5 ± 1.1	39.0 ± 2.3	6.5
TBC	31.2 ± 0.8	36.8 ± 1.9	5.6

Emulsions of the plasticisers with aqueous HPMC-solutions resulted in decreased surface tensions (Table 22). The capillary pressure of these systems is thus lower, leading to unfavourable conditions for coalescence. Moreover, the contact angle of the emulsions on ethylcellulose was increased compared to the pure plasticisers, resulting also in a poorer wetting of the polymer powder (Table 23). Thus, the polymer-plasticiser interaction is hampered, resulting also in a less effective coalescence. Applying the pure plasticiser during coating will insure superior plasticisation of the polymer.

Film formation can be achieved without the use of additional water not only for Eudragit® RS, a polymer of low Tg (58 °C) but also for ethylcellulose (Tg: 133 °C) under optimal formulation and process parameters (Fig. 74).

The drug release was comparable to the coated pellets without the application of water. Most importantly the applied temperature, either during coating or curing, needs to be above the Tg of the polymer, to induce the viscous flow of the particles to coalesce. In general that

means to be 10-50 °C above the Tg (Cerea et al., 2004; Engelmann, 2004; Kablitz et al., 2006; Pearnchob and Bodmeier, 2003a; c).

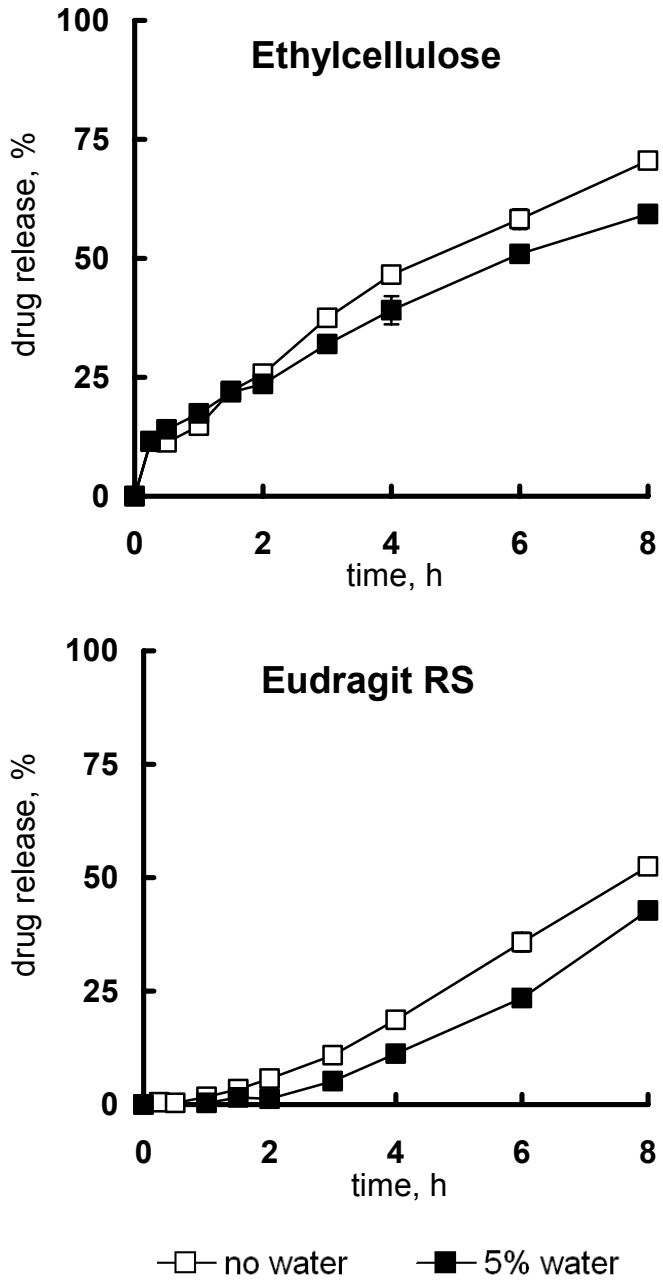

Figure 74 Effect of water on film formation and drug release from DPC-coated pellets (coating level: 15 %; curing: EC: 80 °C/24 h; Eudragit® RS: 60 °C/2 h; release medium: pH 6.8)

DMA-measurements supported the results. The modulus of elasticity (E´) of unplasticised films of Eudragit® RS is lower than of ethylcellulose (Fig. 75). However, ethylcellulose with 20 % (w/w) TBC yielded in a comparable modulus of elasticity in the rubbery state as pure Eudragit® RS. This confirms that with the appropriate type and amount of plasticiser ethylcellulose can acquire similar mechanical behaviour as Eudragit® RS and film formation gets possible.

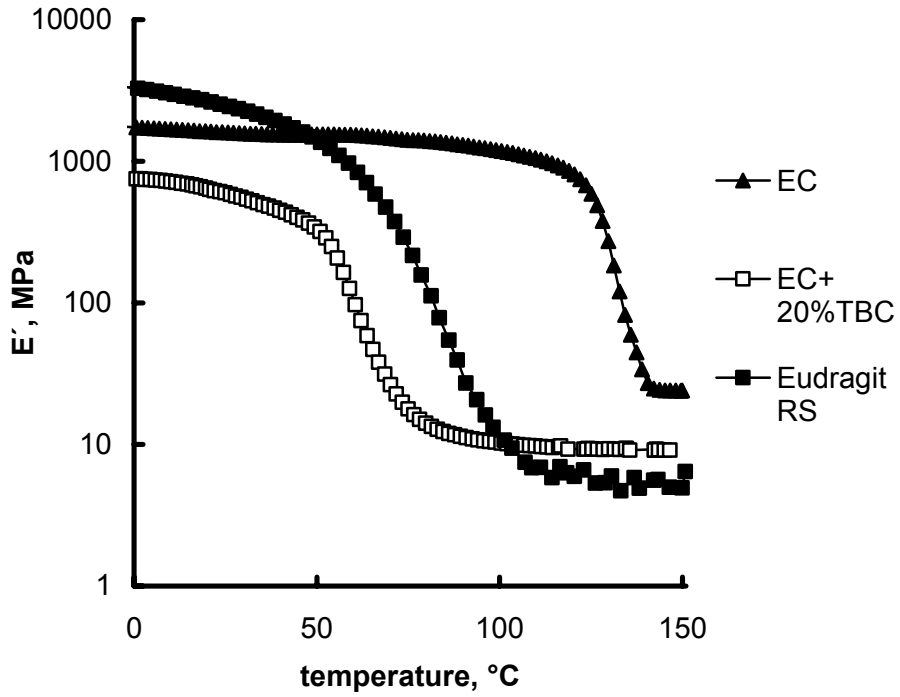

Figure 75 Modulus of elasticity (E´) of ethylcellulose with or without plasticiser vs. Eudragit® RS-films (plasticiser: 20 % TBC w/w, based on the formulation; film thickness: 100-150 µm)

b. Formulation and process parameters

In the past, uncured pellets coated by dry powder coating resulted in porous, non-homogeneous films with fast drug release (Cerea et al., 2004; Kablitz et al., 2006; Pearnchob and Bodmeier, 2003a; c). Neither extended release nor gastric resistance or taste masking could be achieved even for drugs of low or moderate solubility (e.g. theophylline

and propranolol HCl) without a thermal after-treatment (curing) at elevated temperatures. The formation of a dense, continuous film was only achieved after curing. However, a porous film is not able to effectively retard the release of a freely soluble drug.

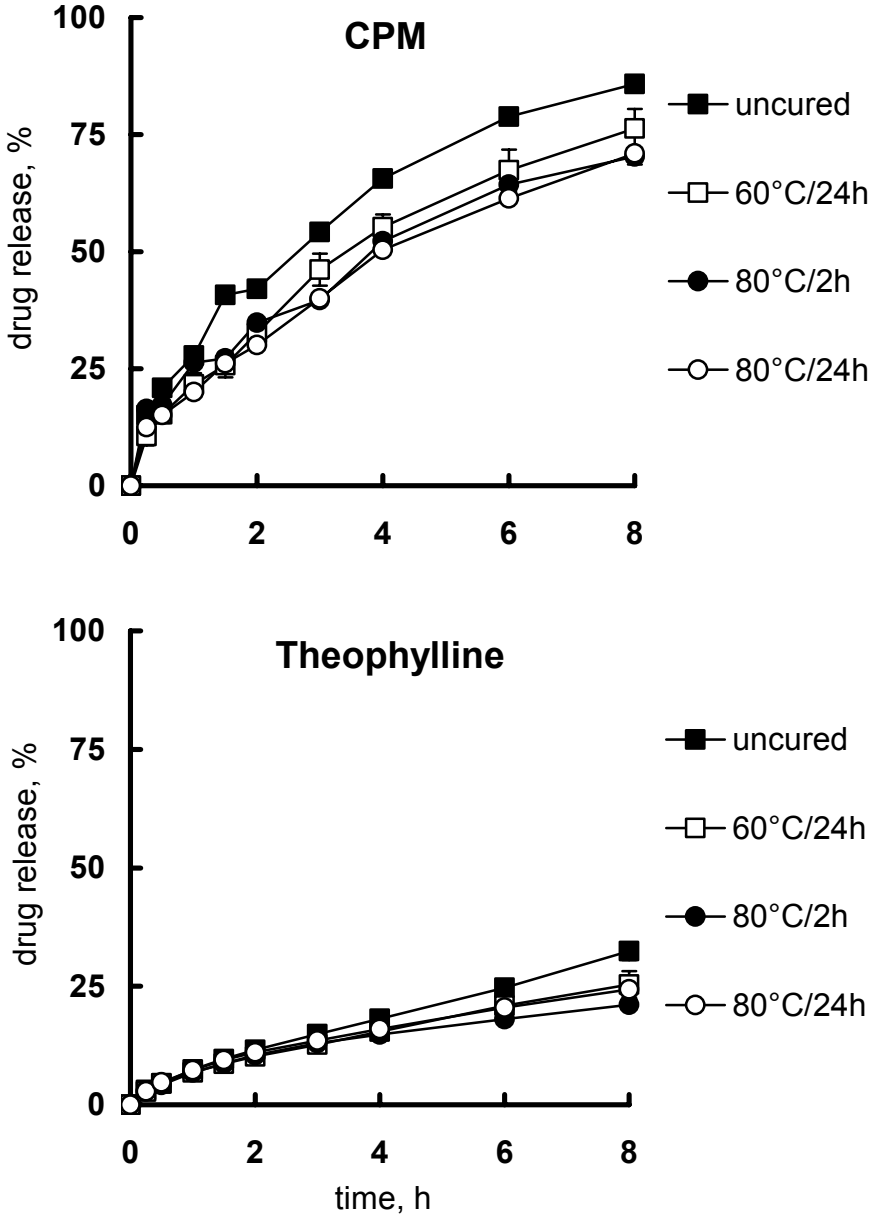

Figure 76 Effect of drug solubility on the drug release from DPC-pellets with ethylcellulose (coating level: 15 %; plasticiser: 50 % TBC w/w, based on the polymer)

To challenge the performance of coatings applied by dry powder coating, CPM, a freely soluble drug was used as model (solubility in pH 7.4: 562 mg/ml (Bodmeier and Paeratakul, 1991)). The drug release was enhanced compared to theophylline, a slightly soluble model

drug (solubility in pH 7.4: 12.0 mg/ml (Bodmeier and Chen, 1989)) (Fig. 76), but extended release was achieved for CPM already at coating levels of 15%. No further retardation of the drug release was achieved with curing, even at 80 °C for 24 h. TBC, which was used as plasticiser here, is a one with optimal efficiency for ethylcellulose (Terebesi and Bodmeier, 2006b).

The coalescence and film formation of pellets coated by dry powder coating was confirmed by ESEM-pictures. The cross section of the coated pellets proved, that a dense, continuous film was formed and the former distinct particles were coalesced (Fig. 77A).

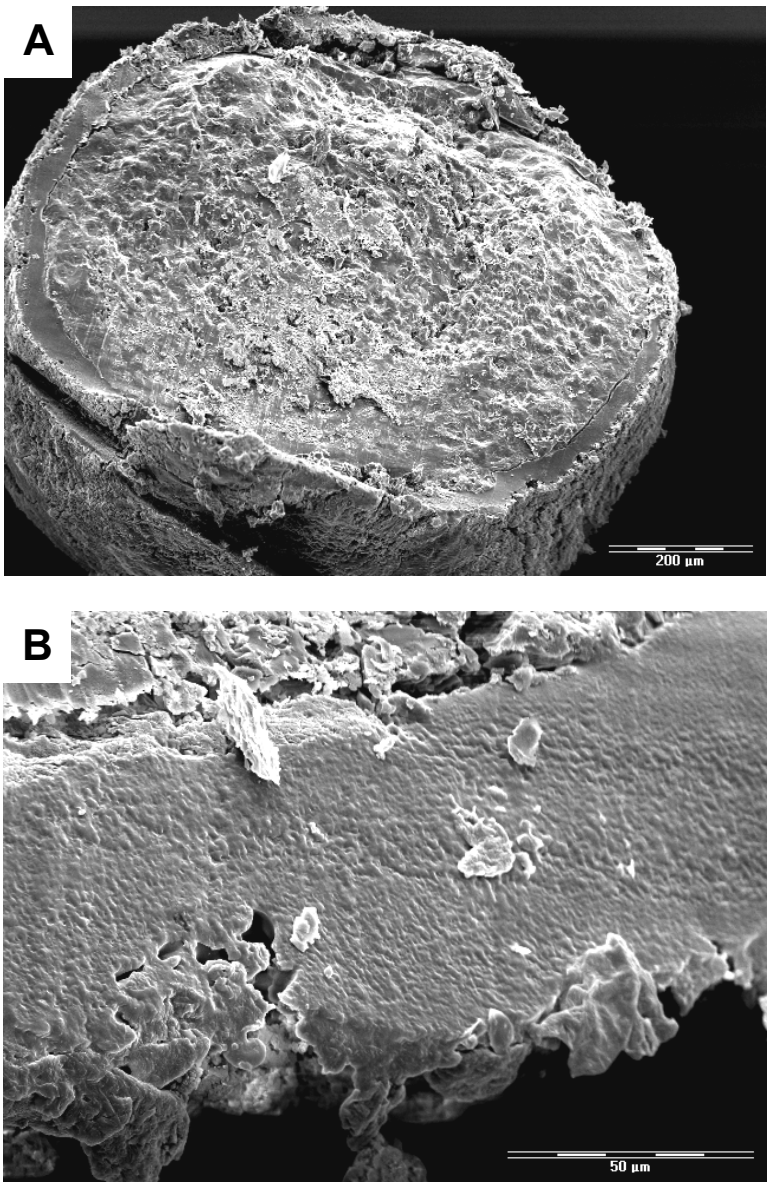

Figure 77 ESEM-pictures of DPC- pellets with ethylcellulose: A: cross-section; B: magnification of the coat (coating level: 15 %; plasticiser: 50 % TBC w/w, based on the polymer)

The shape of the initial single particles was not visible any more throughout the film, even at high magnification (Fig. 77B). However, due to the random deposition of the polymer particles on the surface of the dosage form imperfections may occur, which can result in a varying thickness of the film.

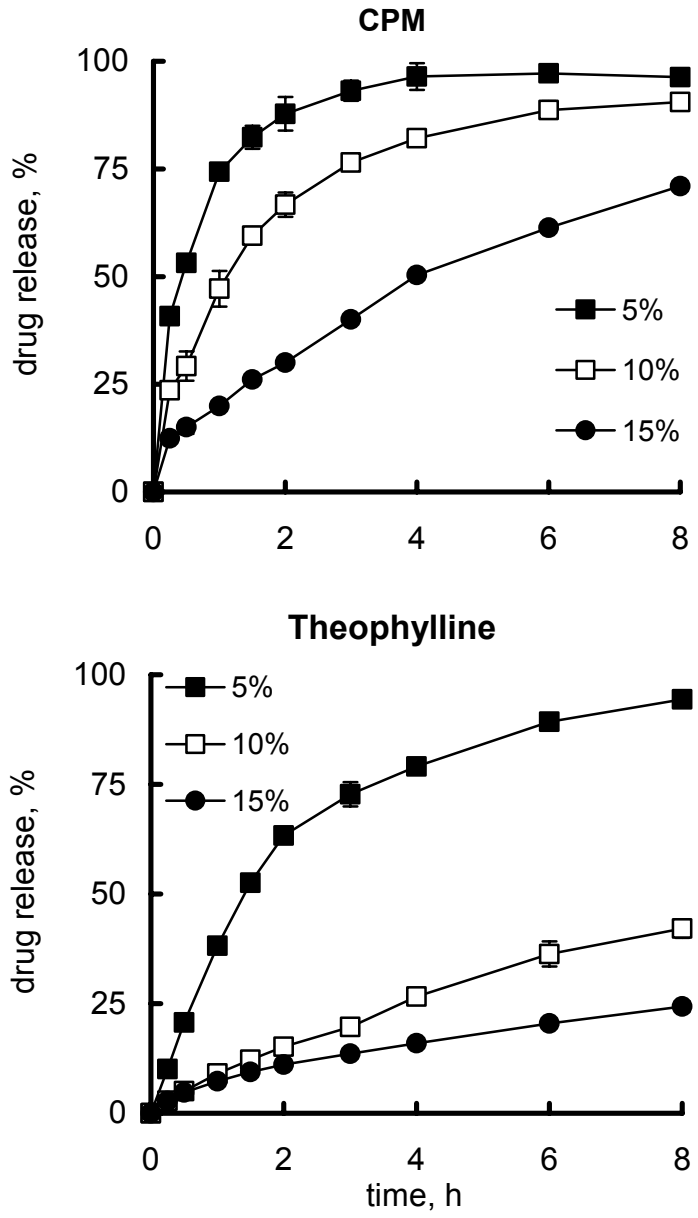

Figure 78 Drug release from DPC- pellets with ethylcellulose in dependence of the coating level (plasticiser: 50 % TBC, based on the polymer; curing: 80 °C/24 h)

Extended drug release could be obtained for theophylline already at a coating level of 10 %, while to achieve a similar release profile for CPM 15 % was required (Fig. 78). CPM was released with an initial burst, which was reduced to ~12.5 % at a coating level of 15 % and was followed by a zero-order release kinetic. In conclusion, extended release can be achieved for drug of varying solubility (slightly to freely soluble) at comparably low coating level between 10 and 15 %.

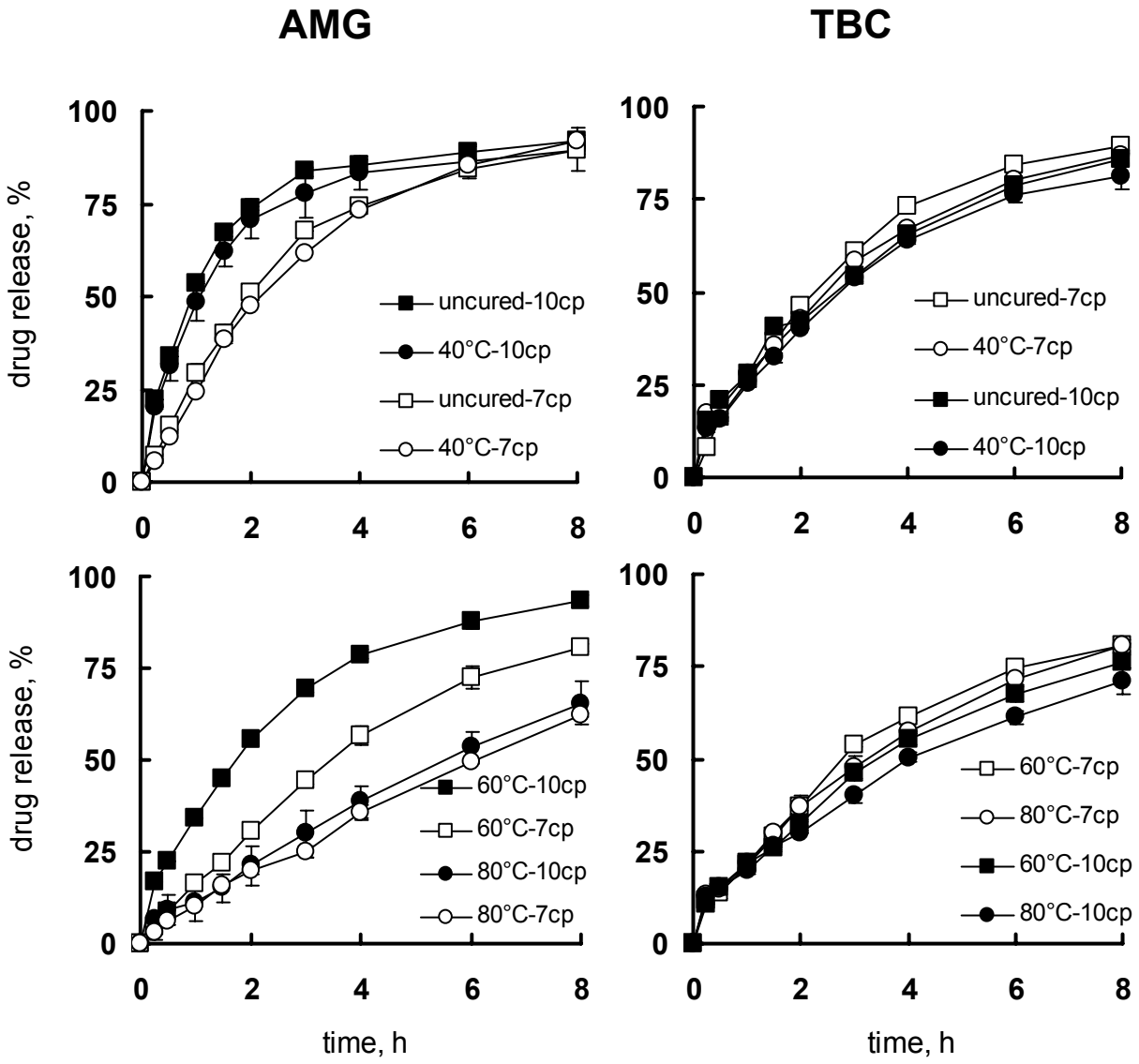

Figure 79 Effect of the viscosity of the polymer on the drug release from uncured and cured DPC-pellets (plasticiser: 50 % w/w, based on the polymer; curing time: 24 h)

Based on the mechanism of coalescence, the extent of film formation is mainly influenced by the viscosity and the particle size of the polymer (Dillon et al., 1951; Frenkel, 1945). The viscosity can be reduced by plasticisers or at elevated temperature, but is also dependent on the molecular weight of the polymer. Increasing chain length results in an increased viscosity and tougher films with higher yield strength, whereas lower permeability (DOW, 1998). The change of the ethylcellulose powder from a nominal viscosity of 10 cP to 7 cP remarkably improved the film formation and reduced the drug release, even if AMG was used, one of the less effective plasticiser for ethylcellulose (Fig. 79).

The already visible difference for the uncured pellets was even higher after curing at 60 °C. For curing at 80 °C, the limiting release profile was obtained independent of the polymer viscosity. The results were different, if a plasticiser with optimal performance was used. TBC resulted in extended drug release already for the uncured pellets. Curing, even at 80°C, could not decrease the drug release more than 15% compared to the uncured pellets, confirming a very good initial film formation during the coating process. Moreover, the higher permeability of the polymer with decreasing viscosity seems to get more relevant, as the drug release was always a bit faster for the lower viscosity formulation (Fig. 79).

Ethylcellulose often results in very impermeable coatings, especially for drugs of low solubility. Water soluble polymers such as HPMC are often added as pore formers to enhance the drug release from ethylcellulose coated dosage forms (Bodmeier et al., 1997; DOW, 2004; Wheatley and Steuernagel, 1997). However, if used with aqueous dispersions, HPMC may induce flocculation of the dispersion (Bodmeier et al., 1997; Wong and Bodmeier, 1996). Moreover, the viscosity of the system may increase to a range, were the subsequent spraying gets difficult.

Dry powder coating would avoid these problems, as both polymers are in the dry state during this process. Micronised HPMC with 20 % in a mixture of ethylcellulose increased the drug release of theophylline only slightly for the uncured pellets and those cured at 60 °C for 24h (Fig. 80). This confirmed a still excellent film formation in spite of the increased particle size of the HPMC compared to the pure ethylcellulose (13.3 µm vs. 2.8 µm).

Pellets cured at 80 °C for only 30 min already resulted in the same release profile as pure ethylcellulose coated pellets. With 33 % HPMC in a mixture with ethylcellulose the drug release was significantly increased, without being further decreased upon curing.

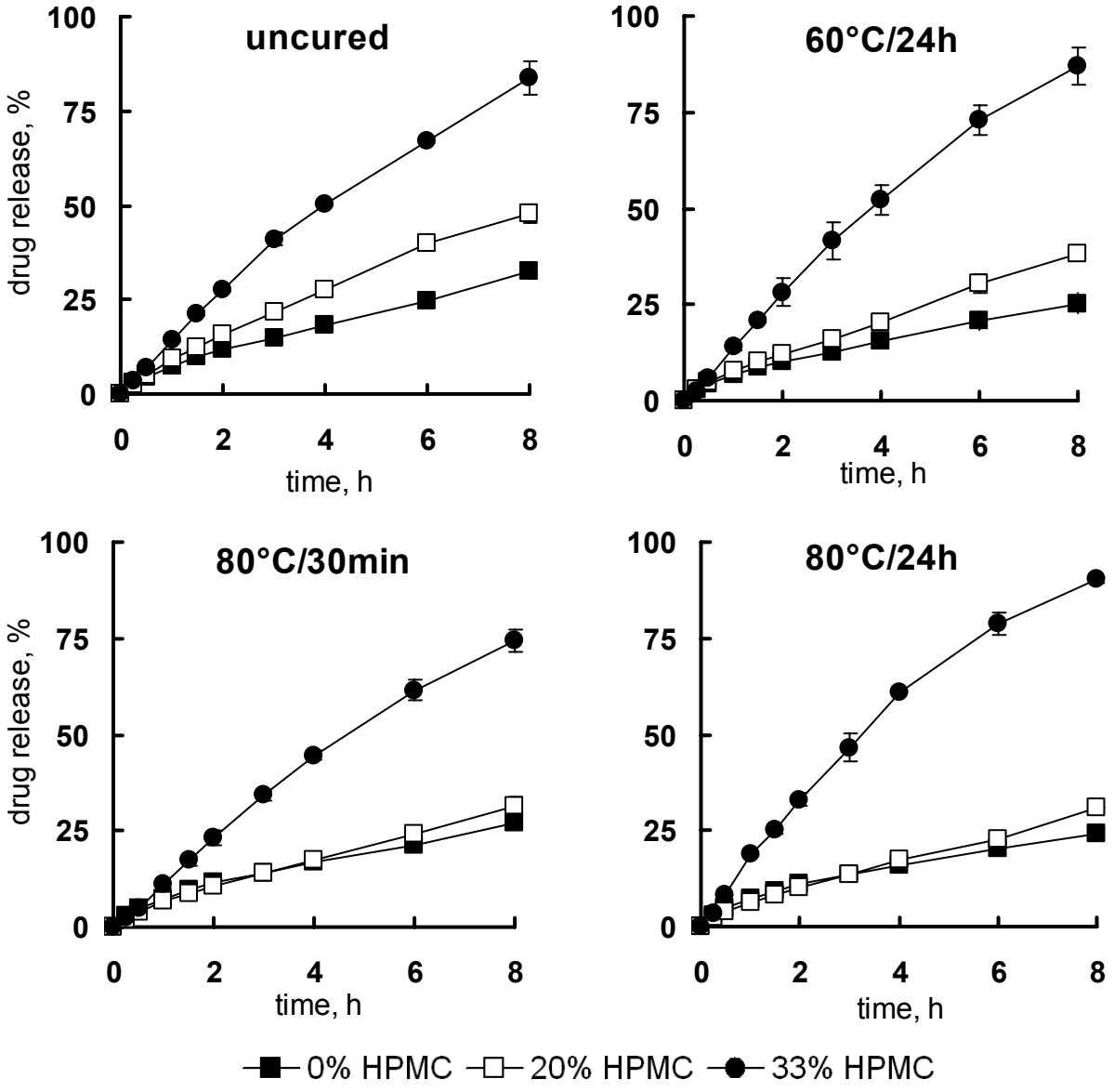

Figure 80 Influence of HPMC as pore former on the drug release of DPC-pellets with ethylcellulose (coating level: 15 %; plasticiser: 50 % TBC w/w, based on the polymer)

The results confirm the theory that considerable increase of the permeability of ethylcellulose films by high molecular weight water-soluble polymers such as HPMC occurs only above a certain critical HPMC-concentration of about 24% (Lindstedt et al., 1989; Lindstedt et al.,

1991). Below this critical concentration the leaching of the large HPMC-molecules is insufficient to build pores, and thus no effect can be observed during the drug release.