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Research paper

The role of capillary force promoters in dry coating procedures – Evaluation of acetylated monoglyceride, isopropyl myristate and palmitate

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ABSTRACT

Previous studies described several dry powder coating procedures. Most of these techniques used polymer powders and plasticizers for attaining film formation. Thermo analytical methods showed that some of the used plasticizers did not reduce the glass transition temperature of the polymer markedly and consequently did not act as a plasticizer in a typical way. Further studies suggested that these substances were promoting capillary forces between the polymer particles thereby promoting the adhesion of the polymer on the cores and enhancing the coating efficiency. In this study these substances will be called capillary force promoters (CFP). The aims of this study are to evaluate the effectiveness of acetylated monoglyceride, isopropyl myristate and palmitate in terms of coating efficiency enhancement and to shape the idea about the way of action of CFPs in dry coating procedures. One of the main features of a good CFP represents its ability not to be taken up by the polymer but to remain on the polymer's surface being able to build up interparticle capillary forces. A CFP is further characterised by a good spreadability on the polymer. In this context, the lowering of the glass transition temperature has been found to be a good indicator for the affinity of the CFP to the polymer and its uptake by the polymer, whereas the contact angle between the polymer and the CFP represents a measure of its spreadability.

1. Introduction

To control drug release from solid pharmaceutical dosage forms polymer-based film coatings have been used since the 1950s [1,2]. Besides aqueous and organic solutions, aqueous dispersions of the film forming polymer are in use [3,4]. Obara et al. [5] were the first who put the idea of a water and solvent less coating process into practice. Their initial approach was modified by Kablitz et al. [6]. They used hydroxypropylmethylcellulose acetate succinate (HPMCAS) as enteric resistant polymer. Other groups developed different dry coating procedures [7,8] using also other polymers as film formers, for example ethylcellulose or methacrylic acid derivatives. However, many of these techniques cannot disclaim of water completely [9,10].

Irrespective of which coating procedure is applied, usually plasticizers are required in order to reduce the glass transition temperature (T_g) of the polymer and consequently the brittleness of the polymeric films [3]. Kablitz et al. [6] used triethyl citrate (TEC) as plasticizer.

In addition to the plasticizer, Obara et al. [5] suggested the use of a second liquid component for the dry coating process reducing the contact angle of the liquid on the polymer thereby increasing spreadability and promoting capillary forces between the polymer particles and the core, finally leading to enhanced attachment of the polymer particles on the core and enhanced coating efficiency. They found a reciprocal relation between the contact angle and the coating efficiency which seems to be reasonable. However, this dependence was not confirmed by Kablitz [11]. She postulated that the major criterion for a high coating efficiency is a poor miscibility of the liquid additive and the film forming polymer, because poor solvents are not likely to be taken up into the polymer particles but to remain on their surface instead, building up interparticle capillary forces. In this study, these substances will be called capillary force promoters (CFP). The liquid additive used by Kablitz [11] was Myvacet® 9–45 K, a mixture of acetylated monoglycerides. By atomic force microscopy (AFM) Kablitz et al. [12,13] demonstrated that the adhesion forces between the polymer particles were enhanced and the coating efficiency was increased when using Myvacet® 9–45 K in addition to the plasticizer. Furthermore, it was demonstrated that Myvacet® 9–45 K did not influence the T_g of the polymer [12], so it has not the function of a plasticizer. According to this Myvacet® 9–45 K may act as a capillary force promoter (CFP) for the dry coating process.

The aims of this study are to evaluate the effectiveness of the acetylated monoglyceride Myvacet® 9–45 K, isopropyl myristate (IPM) and isopropyl palmitate (IPP) in terms of coating efficiency enhancement and to shape the idea about the way of action of CFPs

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in dry coating procedures. Some criteria for valuable CFPs are known by the literature [5,9,11,14,15]. First, the substance has to be toxicologically inert. Furthermore, the substance has to be miscible with the plasticizer. The esters of propane-2-ole with fatty acids, IPM and IPP, fulfil the abovementioned criteria. IPM and IPP are liquid waxes, they are lipid-like liquids, which are miscible with oils. Because of the small propane-2-ole part these esters show more polarity than esters of fatty alcohols. Thus they are miscible also with some polar substances, for example ethanol or TEC. So we tested them in the dry coating process and compared them with Myvacet® 9–45 K which has been used by Kablitz [11] in terms of dissolution behaviour and coating efficiency.

2. Materials and methods

2.1. Materials

Hydroxypropylmethylcellulose acetate succinate (HPMCAS, AQOAT® Type MF, Shin-Etsu Chemical Co., Niigata, Japan) was used as enteric film former. Theophylline pellets were donated by Klinge Pharma, Muenchen, Germany. Triethyl citrate (TEC) was purchased from Merck KgaA (Darmstadt, Germany). Myvacet® 9–45 K (Kerry Bioscience, Almere, Netherlands), isopropyl myristate and isopropyl palmitate (Cognis, Duesseldorf, Germany) were used as capillary force promoters (CFPs). Colloidal silicium dioxide (Aerosil® 200, Evonik Degussa GmbH, Essen, Germany) was used as glidant and anti-tacking agent.

Silica gel (Carl Roth GmbH + Co. KG, Karlsruhe, Germany), hydrochloric acid and tri-sodium phosphate dodecahydrate (Merck KgaA, Darmstadt, Germany) were obtained in analytical grade. Paraffin wax lozenges were obtained from Caesar & Loretz GmbH (Hilden, Germany). All these substances were used as received. Liquid nitrogen 5.0 was obtained by Linde AG, Pullach, Germany. Acetone pro analysis was purchased from Riedel de Haën (Seelze, Germany) and freshly distilled at 40 °C under vacuum before used.

2.2. Methods

2.2.1. Preparation of the TEC/CFP mixture

As liquids the pure plasticizer TEC, the pure capillary force promoters (CFP) and mixtures of both were employed in the process (Table 1). The liquid mixtures containing 70% (w/w) TEC and 30% (w/w) CFP were weighed and stirred by an automatic mixer.

2.2.2. Particle size measurements

The particle size distribution was determined using a Sympatec HELOS H1402 & RODOS Laser diffractometer (Sympatec GmbH, Clausthal-Zellerfeld, Germany). The powders were dispersed by compressed air of two bar.

2.2.3. Preparation of coated pellets

We used the dry coating method, which was developed by Kablitz et al. [6]. As cores theophylline pellets were used. Their diameter was between 0.8 and 1.25 mm. The process was carried out in a fluidized bed with a rotor insert (GPCG 1.1, Glatt GmbH, Binzen, Germany) together with a three-way nozzle aligned to the direction of the fluid bed (Fig. 1). The nozzle was connected with a twin screw powder feeder (K-Tron Soder K-CL-24-KT20, K-Tron, Gelnhausen, Germany). The HPMCAS powder was passed through the powder feeder to the three-way nozzle and applied simultaneously with the liquid TEC/CFP mixture through the nozzle.

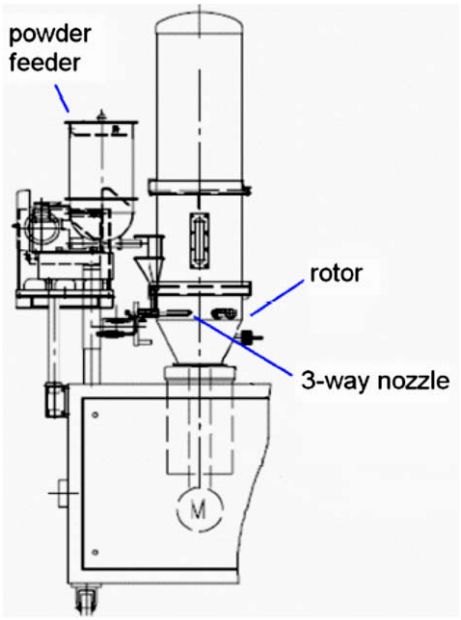

Fig. 1. Scheme of a rotary fluid bed type GPCG 1.1 modified from [11].

The coating process took 23 min and was conducted using a batch size of 1.0 kg. The following parameters were adjusted: inlet temperature: 26–28 °C, product temperature: 25–26 °C, outlet temperature: 24–25 °C, air flow rate: 70 m^3/h, rotor speed: 230 rpm, powder feed rate: 11.1 g/min, TEC/CFP mixture feed rate: 3.5 g/min. The coating level was 25% calculated by the weight of the pellets. The curing process took 45 min at a product temperature of 55–58 °C. The air flow rate was 120 m^3/h. Three batches of each composition (Table 1) were prepared.

2.2.4. Dissolution studies

Drug release was tested using the method A rotating paddle apparatus (DT 6 R, ERWEKA, Heusenstamm, Germany) according USP XXIX. The dissolution testing was carried out at a temperature of 37 ± 0.5 °C and a stirring rate of 50 rpm in 750 ml of 0.1 N HCl (pH 1) for 120 min and after addition of 250 ml of 0.2 M tri-sodium phosphate solution in order to increase the pH (pH 6.8) for further 60 min using approximately 40 mg pellets exactly weighed in each vessel. Samples were withdrawn every 3 min. The theophylline concentration was determined spectrophotometrically in flow-through cells (Lambda-2-Spectrometer, Perkin–Elmer, Ueberlingen, Germany) at λ = 272 nm. The drug release of six samples of each batch was determined.

2.2.5. Scanning electron microscopy (SEM)

The samples were frozen under liquid nitrogen and broken using a small hammer. Then the samples were fixed on a double-sided electroconductive adhesive tape, dried over silica gel for

Table 1
Compositions of coating formulations

Formulation	A	B	C	D	E	F	G
HPMCAS (%)	75.0	75.0	75.0	75.0	75.0	75.0	75.0
Plasticizer (%)	TEC 17.5	TEC 17.5	TEC 17.5	TEC 25.0	–	–	–
Capillary force promoter (%)	Myvacet® 7.5	IPM 7.5	IPP 7.5	–	Myvacet® 25.0	IPM 25.0	IPP 25.0

Fig. 2. TMA sample holder designed for measuring the T_g of a film on a pellet (in situ).

48 h and sputter-coated with gold during 180 s in an argon atmosphere using the Agar Sputter Coater B7640 (Agar Scientific Ltd., Stansted, UK). The scanning electron micrographs were taken using a LEO VP 1430 (Carl Zeiss NTS GmbH, Oberkochen, Germany) at 20 kV voltage under vacuum. The photographs were taken using a magnification of 500.

2.2.6. Differential scanning calorimetry (DSC)

Thermal investigations were performed using a DSC 821e with the Star^e-Software (Mettler Toledo, Giessen, Germany). Indium was used to calibrate the temperature and enthalpy reading according the manufacturers' instructions. The temperature ranged from −60 to +120 °C with a heating rate of 10 K/min. Every sample was heated up, cooled down and heated up again. Experiments were carried out in aluminium pans of 40 μl volume with a pierced lid. The nitrogen flow rate was adjusted to 50 ml/min. The samples' weight was approximately 6 mg, accurately weighed. However, the DSC traces of Fig. 3 are based on 1 mg sample weight in order to be comparable. Traces display the second heating step. Experiments were performed in triplicate.

2.2.7. Thermo mechanical analysis (TMA)

To determine the glass transition temperature (T_g) of the film on the coated pellets thermo mechanical measurements were conducted using a Mettler TMA40 with the Star^e-Software (Mettler Toledo, Giessen, Germany). Indium was used to calibrate the temperature reading according the manufacturers' instructions. The measurements have been carried out in triplicate under liquid nitrogen atmosphere over a range of −20 to 120 °C at a heating rate of 10 °C/min. The coated pellets were examined using a special sample holder (Fig. 2) to determine the T_g of the film on a pellet (in situ).

2.2.8. Calculation of the coating efficiency

The coating efficiency was calculated by dividing the actually achieved weight gain of the coated pellets by the theoretically achievable weight gain of the coated pellets.

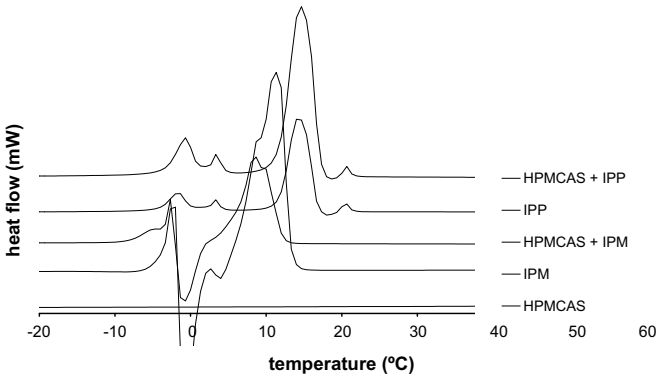

Fig. 3. DSC measurements of IPM and IPP and their mixtures (1:1) with HPMCAS as well as pure HPMCAS. Traces display the second heating step and are based on the sample weight. Mean of 3 measurements each.

2.2.9. Contact angle measurements

The contact angles of the plasticizers, the capillary force promoters and the mixtures of both on HPMCAS were determined using the sessile drop method. Tablets of HPMCAS (diameter: 13 mm, height: 1.4 mm, weight: 0.2 g) were compressed for 5 min using a hydraulic press (64 kp/cm^2, hydraulic IR press, PerkinElmer LAS (Germany) GmbH, Rodgau – Juegesheim, Germany). They were stored over silica gel for 48 h. Films of HPMCAS (thickness: 0.02 mm) were obtained by casting an organic solution of the polymer. A 2% HPMCAS solution was prepared by dissolving HPMCAS in freshly distilled acetone. The solution was poured out in Petri dishes and air-dried. The received films were stored over a mixture of silica gel and paraffin wax lozenges for 48 h.

The contact angles were determined using a drop-shape analysis system with the DSA1 software (DSA 100, Kruess GmbH, Hamburg, Germany). The liquid (2 μl) was placed on the tablet or the film using a micrometre syringe automatically navigated by the software and the contact angle was detected after 4 s by using the sessile drop method. Experiments with $n = 9$ were performed.

3. Results and discussion

The dry coating in the rotary fluid bed was performed based on the method developed by Kablitz et al. [6]. Hydroxypropylmethylcellulose acetate succinate (HPMCAS) was used as micronized powder. The mean particle size determined by laser diffraction was 4.8 μm. The pure material had a glass transition temperature (T_g) of approximately 110 °C.

The coating step of a dry coating process is characterised by the application of the polymer powder and the liquid plasticizer or plasticizer mixture on the cores. In terms of economy, the application of the coating material consisting of the polymer and the plasticizer or plasticizer mixture should be fast, the distribution of the coating material on the cores should be homogeneous and the loss of the coating material should be low. Especially with respect to the latter, forces between the cores and the polymer particles and between polymer particles and other polymer particles already attached to the cores have to be high. Capillary forces which are known to represent the strongest interparticle forces may be built by liquid bridges of the plasticizer or plasticizer mixture between two or more particles. However, because of the plasticizer's affinity to the polymer it may be absorbed by the polymer, so capillary forces may exist just for a short time. Contrarily, substances with low affinity to the polymer will be absorbed slowly if at all, thereby building up permanent capillary forces. As the alteration of the T_g is a measure for the miscibility of two components, the T_g may be taken as a measure for the affinity of a liquid to the poly-

Table 2
Melting enthalpies of the first melting peak of the second heating step of IPM and IPP and their mixtures (1:1) with HPMCAS based on the weight of the CFP and determined by DSC, $n = 3$, mean ± SD

Sample	Nominal melting enthalpies ($J\,g^{-1}$)
IPM	27.08 ± 3,93
IPM + HPMCAS	27.63 ± 0.80
IPP	24.59 ± 0.53
IPP + HPMCAS	24.61 ± 0.65

Table 3
Glass transition temperatures (T_g) of coating formulations A (HPMCAS/TEC/Myvacet® 9–45 K = 75/17.5/7.5), B (HPMCAS/TEC/IPM = 75/17.5/7.5), C (HPMCAS/TEC/IPP = 75/17.5/7.5) and D (HPMCAS/TEC = 75/25) determined by thermo mechanical analysis (TMA), $n = 3$, mean ± CI (95%)

Formulation	A	B	C	D
T_g (°C)	55.7 ± 2.7	51.5 ± 3.1	53.9 ± 1.9	51.7 ± 3.3

mer. So it is interesting to investigate the influence of liquids on the T_g of the polymer.

3.1. Differential scanning calorimetry (DSC)

Alteration of the polymer's T_g by any other substance can be tested by DSC measurements. Kablitz et al. demonstrated that Myvacet® 9–45 K had no influence on the T_g of HPMCAS [12]. One part of our investigation was to detect if isopropyl myristate (IPM) and isopropyl palmitate (IPP) act in the same way. So mixtures (1:1) of HPMCAS and IPM or IPP were measured by DSC. Differences in the T_gs (DSC traces not shown) are not obvious: HPMCAS/IPM mixture 105.0 ± 2.7 °C; HPMCAS/IPP mixture 105.5 ± 2.1 °C; pure HPMCAS 103.2 ± 1.6 °C (mean ± standard deviation). Furthermore, the thermograms of the pure liquids reveal some characteristic transitions including the melting peak (Fig. 3). This thermal behaviour does not differ significantly from the one of their binary mixtures with HPMCAS (Fig. 3). Calculating the melting enthalpies of the pure liquids and their mixtures with HPMCAS reveals that there is no marked difference either (Table 2). This demonstrates that interactions between HPMCAS and IPM or IPP do not exist and IPM and IPP may be suitable capillary force promoters (CFP).

3.2. Thermo mechanical analysis (TMA)

TMA measurements were performed to determine the T_g in situ, which means to determine the T_g of the dry coated film on the coated cores. For formulation D, containing the plasticizer triethyl citrate (TEC) but not CFP the T_g is 51.7 ± 3.3 °C (mean ± confidence interval). The T_gs of the other formulations (Table 3), which contain one of the CFPs in addition to the plasticizer TEC, are in the same range, differences are not perceptible. This is in good accordance to the DSC measurements and demonstrates, that the T_g of the polymer is influenced just by the plasticizer but not by the CFP. In consequence, the curing temperature of the dry coating process,

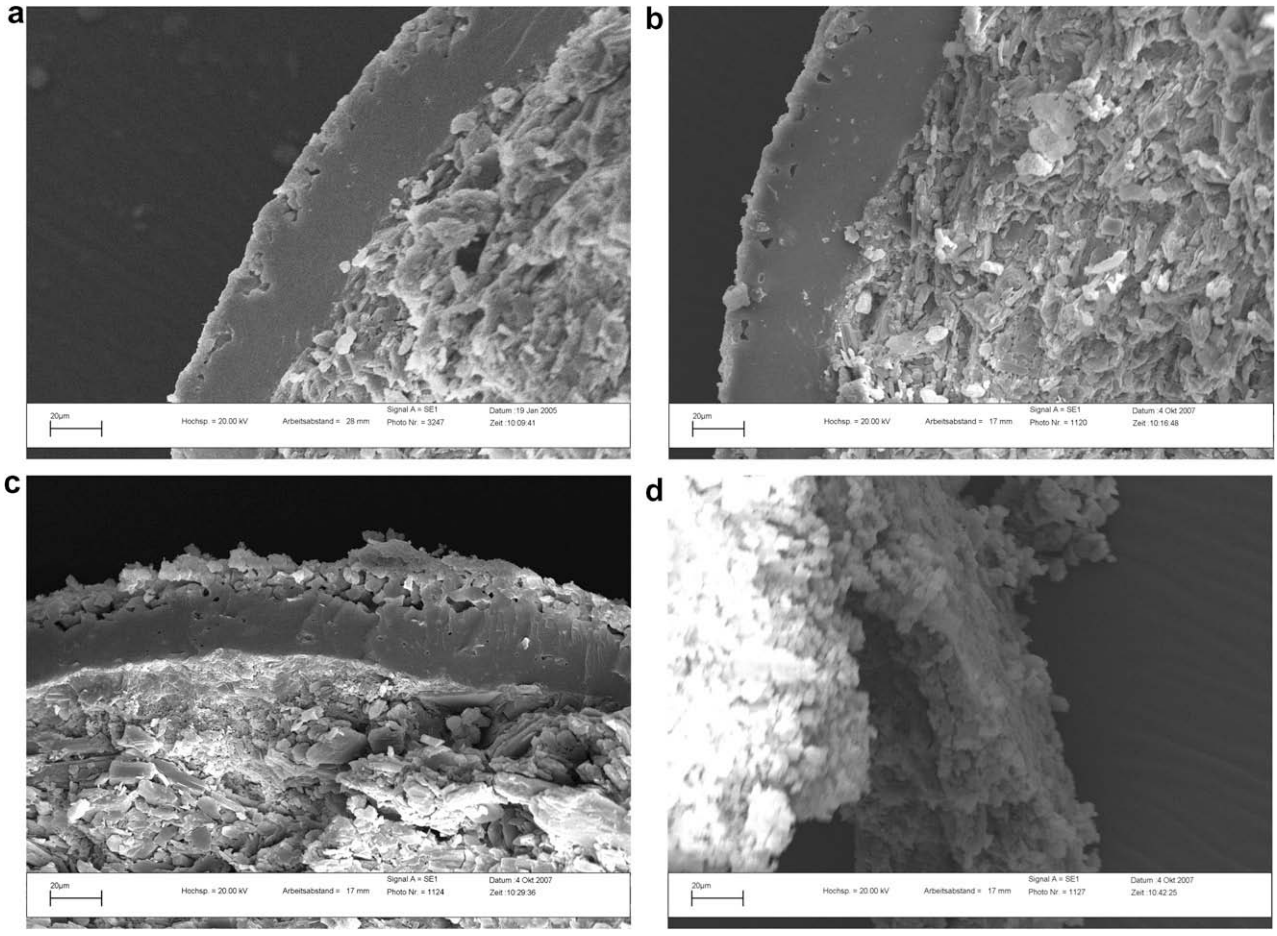

Fig. 4. Scanning electron micrographs of the cross-sectional of a dry coated pellet with (a) Formulation A (TEC 70%/Myvacet® 9–45 K 30%), (b) Formulation B (TEC 70%/IPM 30%), (c) Formulation C (TEC 70%/IPP 30%) and (d) Formulation F (IPM 100%).

ensuring the formation of a crackless film, depends on the plasticizer used but is independent of the CFP.

3.3. Scanning electron microscopy (SEM)

The morphology of the coated cores was observed using scanning electron microscopy (SEM). On SEM pictures of pellets coated with formulations containing TEC and CFP (formulation A, B and C) films can be detected easily (Fig. 4a–c). When using just a CFP without TEC, film formation is poor (IPM as example for a CFP, Fig. 4d): a huge amount of agglomerated but not coalesced polymer particles is perceptible.

3.4. Dissolution studies

Enteric resistance was investigated by dissolution testing. Enteric resistance is the most important quality of enteric resistant coated pellets. The dissolution test of the USP XXIX requires that enteric resistant articles do not release more than 10% of the drug during the first 120 min of the acid stage (pH 1). After addition of a buffer substance consisting of sodium phosphate, the whole drug has to be released within further 45 min. Formulations A, B and C fulfil these criteria (Fig. 5), the drug amounts dissolved at the acid stage after 120 min are 3.1 ± 0.9% (formulation A), 1.5 ± 0.5% (formulation B) and 2.0 ± 0.4% (formulation C). Drug release is completed within the following 35 min in the buffer stage. Moreover, the formulation containing TEC and no CFP (formulation D) meets the criteria of the USP (Fig. 6). In contrast, formulations E, F and G containing no TEC but a CFP (Fig. 6) do not show enteric resistance. Already during the acid state 100% of the drug is dissolved. Due to the absence of any plasticizing agent the T_g of HPMCAS was not reduced. Consequently, film formation was not accomplished, because the T_g of HPMCAS was higher than the curing temperature (55–58 °C). So, using solely CFP without plasticizer results merely in the agglomeration of the polymer particles. Concluding, the data of SEM measurements confirmed the dissolutions tests. Furthermore, these results indicate once more that CFPs do not act as plasticizers.

3.5. Coating efficiencies and contact angle measurements

The coating efficiency is an appropriate measure for the performance of any coating process. It indicates the loss of coating material during the coating procedure [16,17]. The coating efficiencies of formulations A, B and C containing plasticizer and CFP are similar to conventional coating methods (Table 4). Just the coating efficiency of formulation D, containing no CFP is quite low (72.5 ± 0.4%). Obara et al. [5] assumed that high contact angles of the liquid consisting of plasticizer or CFP or mixtures of both on the polymer result in a poor coating efficiency. They supposed that the coating efficiency decreases with the increase of the contact angle. Indeed, the pure plasticizer TEC has the highest contact angle (16.4 ± 1.1°) and the corresponding formulation D has the lowest coating efficiency. However, the contact angle of Myvacet® 9–45 K is not significantly lower than the one of TEC, but the coating efficiency is much higher (87.3 ± 1.0%). This indicates, that the contact angle is not the only factor influencing the coating efficiency, and contradicts the hypothesis of Obara et al. [5]. As already postulated by Kablitz [11] this is due to the fact that TEC is taken up by the polymer instead of remaining on its surface and building up capillary forces like Myvacet® 9–45 K. In order to evaluate whether the contact angle might be an appropriate indicator of the coating efficiency within the group of the CFPs, that is characterited by not affecting the T_g of HPMCAS and that is supposed not to be taken up by the polymer, contact angles and coating efficiencies of several CFPs mixed with TEC have been compared. The TEC/Myvacet® 9–45 K mixture (70/30) exhibits the highest contact angle (Fig. 7). The corresponding coating formulation (formulation A, Table 4) shows the lowest coating efficiency.

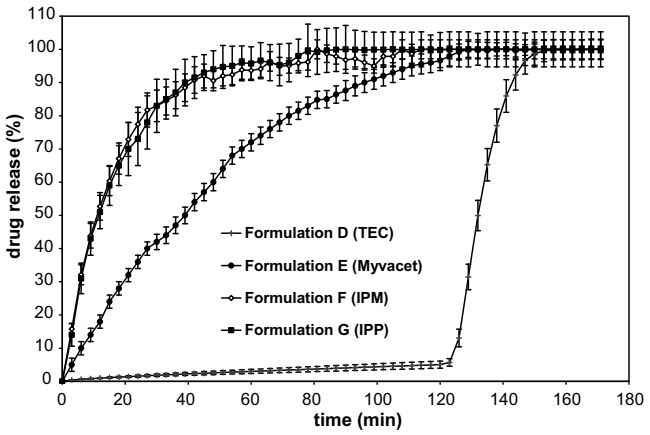

Fig. 6. Drug release of dry coated theophylline pellets with formulations D, E, F and G in 750 ml of 0.1 N HCl (pH 1) for 120 min and after addition of 250 ml 0.2 M Na_3PO_4 solution (pH 6.8) for further 50 min using 40 mg pellets in each vessel. Mean and SD of 18 measurements each.

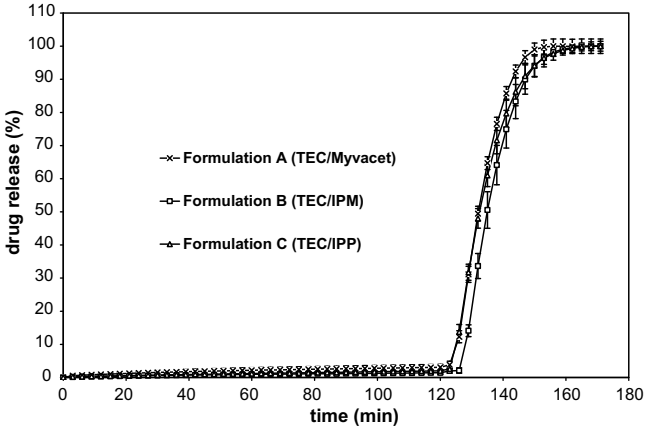

Fig. 5. Drug release of dry coated theophylline pellets with formulations A, B and C in 750 ml of 0.1 N HCl (pH 1) for 120 min and after addition of 250 ml 0.2 M Na_3PO_4 solution (pH 6.8) for further 50 min using 40 mg pellets in each vessel. Mean and SD of 18 measurements each.

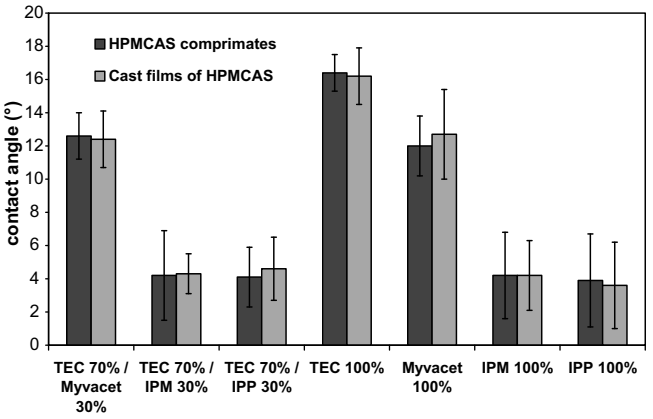

Fig. 7. Contact angles of the plasticizer TEC, the CFPs IPM, IPP and Myvacet® 9–45 K as well as mixtures of both on HPMCAS comprimates and casted films. Mean and SD of 9 measurements each.

Table 4
Coating efficiencies of coating formulations A (HPMCAS/TEC/Myvacet® 9–45 K = 75/17.5/7.5), B (HPMCAS/TEC/IPM = 75/17.5/7.5), C (HPMCAS/TEC/IPP = 75/17.5/7.5), D (HPMCAS/TEC = 75/25) and E (HPMCAS/Myvacet® 9–45 K = 75/25), $n = 3$, mean ± CI (95%)

Formulation	A[a]	B	C	D[a]	E[a]
Coating efficiency (%)	84.0 ± 0.6	89.8 ± 1.7	90.2 ± 1.3	72.5 ± 0.4	87.3 ± 1.0

[a] The data of the measurements A, D and E are adopted from Kablitz et al. [12].

The contact angles of the TEC/IPM and the TEC/IPP mixtures (70/30) are lower (Fig. 7) in comparison to the TEC/Myvacet® 9–45 K mixture resulting in a higher coating efficiency of the corresponding formulations B and C (Table 4). This supports the findings of Obara et al. [5]. In conclusion, the contact angle may be taken as an indicator of coating efficiency provided that the liquid is not taken up by the polymer.

As contact angles on solid materials depend on many qualities of the solid, for example on its porosity and on contact time [18], casted films and comprimates of HPMCAS have been used. However, differences between the data of the casted film and the comprimate are not significant.

4. Conclusion

Evaluating the role of acetylated monoglyceride (Myvacet® 9–45 K), isopropyl myristate (IPM) and isopropyl palmitate (IPP) for the dry coating process, it was found, that, in contrast to the plasticizer triethyl citrate (TEC), these substances do not alter the glass transition temperature T_g of the coating polymer hydroxypropylmethylcellulose acetate succinate (HPMCAS), indicating negligible miscibility of these substances with the polymer. As a result, film formation in the presence of these substances and the absence of the plasticizer is poor as observed by scanning electron microscopy. These findings are supported by dissolution data, which show, that enteric resistance is not achieved in the absence of the plasticizer. In conclusion, the lowering of the T_g and sufficient film formation requires the presence of the plasticizer. However, the presence of the plasticizer does not produce a high coating efficiency. That is what Myvacet® 9–45 K, IPM and IPP provide for. Due to their negligible miscibility with the polymer, they are likely not to be taken up by the polymer but to remain on the polymer's surface building up interparticle capillary forces. So the presence of these substances on the polymer's surface is the prerequisite for the formation of capillary forces. In this study, these substances are called capillary force promoters (CFPs). Plasticizers and CFPs are different types of substances. Their way of action in relation to the dry coating process can be predicted by using thermal analysis. While the plasticizer has a high affinity to the polymer and the ability to reduce the T_g, the CFP exhibits poor miscibility with the polymer and remains on the polymer's surface building up capillary forces between the polymer particles during the dry coating process.

Within the group of the CFPs it was shown, that the lower the contact angle built by the CFP or plasticizer/CFP mixture on the polymer is, the higher the coating efficiency becomes. IPM and IPP are good CFPs in respect to the enhancement of the coating efficiency. They are slightly better than Myvacet® 9–45 K.

In summary, this study gives evidence of the importance of CFPs for dry coating processes in terms of coating efficiency. The need of CFPs represents a general difference in comparison to conventional coating techniques.

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