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Research Paper

Parameters influencing polymer particle layering of the dry coating process

Caroline Désirée Kablitz [a], Michael Kappl [b], Nora Anne Urbanetz [a,*]

[a] Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany
[b] Max Planck Institute for Polymer Research, Mainz, Germany

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Abstract

The dry coating process is an emerging coating technology using neither organic solvents nor water. In contrast to liquid-borne coatings, coating material application and film formation are divided into two phases, the coating phase where the powdery coating material is applied together with the liquid plasticizer, and the curing phase. In this study the coating phase was characterized with respect to the forces acting between the polymer particles during material application. Atomic force microscopy was conducted measuring the interparticle forces which were related to the coating efficiency. The influence of different liquid additives on the interparticle forces and the coating efficiency were evaluated. HPMCAS was used as enteric resistant polymer, triethylcitrate (TEC), Myvacet® (diacetylated monoglyceride) and a mixture of both as liquid additives.

Interparticle forces were found to be similar when using TEC or a mixture of TEC and Myvacet®. In contrast, interparticle forces were higher when using solely Myvacet®. This is attributed to the fact that Myvacet® does not penetrate into the polymer without TEC which is acting as a penetration enhancer. As Myvacet® remains predominantly on the particle surface, capillary forces act between the particles explaining high interparticle forces. The highest interparticle force determined by AFM is in accordance to the highest coating efficiency which has been found for the corresponding coating formulation containing HPMCAS and Myvacet®. Consequently, it is demonstrated that the ability of the liquid to remain on the surface of the polymer and to build up capillary forces is crucial for the material application.

Keywords: Dry coating; Atomic force microscopy; AFM; Interparticle interaction; Material application; Coating

1. Introduction

Coating of solid oral dosage forms is a common technique in order to protect the active pharmaceutical ingredient (API) against environmental impact or the body fluids or rather to protect the body against adverse effects of the API. The origin of the coating technology of the modern times is the coating process based on organic polymer solutions which have been replaced gradually by aqueous dispersions in order to avoid the disadvantages of organic solvent based processes like toxicity and environmental pollution [1,2]. However aqueous dispersions have the disadvantage that the energy input to evaporate the dispersion medium water is high due to the high latent heat of evaporation [3]. Another drawback is the low amount of coating material in the dispersion and, consequently, the large amount of dispersion medium which has to be evaporated. Also low spraying rates must be employed to prevent water from penetrating the surface of the substrate. This prolongs processing time [4]. Furthermore, the API may interact with the water and hydrolysis may occur for example.

A further development of coating technology is the coating without the use of organic solvent, respectively, water,

* Corresponding author. Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University Duesseldorf, Universitaetsstrasse 1, D-40225 Duesseldorf, Germany. Tel.: +49 211 8114385; fax: +49 211 8114251.
E-mail address: noraanne.urbanetz@uni-duesseldorf.de (N.A. Urbanetz).

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namely the dry coating process, where polymer powder particles are layered on the core [5]. Attachment of the polymer particles to the core and to the already applied polymer particle layer is facilitated by using a liquid plasticizer. This innovative alternative is still in the stage of development and needs further optimization and characterization. Different interpretations of the process have been performed and introduced in the literature [6–11], however, little information about the coating mechanism is documented [12]. Obara et al. investigated the influence of the contact angle with regard to the coating efficiency of the process which is a measure for the efficiency of material application. It was shown that due to the addition of Myvacet the contact angle of the plasticizer mixture on the polymer powder was reduced, thereby improving the wetting of the polymer which results in higher capillary forces, efficiency of material application and coating efficiency [7]. However, the correlation was based on a different powder composition containing additionally talc as glidant and was not confirmed by our previous studies using solely HPMCAS as coating powder [5]. To the best of our knowledge no further information about the material application and its prerequisites are described in the literature up to now.

Generally, during the coating material application of aqueous dispersion based coating processes film formation occurs already during coating. In contrast to liquid-borne coatings, coating material application and film formation of the dry coating process are divided into two phases, the coating phase where dry powder and plasticizer are applied to the cores, and the curing phase where film formation takes place. The second phase of the dry coating process has been described in previous studies [13]. The present study focuses on the first phase, the coating phase where the powdery coating material is applied together with the liquid plasticizer. During the application it has to be ensured that in the beginning the first layer of the coating material gets attached to the cores and subsequent layers get attached to the polymer layers already built up later on in order to achieve a certain thickness of the film forming material. Thus, the coating material has to adhere during this phase without any dispersion media in contrast to the conventional coatings. Nevertheless, the liquid plasticizer acts as an attachment enhancer since it wets the particleś surface and builds up liquid bridges between them. Furthermore, due to the penetration of the plasticizer into the polymer particles capillary forces are not exerted but temporarily as long as liquid still remains between the polymer particles. After the plasticizer is penetrated completely into the particles capillary forces will disappear and van der Waals forces and electrostatic forces will become important [14,15]. Additionally, it has to be considered that the plasticizer softens the polymer's surface, which will influence the adhesion of the particles as well by increasing the stickiness and the contact area. Furthermore, the selected plasticizer composition may affect the interparticle forces by its physicochemical properties, which may lead to alterations with respect to H-bonds [16,17] and polar interactions [18].

In order to investigate the parameters influencing the material application during the coating phase, interparticle forces have been determined. There are several methods described in the literature to measure interparticle forces like the centrifuge technique where particles are adhered to a disc in a special device rotating in a centrifuge. The amount of detached particles depending on the centrifugal speed is determined [19]. Another method to determine interparticle forces is the tensile strength method where the forces acting between two powder layers are measured. The method is mostly used for the determination of cohesion forces between like materials for example to evaluate the influence of the porosity of a powder bed, the relative humidity or flow conditioners [20,21]. However, it is rarely used for the determination of forces between unlike materials [22].

Atomic force microscopy is a well-established technique for high resolution imaging of surfaces. It can also be used to measure surface forces with sub-nano Newton resolution [23,24]. By using the so-called colloid probe technique [25,26], where micrometer-sized particles are attached to the end of the AFM force sensor, forces between single particles or particles and surfaces can be studied. In this study atomic force microscopy was conducted analyzing the interparticle forces of the coating polymer particles with respect to the influence of the different liquid additives on the coating efficiency. It is expected that a high adhesion force between the particles will lead to a high coating efficiency.

The coating efficiency (CE) gives a measure of the efficiency of material application. However, it has to be kept in mind that the CE is determined after the curing phase and, consequently, after the complete process. Therefore a possible loss of coating material during this second phase is disregarded. Nevertheless, the results obtained by atomic force microscopy were related to the coating efficiency of the differently composed formulations since the parameters of the curing phase were kept constant for all formulations under investigation, so every formulation experiences the same treatment in this phase.

2. Materials and methods

2.1. Materials

Theophylline pellets donated by Klinge Pharma (Muenchen, Germany) were chosen as cores. The sieve fraction of 800–1200 μm was used. Hydroxypropyl methylcellulose acetate succinate (HPMCAS – MF, AQOAT®) as enteric film former was provided by Shin-Etsu Chemical Co. (Niigata, Japan). As liquid plasticizers triethyl citrate (TEC, Jungbunzlauer Ladenburg GmbH, Ladenburg, Germany) and acetylated monoglyceride (AMG, Myvacet® 9-45K, Kerry Bio-science, Almere, The Netherlands), acting as well as wetting agent, were used.

2.2. Methods

2.2.1. Coating process

The process was conducted in a rotary fluid bed (Glatt Rotor-GPCG-1.1, Glatt GmbH Binzen, Germany) with a three way nozzle aligned to the direction of the fluid bed movement. HPMCAS was quantitatively passed with a powder feeder (K-Tron Soder K-CL-24-KT20, K-Tron, Gelnhausen, Germany) to the three way nozzle and was applied together with the plasticizer compositions through the nozzle. The coating process took 23 min and was carried out using a batch size of 1.0 kg, adjusting the following parameters: inlet temperature: 50–55 °C, product temperature: 40–42 °C, outlet temperature: 38–40 °C, air flow rate: 70 m^3/h, powder feed rate: 11 g/min, plasticizer feed rate: 3–4 g/min. Immediately following the coating process film formation was achieved by a curing step in the rotary fluid bed which took further 45 min at an inlet temperature of 60–65 °C, a product temperature of 53–55 °C and an air flow rate of 120 m^3/h [5]. Three batches of each formulation were prepared.

2.2.2. 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. The results were expressed in percent being the mean value of three batches (means ± CI (95%).

2.2.3. Preparation of plasticized powders

The preparation was also conducted using the fluid bed equipment. Mixtures of powder and plasticizer were prepared by mounting the spray nozzle together with the powder feeder on a vial (Fig. 1). An advantage of this method is that the plasticizer is sprayed under conditions similar to the actual process conditions [5]. The powder and the plasticizer are fed in the same ratio as applied during the process and are collected in the vial. With the determination of the T_g the similarity of the samples was proved. The T_g was determined to be 57.0 °C ± 1.3 °C of the mixture consisting of 75% (w/w) HPMCAS and 25% (w/w) plasticizer demonstrating that the plasticized powder mixture is similar to organic casted films having a T_g of 51.7 °C ± 3.3 °C [13].

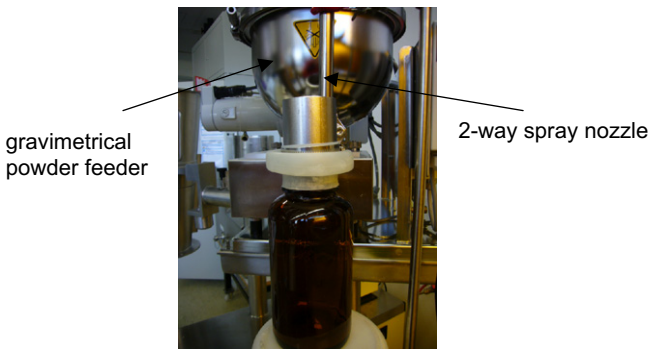

Fig. 1. Scheme of the equipment used to prepare plasticized powders.

Using this technology plasticized powders were prepared containing HPMCAS as polymer and TEC (sample b) as well as a mixture of TEC and Myvacet (sample c) and Myvacet (sample d and e) in different concentrations (Table 1).

2.2.4. Thermal mechanical analysis

The T_g of HPMCAS powder and plasticized powders containing HPMCAS, triethyl citrate and Myvacet® was obtained by thermo mechanical analysis (Mettler TMA 40 with Star^e-Software, Mettler Toledo, Giessen, Germany). The powders were compressed to compacts (20 mg, diameter: 5 mm) using a torque hand press (6 Nm) ensuring a smooth surface similar to the film's surface. After the TMA was calibrated with indium, the analysis has been carried out in triplicate under nitrogen atmosphere over a range of −20 °C to 120 °C at a heating rate of 10 °C/min (mean ± CI (95%)).

2.2.5. Atomic force microscopy (AFM)

2.2.5.1. Substrate preparation. The powders were compressed to compacts (20 mg, diameter: 5 mm) using a torque hand press (6 Nm) in order to achieve a macroscopically smooth surface. Afterwards, the samples were cured above the T_g (122 °C) for 24 h ensuring coalescence of the polymer and an even smoother surface.

2.2.5.2. Surface imaging. All AFM experiments were carried out with a Nanowizard AFM (JPK Instruments, Berlin, Germany). Imaging of the substrate surfaces was done in contact mode using triangular silicon nitride cantilevers in order to determine the roughness of the substrates (NP-S, Veeco, Santa Barbara, USA) with a nominal spring constant of 0.3 N/m.

2.2.5.3. Tip preparation – adhesion force measurements. Adhesion forces were measured using the force spectroscopy mode of the Nanowizard AFM using the colloid probe technique. Particles were attached to the end of triangular tipless silicon nitride cantilevers (NP–OW, Veeco, Santa Barbara, USA) with the help of an micro-manipulator (3 D oil-hydraulic manipulator MMO–203, Narishige Group, New York, USA). The particles, which were spread on an object slide, were attached to the cantilever tip by moving the cantilever towards a particle with the micromanipulator and collecting it from the object slide just by the adhesion force. Afterwards the attached particle was

Table 1
Formulations of plasticized powders and pure HMCAS

SAMPLE	HPMCAS	TEC	Myvacet®
a	100 parts	–	–
b	75 parts	17.5 parts	–
c	75 parts	17.5 parts	7.5 parts
d	75 parts	–	7.5 parts
e	75 parts		25 parts

cured for 2 h in an oven at 150 °C achieving sintering of the particle on the cantilever. After the measurement of each substrate the particle's intactness was checked using the inverted optical microscope on which the AFM was mounted.

2.2.6. Differential scanning calorimetry

The determination of excess plasticizer being immiscible with the polymer was performed using the DSC 821e (Mettler Toledo GmbH, Giessen, Germany). As reference an empty aluminum pan was used. The calibration of temperature and heat flow was conducted using indium. The analysis was performed with sealable 40 µl aluminum pans using approximately 5 mg sample. The measurement was carried out applying a continuous flow of nitrogen adjusting a flow rate of 50 ml/min. The sample was frozen to −60 °C with a freezing rate of 10 °C/min, kept constant 30 min and heated up to 50 °C setting 2 °C/min as heating rate. All measurements were performed in triplicate. The analysis of the results was performed using the STAR^e – Software version 6.01 (Mettler Toledo GmbH). All measurements were carried out in triplicate. The mean ± CI (95%) was calculated. The shown thermograms always represent the second of three measurements.

2.2.7. Drug release

The drug release of pellets dry coated with HPMCAS (100 T) and Myvacet® (25 T) was conducted according to the USP XXIX method A, rotating paddle method (Sotax AT6, Sotax GmbH, Loerrach, Germany). The dissolution was studied at 37 °C ± 0.5 °C in 750 ml of 0.1 N HCl (pH 1) for 120 min and after addition of 250 ml of Na_3PO_4 12 H_2O solution (65 g/l) (pH 6.8) for further 80 min using 40 mg pellets in each vessel. The paddle rotation was adjusted at 50 rpm. The drug release was analyzed spectrophotometrically at 272 nm using a continuous flow-through system attached to the UV spectrophotometer (Lambda 2, Perkin-Elmer, Rodgau-Juegesheim, Germany) transporting the liquid with a peristaltic pump (50 rpm) (IPC, Ismatec, Glattbrugg, Schweiz) with modified PVC tubings (Tygon R 3603, Norton, USA). The drug release of the coated pellets was determined from six samples calculating the mean and the CI (95%).

2.2.8. Scanning electron microscopy

Pellets were shock-frozen with liquid nitrogen and broken in pieces. The pieces were fixed on a brass plate using adhesive tape before they were sputter coated with gold for 240 s (Agar Manual Sputter Coater, Agar Scientific Ltd., Stansted, Essex, England). Afterwards the samples were examined by observing their surface and cross-sectional morphologies with a scanning electron microscope (LEO VP 1430, Carl Zeiss NTS GmbH, Oberkochen, Germany) under vacuum adjusting 20 kV operating voltage.

3. Results and discussion

The application of the coating material takes place during the first phase, the coating phase of the dry coating process. The polymer and the plasticizer were applied to the cores at constant feeding and spraying rates. As the plasticizer has been sprayed 30 s before the feeding of the dry polymer was started, wetting of the pellets' surface was ensured facilitating the adhesion of the polymer powder to the surface of the cores. Thus, at the beginning of the coating phase, the ratio of plasticizer and polymer powder was higher than the named ratio of 25/75 and approached this ratio gradually once the application of the powder had been started. As long as the liquid will not have been taken up by the polymer particles completely, the adhesion of the polymer particles will be promoted mainly by capillary forces, which are the strongest interparticle forces. Afterwards van der Waals forces and electrostatic forces will be responsible for the particle interaction [14,15]. Additionally, the plasticizer also influences the interparticle forces by its ability to lower the T_g of the polymer, thereby softening the polymer and increasing stickiness and the area of contact between polymer particles, the latter resulting in an increase of van der Waals forces.

3.1. Preparation of the AFM substrate and the cantilever tip

The polymer particles used in this study had a rough surface and an irregular shape. This makes meaningful measurements of the interparticles forces difficult since the area of contact between two surfaces strongly influences the interparticle force and is expected to be dominating compared to the influence of the coating formulation for rough surfaces. To minimize the influence of surface roughness and particle shape, the coating material was modified in order to obtain a smooth and flat surface. Macroscopically smooth comprimates of the particles were prepared and the surface topography was analyzed prior to the adhesion force measurement. The AFM surface scan (Fig. 2(A)) reveals the pronounced micro-roughness of the comprimates where single particles are still observable. To improve the surfaces quality, the samples were subject to a second preparation step. The comprimates were cured for 24 h above their T_g ensuring coalescence of the compressed particles in order to obtain smooth films. Alternatives for the preparation of smooth surfaces are described in the literature [27,28]. The thermal treatment resulted in much smoother surfaces (Fig. 2(B)). The remaining roughness of the cured samples is not constricting the measurement as the area used for the force measurements (1 × 1 µm) exhibits a satisfactory smoothness.

Additionally, the particles attached to the cantilever tips were modified. Commonly, colloid probes are prepared by attaching the particles to the AFM cantilever using a glue. This poses the risk that the particles surface may become covered by the glue, leading to erroneous adhesion force results. Hence, in order to avoid this, the particles were

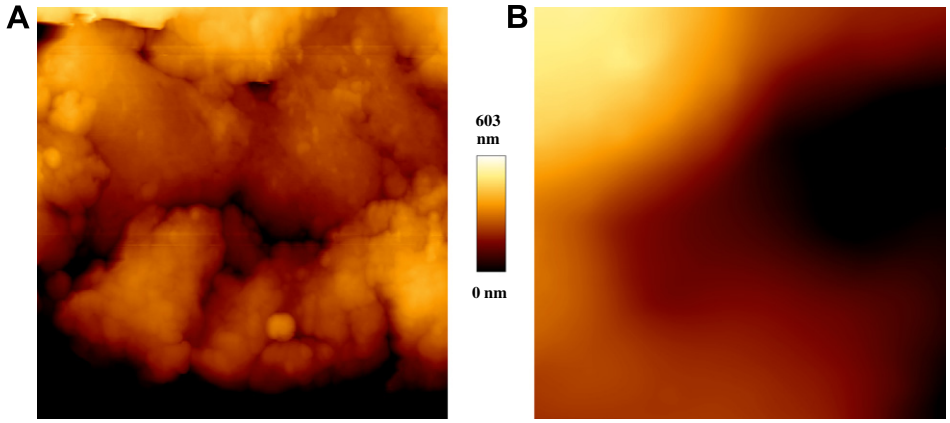

Fig. 2. AFM surface scans of uncured (A) and cured (B) HPMCAS comprimates, $A = 5 \times 5$ μm.

picked up just by their adhesion to the AFM cantilever and then sintered onto the cantilever by heating them above the T_g determined to be 122 °C in a previous study [5]. This approach at the same time changed the shape of the particle that became droplet like and the particle surface became smoother also ensuring a much more defined and reproducible contact area with the substrate's surface.

3.2. Influence of the liquid additives on interparticle interactions

In order to determine the influence of the plasticizers on the interparticle force, different substrates consisting of various ratios of hydroxypropylmethylcellulose acetate succinate (HPMCAS), triethylcitrate (TEC) and Myvacet® were prepared (see Table 1). The powders were compressed, cured and stored above silica gel until further required. The particle sintered to the cantilever tip consisted of HPMCAS. It was not possible to attach plasticized particles to the tip as sintering did not lead to a sufficiently strong attachment to the cantilever. Nevertheless, it should be possible to evaluate the effect of the plasticizer by varying merely the substrate. In order to keep the contact area constant, the same particle on the cantilever tip was used for the measurements on every single substrate. However, due to the fact that this particle got in contact with different substrates a blank measurement was performed in between each measurement in order to check whether an alteration of the particle had taken place. The inert substrate used as reference was mica, a dioctahedral and trioctahedral silicate, which is outstanding for its excellent smoothness on the molecular level [29].

The adhesion forces of the HPMCAS particle on HPMCAS and plasticized HPMCAS substrates are displayed in Fig. 3. The mean of the interparticle force determined on 8 squares of 1×1 μm, each giving 1024 single force values is shown (CI = 95%). Before the first and after each of the subsequent measurements a blank measurement was performed. In comparison to the values of the sample measurements the blank values are 3–4 times higher. The

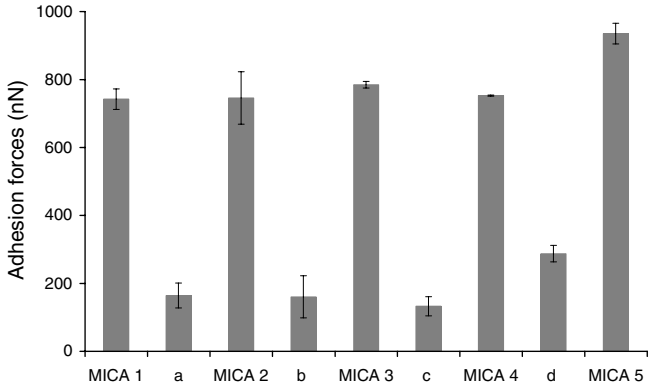

Fig. 3. Measurements of HPMCAS at the tip against HPMCAS (a), HPMCAS and TEC (b). HPMCAS, TEC and Myvacet® (c) and HPMCAS, Myvacet® (d) as substrate controlled alternately with mica measurements, $n = 8$ x 1024, mean ± CI (95%).

high interparticle force of the blank measurements can be explained by the absolute smoothness of mica. Due to this smoothness the contact area and consequently the interparticle force is high.

Regarding the interpretation of the data no significant differences can be observed between the samples consisting of pure HPMCAS, HPMCAS and TEC and, HPMCAS with the plasticizer blend of TEC and Myvacet®. In contrast, the last substrate, containing solely Myvacet® as liquid, shows increased interparticle forces. Generally, it might have been expected that the adhesion of HPMCAS on pure HPMCAS was lower compared to the adhesion between HPMCAS and plasticized HPMCAS. Indeed, the plasticizer enables the emergence of capillary forces and, due to the lowering of the polymer's T_g, leads to an increase in stickiness and contact area. However, in contrast to the conditions of the dry coating process where a temperature close to the T_g had been adjusted, the temperature at which AFM measurements had been performed was at room temperature, well below the T_g. This explains that the samples' stickiness during the AFM measurement is similar and irrespective of whether a plasticizer has been used or not.

The adhesion force on the substrate containing solely Myvacet® as plasticizer is two third higher than the forces determined on the other samples. This indicates that Myvacet® has a high influence on the adhesion forces. Furthermore, it was observed that Myvacet® only partly penetrated into the polymer and remained mainly on its surface. Nevertheless, the adhesion force of the sample containing Myvacet® in combination with TEC is not enhanced which indicates that the phenomenon of the increased adhesion force only appears when using Myvacet® without TEC. It might be presumed that TEC acts as a penetration enhancer for Myvacet® to be taken up by the polymer.

Regarding the adhesion forces of the blank measurements with mica, determined before the first and after all subsequent measurements, no change of the adhesion force was determined. Accordingly, the particle at the cantilever's tip is assumed not to undergo any alteration between the measurements. However, after having performed the measurement of the substrate containing solely Myvacet® as plasticizer the blank measurement with mica was increased as well. Visual inspection of the cured comprimate revealed a thin liquid layer on the surface. By laying the sample on blooding paper dark spots of liquid were detected after getting in contact with it. The liquid layer of Myvacet® on the surface of the substrate caused that Myvacet® was transferred from the substrate to the particle on the cantilever tip resulting in higher interparticle forces of the following blank measurement due to the emerging capillary forces. In conclusion, the presence of capillary forces seems to be crucial with respect to a high interparticle interaction.

The intention of the AFM measurements was to find a relation between the interparticle force and the coating efficiency. The coating formulations and coating efficiencies are shown in Table 2. It has to be considered that instead of plasticized powders consisting of 75 parts HPMCAS and 17.5 parts TEC, 7.5 parts Myvacet® or a mixture of 17.5 parts TEC and 7.5 parts Myvacet® (samples b–d, Table 1), formulations containing 75 parts HPMCAS and 25 parts TEC, 25 parts Myvacet® or a mixture of 17.5 parts TEC and 7.5 parts Myvacet® were investigated (formulations b–d, Table 1).

The coating efficiency is highest using the formulation containing HPMCAS and Myvacet®. This is in relation to the obtained interparticle forces as the highest interparticle force was observed when using the substrate consisting of HPMCAS and Myvacet®. According to the hypothesis that the use of Myvacet® leads to the emergence of capillary forces resulting in an increased interparticle force and hence increased coating efficiency, the lower coating efficiency and interparticle force determined on substrates containing TEC in addition to Myvacet® are caused by the missing capillary forces since TEC enhances the liquid uptake by the polymer. The even lower coating efficiency of the formulation containing solely TEC cannot be explained by AFM measurements. The interparticle forces of the samples containing TEC and Myvacet® are equal to those of the samples containing solely Myvacet®. Nevertheless, it has to be kept in mind that the experimental conditions of the AFM measurements differ from those of the dry coating process because the time the plasticizer, respectively, the plasticizer mixture is allowed to be taken up by the polymer is much longer under the experimental conditions of the AFM measurements in comparison to the dry coating process. Keeping in mind that Myvacet® stays on the surface and exerts capillary forces whereas TEC is taken up by the polymer rapidly it may be assumed that, when using TEC in combination with Myvacet® the time needed for the penetration of the mixture is prolonged leading to an extension of the effect of capillary forces compared to pure TEC. This presumption explains the decrease of the coating efficiency in the order formulation D, formulation C and formulation B. However the time dependent decrease of the capillary forces in the same order cannot be reflected by the AFM measurements because the time the plasticizer, respectively, the plasticizer mixture is allowed to be taken up by the polymer is too long to differentiate between formulations containing a mixture of Myvacet® and TEC and formulations containing solely TEC. In order to prove the lasting existence of capillary forces when using Myvacet® plasticized powders were prepared and characterized with regard to the plasticizing effect of the liquids and the amount of excess liquid which presumably is responsible for the formation of capillary forces.

Table 2
Coating efficiency of formulations B–D

Formulation	B	C	D
HPMCAS	75 parts	75 parts	75 parts
TEC	25 parts	17.5 parts	–
Myvacet®	–	7.5 parts	25 parts
Coating efficiency	72.5% ± 0.4%	84.0% ± 0.6%	87.3% ± 1.0%

3.3. Plasticizing effect and determination of the presence of excess liquid in the plasticized powders

In order to confirm the phenomenon that Myvacet® is not penetrating into the polymer the presence of free liquid in the plasticized powders was checked by differential scanning calorimetry (DSC) and thermal mechanical analysis (TMA). Thermal analysis was applied to find out whether plasticizers are miscible with the polymer increasing the polymer chains flexibility and mobility. With regard to the DSC traces miscibility leads to the disappearance of the melting peak of the plasticizer and to a lowering of the polymer's T_g. This can be measured with the TMA even more precisely.

The different plasticized powders containing TEC, Myvacet® or a mixture of both (sample b–d, Table 1) were frozen down to −60 °C and kept at this temperature for 30 min ensuring a complete solidification of the materials. Afterwards the samples were heated up to 50 °C increasing

the temperature by 2 °C per minute. Regarding the different curves it can be shown that no melting peak of the samples containing TEC and only a small peak for the mixture of TEC and Myvacet® are found (Fig. 4). The sample containing Myvacet® and no TEC shows a high freezing peak (recrystallization) between 5 °C and −5 °C which is only slightly below the melting temperature interval of 4–12 °C indicated by the supplier for Myvacet® [30] (Fig. 5). This slight deviation between melting interval and freezing interval may be caused by supercooling of the liquid. Hence, free Myvacet® is detected in the plasticized powder and the hypothesis that Myvacet® does not mix with the polymer is confirmed. Regarding the heating curve a peak can be detected as well covering a broad interval due to the impurities of the diacetylated monoglyceride Myvacet®. Consequently, the hypothesis that Myvacet® builds up capillary forces between the polymer particles due to its at least partial immiscibility with the polymer is supported and explains why the interparticle forces are increased in comparison to the mixtures without Myvacet®.

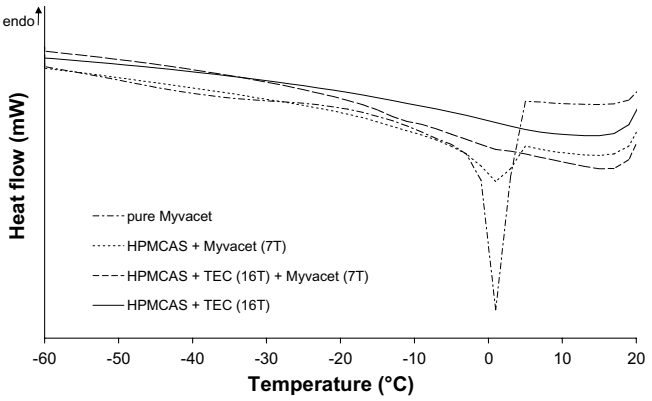

Fig. 4. DSC cooling curves of plasticized powder containing HPMCAS and TEC, HPMCAS and Myvacet and HPMCAS, TEC and Myvacet® and pure Myvacet.

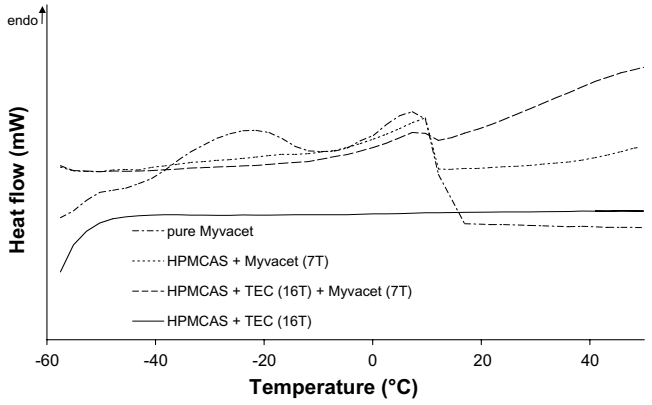

Fig. 5. DSC heating curves of plasticized powder containing HPMCAS and TEC, HPMCAS and Myvacet and HPMCAS, TEC and Myvacet® and pure Myvacet.

Although excess Myvacet® is observed by DSC, it has to be considered that Myvacet® could be condensed in capillaries of the polymer particle instead of staying on the particle surface. Thus, the liquid would not be able to build up capillary forces between the particles. However, condensed liquid materials melt at lower temperatures than the bulk liquid [31] due to interactions with the capillary wall. If capillary condensation occurs a second peak of the condensed Myvacet® will be observable. This phenomenon is commonly used in literature for pore size distribution measurements [32,33]. Having a closer look to the DSC curves this phenomenon can be excluded. Additionally, the melting peak of the mixture was compared to the DSC curve of pure Myvacet® performed with the same settings (Fig. 5) showing no differences with regard to the melting peak and indicating that Myvacet® is not condensed in capillaries of the polymer.

However, in contrast to the mixture of HPMCAS and Myvacet® the excess of Myvacet® is very small in the mixture with TEC supposing that TEC enhances the miscibility of Myvacet® with the polymer (Fig. 4). Further, since the liquids are miscible, it can be assumed that the liquids act as mutual solvents. In the case that Myvacet® is a solvent for TEC a freezing point depression of Myvacet® should have been observed. Therefore DSC measurements were performed with pure TEC and a mixture of TEC and Myvacet® and compared with the thermogram of Myvacet®. Fig. 6 shows the heating curves of Myvacet®, TEC and a mixture of both in the known ratio (70% (w/w)/30% (w/w)). In contrast to the melting point of pure Myvacet® which is 7.5 °C ± 0.2 °C the melting point of Myvacet® in the mixture is lowered being −1.5 °C ± 0.1 °C. The heating curve of pure TEC does not show any melting peak because the melting point of TEC is below −60 °C.

Having a closer look to the glass transition temperatures (T_g) of the plasticized powders the results obtained from the determination of excess plasticizer are in good accordance. Due to the increase of the polymer chains mobility plasticizers lower the T_g of a polymer by penetrating and dissolving in the polymer. Investigating the T_g of plasticized powders containing solely Myvacet® by TMA the

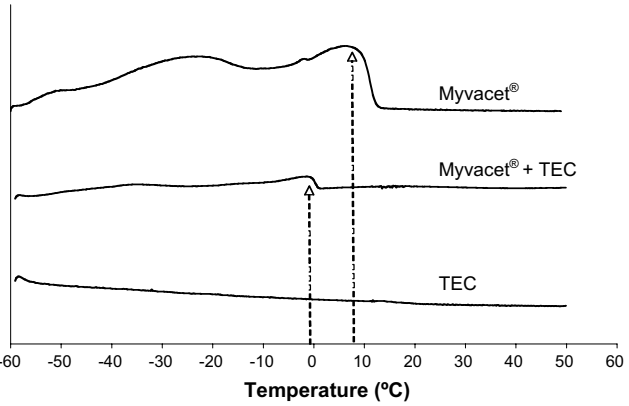

Fig. 6. DSC heating curves of TEC and Myvacet® and the mixture of both containing 70% (w/w) TEC and 30% (w/w) Myvacet®.

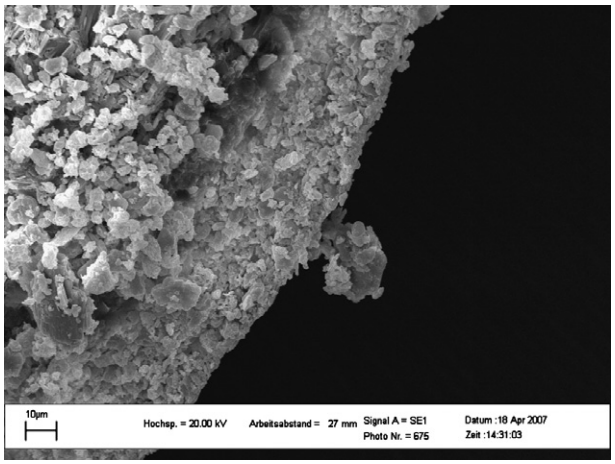

Fig. 7. SEM of pellet coated and cured with HPMCAS and Myvacet®.

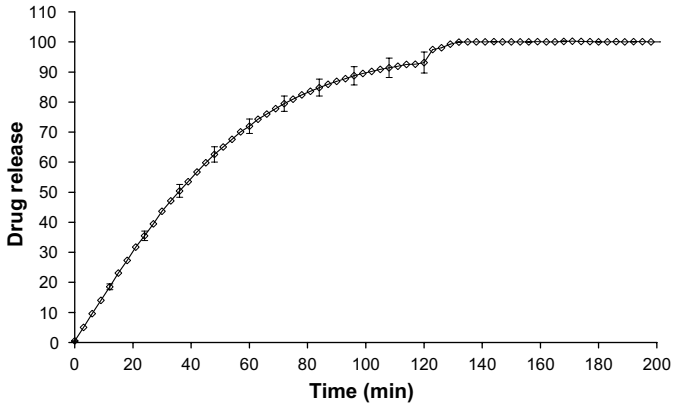

Fig. 8. Drug release of theophylline pellets coated with HPMCAS and Myvacet® in 750 ml of 0.1 N HCl (pH 1) for 120 min and after addition of 250 ml of $Na_3PO_4 \cdot 12\ H_2O$ solution (65 g/l) (pH 6.8) for further 80 min, $n = 18$, mean ± CI (95%).

T_g was not decreased but marginally to 93.4 °C ± 0.4 °C (7.5 parts (w/w) Myvacet®, sample d, Table 1), respectively, 88.5 °C ± 2.1 °C (25 parts (w/w) Myvacet®, sample e, Table 1) indicating that the miscibility of Myvacet® with the polymer is poor. The good compatibility and miscibility of the TEC/Myvacet® mixture with the polymer is demonstrated as only a small melting peak is observable in the plasticized powder indicating that the mixture is mainly dissolving in the polymer. The T_g of the mixture is 57.0 °C ± 1.3 °C. The similar T_g of 55.7 °C ± 2.7 °C of the plasticized powder containing HPMCAS and TEC indicates that TEC has the major plasticizing effect on the polymer.

In conclusion, the hypothesis that Myvacet® does not penetrate into the polymer is confirmed, the excess amount showing a melting peak of Myvacet®. The excess liquid may exert capillary forces during the dry coating process. This results in the highest adhesion force and, correspondingly, in the highest coating efficiency of 87% when using solely Myvacet®. Unfortunately, this composition does show neither film formation (Fig. 7) nor enteric resistance (Fig. 8) which has been expected because the process temperature of the dry coating procedure was well below the T_g of this coating formulation. The plasticized powder containing a mixture of TEC and Myvacet® does show a smaller melting peak indicating that TEC acts as an enhancer for the penetration and dissolution of Myvacet®. Nevertheless, regarding the higher coating efficiency of the formulation containing TEC and Myvacet® (84%) in contrast to solely TEC (72%) it might be assumed that Myvacet® prolongates the penetration of the liquid mixture into the polymer. The liquid remains longer on the surface leading to an extended effect of the capillary forces and resulting in a higher coating efficiency in comparison to the formulation containing pure TEC as plasticizer. However, this still remains a hypothesis that needs to be investigated in future studies.

4. Conclusion

An efficient material application is crucial for the dry coating process with regard to the coating efficiency. The coating efficiency is highly influenced by interparticle forces between the coating polymer particles which largely depends on the properties of the liquid additives used as plasticizers and adhesion force promoters for the polymer particles. The ability of the liquid additives to build up capillary forces had turned out to be the most important factor in order to obtain high interparticle forces and coating efficiencies.

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