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Impact of excipients on coating efficiency in dry powder coating

Martina Smikalla[a,∗], Axel Mescher[b], Peter Walzel[b], Nora Anne Urbanetz[c]

[a] Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Universitaetsstr. 1, 40225 Duesseldorf, Germany
[b] Mechanical Process Engineering, University of Technology Dortmund, Emil-Figge-Straße 68, 44227 Dortmund, Germany
[c] Research Center Pharmaceutical Engineering, Inffeldgasse 21A, 8010 Graz, Austria

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Dedicated to Prof. Dr. B.C. Lippold on the occasion of his 70th birthday.

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ABSTRACT

Dry powder coating is a technique to coat substrates without the use of organic solvent or water. The polymer powder is directly applied to the cores to be coated. Liquid additives are often used to lower the glass transition temperature of the polymer and to enhance the adhesion of the powder to the cores. This leads to an increase in coating efficiency of the process.

The impact of various liquid additives and their properties like spreading behavior, viscosity and plasticizing activity were investigated with respect to their influence on the coating efficiency of the process. Ethylcellulose and hydroxypropyl methylcellulose acetate succinate were used as coating polymers. Spreading behavior of the liquid additive on the polymer was the most influencing parameter and could be successfully predicted with contact angle measurements on polymer films. Calculations of works of adhesion and spreading coefficients also revealed to be promising predictive techniques for choosing suitable additives to improve process efficiency. Isopropyl myristate showed the best spreading behavior resulting in the highest coating efficiency.

Based on these results, a formulation for ethylcellulose containing isopropyl myristate was developed and film formation was examined using dissolution testing and imaging techniques to evaluate the optimum curing conditions.

1. Introduction

Functional coating of pharmaceutical dosage forms to achieve for example controlled release or enteric resistance with polymers is usually carried out with organic polymer solutions or aqueous polymer solutions or dispersions, respectively. Organic solvent based coatings suffer from toxicological, environmental, cost- and safety-related issues (Cole et al., 1995). These disadvantages have been largely eliminated by the introduction of water based coating technologies incorporating the film forming polymer either dissolved or dispersed in water. However, water based coatings have the disadvantage that the energy input to evaporate the dispersion medium is high due to the high latent heat of evaporation (Lide, 2000). Another drawback is the low polymer concentration which is limited due to the otherwise too high viscosity of solutions and possible nozzle blocking in case of dispersions. This prolongs processing time. Furthermore, the active pharmaceutical ingredient may interact with water resulting in instabilities.

Several solvent and water free processes have been described in literature. Obara et al. (1999) developed the so-called dry coating or dry powder coating technique in a pan coater using the polymer hydroxypropyl methylcellulose acetate succinate (HPMCAS). Dry powder coating is a technique with no need of any solvent or dispersion media. The film forming polymer is applied in powdered form to the cores consisting of the active enabling very short process times compared to conventional coating processes. The use of additives, like liquid plasticizers, is often required especially when using polymers with high glass transition temperatures like ethylcellulose and HPMCAS (Terebesi and Bodmeier, 2010). These additives remain within the final film and have not to be evaporated. Furthermore, liquid additives enhance the adhesion of polymer powder to the substrates leading to an increase in coating efficiency of the process and thus to cost reduction. The use of water or aqueous binder solutions was described by Obara et al. (1999) and Pearnchob and Bodmeier (2003) to facilitate the film formation of the polymer powder and to enhance the adhesion of the polymer to the substrates. Heating alone was not sufficient to achieve film formation, especially when using polymers having a high glass transition temperature. Kablitz et al. (2006) transferred the dry powder coating technique developed by Obara et al. (1999) to a rotary fluid bed apparatus. It was possible to achieve film formation without water addition. Recently, Terebesi and Bodmeier (2010) described a coating procedure with the sustained release polymers ethylcellulose and Eudragit® RS using a fluidized bed ball coater. It was also possible to relinquish water.

∗ Corresponding author. Tel.: +49 211 8115693; fax: +49 211 8114251.
E-mail address: martina.smikalla@uni-duesseldorf.de (M. Smikalla).

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Cerea et al. (2004) and Sauer et al. (2007) both used a laboratory scale spheronizer to coat tablets either with pure or preplasticized polymer powder. Using water was not necessary in that case, but the use of molten additives was advantageous to enhance powder adhesion.

Electrostatic dry powder coating has also been reported in literature for pharmaceutical applications in which powder adhesion is achieved by charging of the polymer powder. Nevertheless, the use of plasticizers is also described to increase the electrical conductivity of the cores as pharmaceutically used excipients often exhibit high electrical resistivity (Qiao et al., 2010). Moreover, film formation without the use of plasticizing additives requires high temperatures depending on the used polymer.

The impact of excipients on coating efficiency of the dry powder coating processes has been described by several working groups. Obara et al. (1999) found that the addition of a well spreading substance can lead to an increase in coating efficiency when using HPMCAS as coating polymer. Kablitz et al. (2008) emphasized the importance of interparticle forces, like capillary bridges, for powder adhesion which can be realized by using liquid additives remaining a certain time period on the powder surface before being absorbed.

However, less information has been reported yet about process efficiencies of the various powder coating processes and formulations used. Besides, systematic investigations are not available to the moment, about how to choose additives to improve coating efficiencies. Therefore a systematic approach was chosen to identify important parameters of additives by evaluating various excipients regarding their influence on coating efficiency. The investigated liquid excipients were characterized concerning their spreading behavior, viscosity and plasticizing activity on the polymer. These different characteristics were evaluated with respect to whether they can be used as predictive tools to identify liquid additives leading to high efficiencies. As coating polymers ethylcellulose, a water insoluble polymer used for sustained release, and HPMCAS, an enteric polymer, were used. Based on these results, formulations with ethylcellulose were developed and evaluated regarding their film forming properties.

2. Materials and methods

2.1. Materials

As coating polymers ethylcellulose (Ethocel® Standard 10 FP Premium, DOW Chemical, Midland, USA) and hydroxypropyl methylcellulose acetate succinate (HPMCAS, Aqoat® MF, Shin-Etsu Chemical, Niigata, Japan) were used as received. Acetylated monoglycerides (Myvacet® 9-45K, Kerry Bio-Sciences, Almere, Netherlands), acetyltributyl citrate (Citrofol® B II, Jungbunzlauer, Ladenburg, Germany), cocoyl caprylocaprate (Cetiol® LC, Cognis, Monheim, Germany), diacetylated monoglycerides (Dynacet® 285, Sasol, Witten, Germany), dibutyl sebacate (Sigma–Aldrich, Saint Louis, USA), diethyl phthalate (Acros Organics, Geel, Belgium), glycerol (Caelo, Hilden, Germany), isooctyl stearate (Cognis, Monheim, Germany), isopropyl myristate (Cognis, Monheim, Germany), isopropyl palmitate (Cognis, Monheim, Germany), octyldodecanol (Eutanol® G, Cognis, Monheim, Germany), Miglyol® 808 (Sasol, Witten, Germany), Miglyol® 812 (Sasol, Witten, Germany), oleylalcohol (HD Eutanol®, Cognis, Monheim, Germany), oleyl oleate (Cetiol®, Cognis, Monheim, Germany), paraffin (Caelo, Hilden, Germany), polyethylene glycol 200 (PEG 200, Clariant, Sulzbach, Germany), polyethylene glycol 400 (PEG 400, Clariant, Sulzbach, Germany), polyoxyethylated castor oil (Cremophor® EL, BASF, Ludwigshafen, Germany), polyoxyethylene(30)-glyceryllaurate (Tagat® L, Goldschmidt, Essen, Germany), polysorbate 20 (Caelo, Hilden, Germany), polysorbate 80 (Caelo, Hilden, Germany), propylene glycol (BASF, Ludwigshafen, Germany), propylene glycol dicaprylocaprate (Myritol® PC, Cognis, Monheim, Germany), triacetin (Riedel de Haen, Seelze, Germany) and triethyl citrate (Merck, Darmstadt, Germany) were evaluated as plasticizers and powder adhesion enhancers. Colloidal silicium dioxide (Aerosil® 200, Evonik Degussa, Duesseldorf, Germany) was used to avoid possible sticking phenomena during curing of coated pellets. Acetone (VWR, Leuven, Belgium), ethanol (VWR, Leuven, Belgium) and toluene (Riedel de Haen, Seelze, Germany) were used as solvents. Diiodomethane (Merck, Darmstadt, Germany) and distilled water were used for determination of surface energy. Theophylline pellets were donated by Temmler Ireland (Killorglin, Ireland) and the sieve fraction 1000–1250 μm was used.

2.2. Methods

2.2.1. Differential scanning calorimetry (DSC)

To evaluate the plasticizing activity of commonly used plasticizers on the polymer ethylcellulose thermal investigations of isolated films were performed using a DSC 821e (Mettler Toledo, Giessen, Germany). Free films of pure and plasticized polymer were obtained by solvent casting from organic solution. Ethylcellulose was dissolved in toluene/ethanol (80/20, w/w) in order to get a 10% (w/w) solution. Different amounts of various liquid additives were added and the solutions were stirred over night. The solutions were poured out into petri dishes, air-dried and stored in a desiccator over silica gel. The measurement temperature ranged from −20 to +150 °C at a heating rate of 10 °C/min. Every sample was heated up, cooled down and heated up again. Experiments were carried out in 40 μL aluminium pans with a pierced lid. The weight of the samples was approximately 10 mg. The second heating step was used for the determination of the glass transition temperature (T_g). Experiments were performed in triplicate.

2.2.2. Contact angle measurements

2.2.2.1. Theory of contact angle measurements. Since Obara et al. (1999) proposed the addition of spreading agents, contact angle measurements were evaluated as possible screening tool for choosing liquid additives leading to enhanced powder adhesion.

The contact angle is a measure of spreadability and is defined according to the Young equation as:

$$\cos\theta = \frac{\sigma_S - \gamma_{SL}}{\gamma_L} \tag{1}$$

θ is the contact angle between solid and liquid, σ_S the surface energy of the solid, γ_{SL} the interfacial tension between solid and liquid and γ_L the surface tension of the liquid. Young's equation requires smooth and homogeneous surfaces. This does not allow the direct determination of θ on powders due to the rough surface and requires the use of indirect methods. It is known that processing of materials like milling or compression may influence their surface energy characteristics also influencing contact angle measurements. Therefore different sample preparations of the polymers were tested to examine their influence on spreading behavior.

2.2.2.2. Determination of contact angles. The spreading behavior of the liquid additives on polymer tablets and films was investigated using the sessile drop method ($n = 4$). Tablets of polymer powder (200 mg, 13 mm diameter) were prepared using a hydraulic press (Perkin Elmer, Ueberlingen, Germany) with a pressure of 887 MPa for 5 min. Polymer films were obtained by dipping glass slides in an organic polymer solution prepared as described in Section 2.2.1. Contact angles on tablets and films were measured with a drop shape analyzer (DSA100, Kruess, Hamburg, Germany) equipped with a DSA1 software. A drop of 3 μL was automatically generated with a speed of 210 μL/min by a micrometer syringe and placed on the test substrate. A video was recorded and the contact angles were analyzed after 10 s and 60 s.

2.2.3. Surface free energy determinations

Surface free energy of ethylcellulose tablets and films was determined with contact angle data obtained from the sessile drop technique (Section 2.2.2). Water and diiodomethane were used as probe liquids to assess the polar and disperse fractions of the substrate. Drops of 3 μL (water) and 1 μL (diiodomethane) were placed on the test surface and the contact angles were measured after 1 s. The surface free energies were calculated using the Owens–Wendt equation (Owens and Wendt, 1969):

$$\gamma_L(\cos\theta + 1) = 2\left(\sqrt{\gamma_L^D \gamma_S^D} + \sqrt{\gamma_L^P \gamma_S^P}\right) \tag{2}$$

where γ_L is the surface tension of the liquid, γ_L^D and γ_L^P are the dispersive and polar fractions of the liquid and γ_S^D and γ_S^P the dispersive and polar fractions of the solid, respectively. The surface tension of the liquid additives was investigated by means of the Wilhelmy plate method with a tensiometer (K100, Kruess, Hamburg, Germany). For evaluation of the disperse fractions contact angles were determined on a polytetrafluoroethylene (PTFE) plate as PTFE is expected to provide only dispersive interactions. The surface free energy of the PTFE plate determined with water and diiodomethane was $\sigma_S = \gamma_S^D = 17.8$ mN/m. By substituting these values in the rearranged Owens–Wendt equation (3) it is possible to calculate the disperse fraction of the liquid. The polar fraction can be calculated by subtraction of the disperse part from the total surface tension (4):

$$\gamma_L^D = \frac{\gamma_L^2(\cos\theta + 1)^2}{\left(2\sqrt{\gamma_S^D}\right)^2} \tag{3}$$

$$\gamma_L^P = \gamma_L - \gamma_L^D \tag{4}$$

2.2.4. Coating procedure

The dry powder coating procedure was carried out in a fluid bed apparatus with a rotor insert (GPCG 1.1, Glatt, Binzen, Germany). A gravimetric twin-screw powder feeder (K-Tron Soder K-CL-24-KT20, K-Tron, Gelnhausen, Germany) metered the polymer powder directly to a nozzle simultaneously dispersing the polymer powder as well as the liquid additive with pressurized air. It is tangentially aligned to the fluid bed (Fig. 1). The additives were fed using a peristaltic pump to the same nozzle and sprayed simultaneously with the polymer powder. 1 kg theophylline pellets were used as cores and preheated to a product temperature of 40 °C prior to the coating phase. The process parameters are shown in Table 1. After the coating phase of 18 min, the pellets were further fluidized for 5 min. Subsequent curing steps were conducted in an oven after mixing with 1% colloidal silicium dioxide to avoid possible tacking of the pellets during curing. The coating efficiency (CE) of the process was calculated by dividing the achieved weight gain of coated cores by the mass of the coating material added to the process. Experiments were performed in triplicate.

2.2.5. Thermomechanical measurements (TMA)

Thermomechanical measurements to determine glass transition temperatures were performed on isolated films of ethylcellulose and HPMCAS prepared as described in Section 2.2.1 using a TMA40 (Mettler Toledo, Giessen, Germany). Films consisting of HPMCAS were obtained from acetone solutions. Analysis was carried out under nitrogen atmosphere between −20 and +150 °C at a heating rate of 10 °C/min.

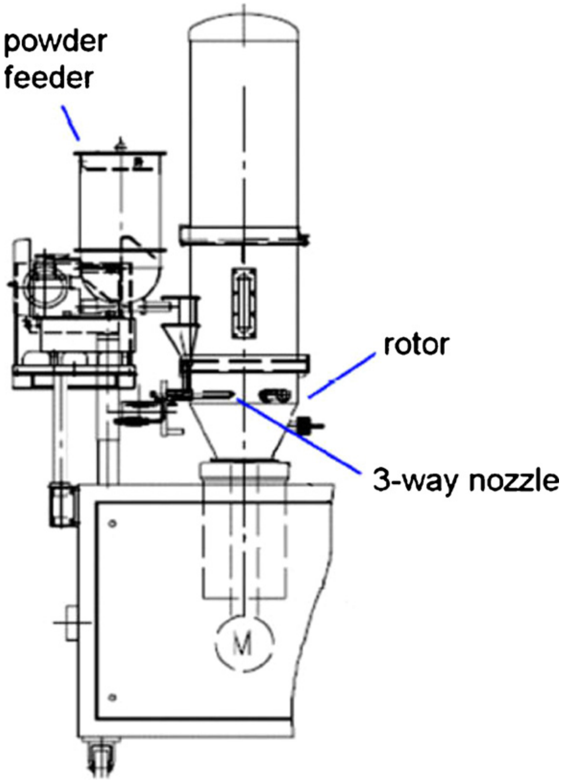

Fig. 1. Schematic of a rotary fluid bed: rotor, three-substance way nozzle, powder feeder.

2.2.6. Viscosity measurements

The viscosity of the liquid additives was determined using a rotational plate–plate (35 mm) rheometer (Rheostress 600, Haake, Germany) at 25 °C.

2.2.7. Droplet size determination

Droplet sizes of the various liquid additives generated by the nozzle (two-substance nozzle 970 S4, Schlick, Untersiemau, Germany) were analyzed with a Spraytec (Malvern Instrument, Herrenberg, Germany). The atomizing air pressure was set at 1.5 bar and the spray rate was adjusted at 3.2 g/min to simulate process conditions.

2.2.8. Statistical evaluation

Multiple linear regression (MLR) was performed using Modde 7 (Umetrics, Umeå, Sweden).

2.2.9. Dissolution testing

Dissolution behavior of pellets was investigated in 900 ml demineralized water (37 °C) using the paddle method (USP apparatus 2, DT 6 Erweka, Heusenstamm, Germany). The rotational paddle speed was set at 50 rotations per minute (rpm) and the theophylline release was determined spectrophotometrically (Lambda-2, Perkin Elmer, Ueberlingen, Germany) in flow through cells at a wave-

Table 1
Process parameters of the dry powder coating procedure.

Inlet air volume flow	70 m^3/h
Inlet air temperature	50–55 °C
Product temperature	40–41 °C
Rotor speed	230 rpm
Powder feed rate	11.1 g/min
Liquid spray rate	3.2 g/min
Atomizing air pressure	1.5 bar

length of 242 nm. Measurements were performed in triplicate. Release profiles were compared according to f_2 similarity test, with n = quantity of measurement points and R_t and T_t the release data from the reference and test curve at time t:

$$f_2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t-T_t)^2\right]^{-0.5}\times 100\right\} \quad (5)$$

Two dissolution curves are assumed to be equivalent having a value between 50 and 100 which corresponds to a deviation of 10% (O'Hara et al., 1998).

2.2.10. Scanning electron microscopy (SEM)

Cured and uncured pellets of the dry powder coating process were sputter coated with gold for 180 s (Agar Manual Sputter Coater, Agar Scientific Ltd., Stansted, Essex, England). Afterwards the samples were examined by visualizing their surface morphologies with a scanning electron microscope (LEO VP 1430, Carl Zeiss, Oberkochen, Germany).

3. Results and discussion

3.1. Ethylcellulose

3.1.1. DSC measurements

Ethylcellulose having a relatively high T_g of 127 °C (Fig. 2) forms films with weak and brittle properties at the same time (Bodmeier and Paeratakul, 1994). These characteristics require the use of plasticizers to lower the minimum film temperature and to improve the film properties. In dry powder coating, plasticizers are of particular importance, as, besides the enhancement of film formation by lowering the T_g, they improve the adhesion of coating material to the core pellets by forming liquid bridges. Due to the fact that no water is used, which could act as temporary plasticizer, a sufficient plasticizing activity of the used additives is necessary. Therefore DSC measurements of plasticized and pure ethylcellulose films were conducted with commonly used plasticizers of various concentrations to evaluate their efficiency in lowering the T_g of ethylcellulose. The results are shown in Fig. 3. In case of triethyl citrate 40% it was not possible to detect a glass transition temperature as no change in heat capacity was visible. This can be explained with the fact, that DSC exhibits sometimes poor resolution regarding T_g measurements (Sakellariou et al., 1985). Therefore thermomechanical analysis was used for subsequent determinations of glass transition temperatures of plasticized polymer (Section 3.1.3.3). These analyses determine changes due to rheological characteristics of the polymer which are often more easy to detect. Myvacet® revealed the most plasticizing activity in the investigated concentrations and was therefore chosen for further experiments.

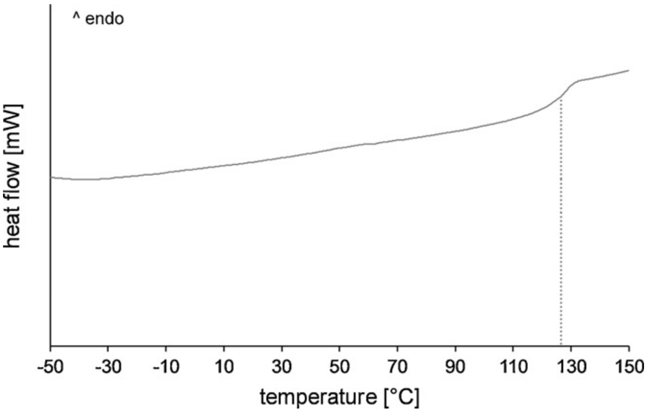

Fig. 2. DSC curve of pure ethylcellulose.

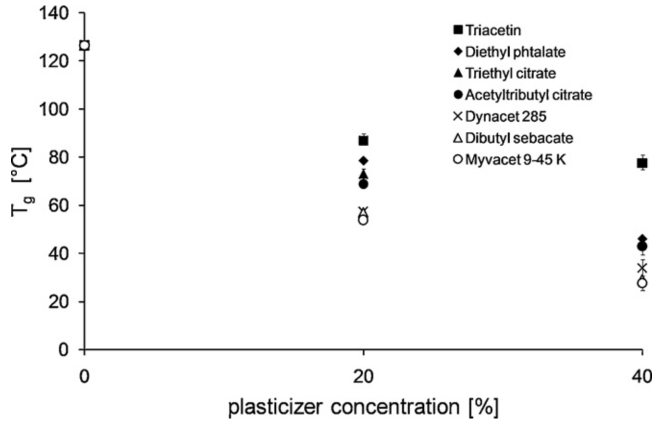

Fig. 3. Glass transition temperatures of plasticized and pure ethylcellulose films measured with DSC (n = 2, mean value, min and max).

3.1.2. Contact angle measurements

The spreading of the liquid additive on the pellet core is relevant only for the very first layer of polymer particles adhered on the core surface. Therefore, the contact angles of the additives on the cores were not determined, since wetting between the core and all investigated liquid additives takes place. As polymer powder is used in the coating process it would be desirable to investigate the spreading behavior of different additives on the powder. However, it is not possible to obtain reliable results with measurements on powders using the sessile drop method due to the roughness of the powder bed's surface (Buckton and Newton, 1986). Indirect measurements on powders like liquid penetration techniques (Washburn method) have several drawbacks described in literature (Buckton and Newton, 1985; Carli and Simioni, 1979). One prerequisite, which is valid for all contact angle determinations, is that no chemical and physical interactions, like swelling and dissolving effects, occur during the measurement. However, these interactions between the liquid additives and the examined polymers cannot be excluded as some liquids may act as plasticizer for the polymer, for instance. In liquid penetration measurements these interactions may be an obstacle in particular, as possible film forming of the polymer may impede the absorption of the liquid into the powder bed. Moreover these interactions are more difficult to detect during the measurement in comparison to the sessile drop technique. Due to the difficulties impairing the measurement of contact angles on powders, two different sample preparations were tested, polymer compacts and polymer films. Fig. 4 shows the results of the contact angle determination on ethylcellulose after 10 s with both sample preparation techniques. Although the measured values reveal slight differences depending on the sample preparation, a correlation between the data is visible (R = 0.986). Nevertheless, the means of the relative standard deviations of the methods differ from 4.1% for films to 8.8% for tablets due to the fact, that the film surfaces are smoother compared to the surfaces of the polymer compacts. Furthermore, contact angle analysis on films is facilitated because reflection of the coated glass slides allows a better drop shape fitting. Since the results of the contact angle determinations are very similar irrespective of the sample preparation technique, the coated glass slides method was chosen for further investigations due to the lower relative standard deviation of the measurements, facilitated analysis and less material consumption. How spreading of the additives on ethylcellulose films proceeds with time is demonstrated in Fig. 5. Only small differences are visible between 10 s and 60 s spreading time. Since the

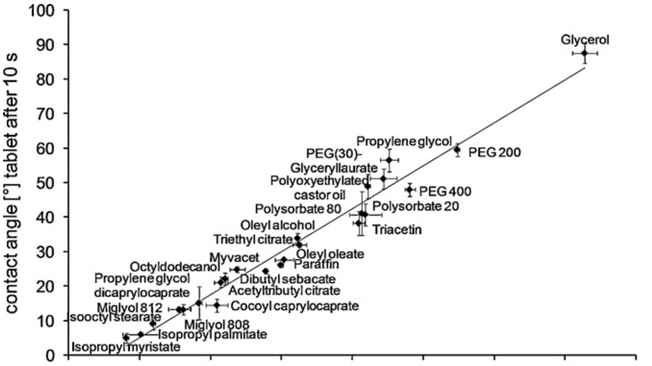

Fig. 4. Contact angles measured after 10 s on ethylcellulose films versus contact angles measured after 10 s on ethylcellulose tablets ($n = 4$, mean value ± standard deviation).

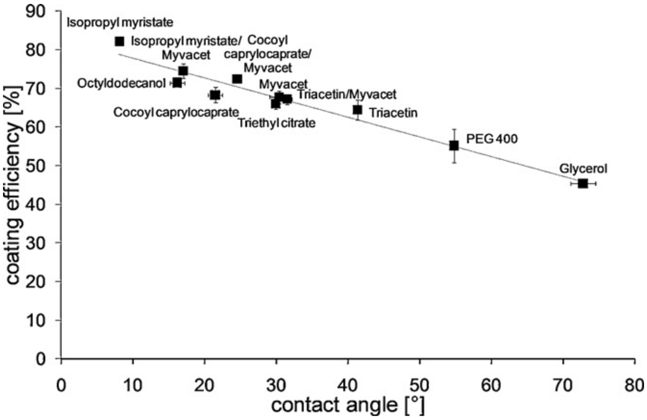

Fig. 6. Contact angles measured after 10 s on ethylcellulose films ($n = 4$, mean value ± standard deviation) versus coating efficiency ($n = 3$, mean value ± standard deviation).

risk of interactions like swelling of the polymer film or dissolving of the polymer in the liquid increases with increasing spreading time, 10 s was chosen for further examinations. To investigate the impact of wetting characteristics on the adhesion of coating material during the process, liquids with varying contact angles (8–73°, values determined after 10 s) were chosen to test their influence on coating efficiency. They are marked by arrows in Fig. 5. Due to the need to apply plasticizers in case of using ethylcellulose as coating polymer three liquid additives were additionally investigated in a 1:1 mixture with Myvacet® for further coating experiments.

3.1.3. *Coating efficiency*

The compositions of the different formulations and the results of the coating procedure with respect to coating efficiency are displayed in Table 2. The dry powder coating process is reproducible with standard deviations ranging from 0.5% to 4.3% (90% of the standard deviations of the formulations were <2.5%).

3.1.3.1. Influence of spreading. To investigate the influence of the spreading behavior of the liquid additives, their coating efficiency was plotted against their contact angle (Fig. 6). The diagram reflects a correlation between the contact angle of the liquid additive and the resulting coating efficiency ($R = 0.974$). With decreasing contact angle the coating efficiency increases. Isopropyl myristate having the lowest contact angle (8°) leads to the highest coating efficiency (82.1%). Glycerol as the additive with the highest contact angle (73°) leads to poor powder adhesion resulting in a coating efficiency of 45.4%. This demonstrates the importance of wetting of the polymer during the process enhancing the formation of liquid bridges being responsible for powder adhesion and confirms the investigations made by Obara et al. (1999). Kablitz et al. (2008) proposed the use of liquid additives remaining a certain time period on the polymer powder surface to achieve higher coating efficiencies. These investigations were done using HPMCAS as coating polymer and triethyl citrate and Myvacet® as plasticizers. Myvacet® led to a higher coating efficiency as triethyl citrate. In this special case, it was possible to detect that Myvacet® was only partly absorbed by the polymer since it remained as a liquid layer on the surface despite mixing, compression to tablets and curing of the plasticizer–polymer mixture. Therefore, it was assumed that Myvacet® led to an increase in

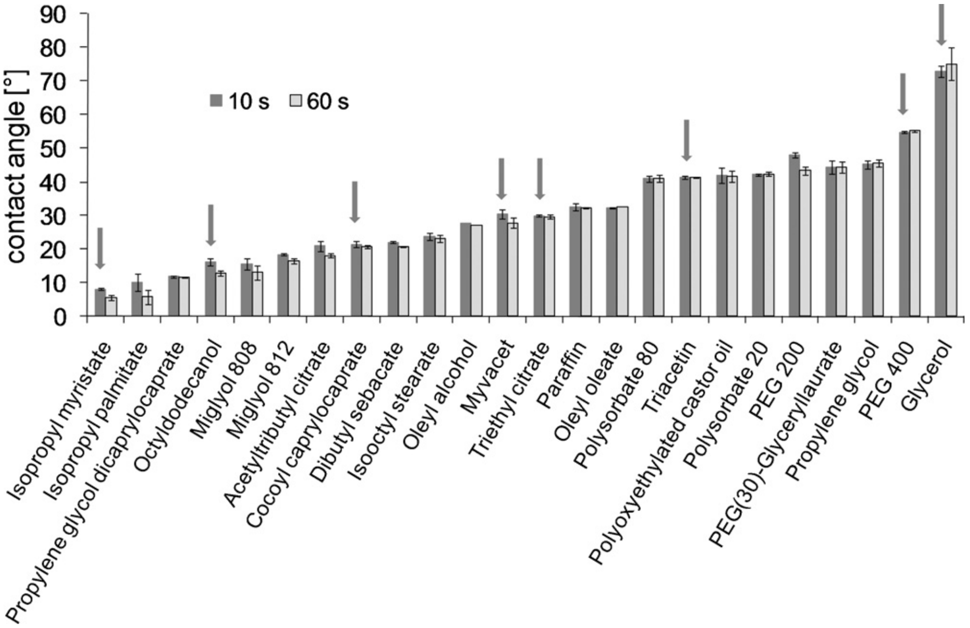

Fig. 5. Contact angles measured after 10 and 60 s on ethylcellulose films ($n = 4$, mean value ± standard deviation). Liquid additives chosen for coating trials are marked by an arrow.

Table 2
Composition of the formulations for dry powder coating and their resulting mean coating efficiency ($n = 3$).

Polymer	Liquid additive	Plasticizer	Liquid amount (rel. to polymer weight)	Coating level of the polymer (target)	Coating efficiency	Standard deviation
Ethylcellulose*	–	–	–	20%	~1%	–
Ethylcellulose	Isopropyl myristate	–	30%	20%	82.1%	0.6%
	Isopropyl myristate	–	40%	20%	85.8%	0.4%
	Isopropyl myristate	–	50%	20%	87.4%	0.3%
	Isopropyl myristate	Myvacet®	30%	20%	74.5%	1.9%
	Cocoyl caprylocaprate	–	30%	20%	68.3%	2.0%
	Cocoyl caprylocaprate	Myvacet®	30%	20%	72.5%	1.1%
	Triacetin	–	30%	20%	64.4%	2.6%
	Triacetin	Myvacet®	30%	20%	67.2%	1.3%
	Octyldodecanol	–	30%	20%	71.5%	0.2%
	PEG 400	–	30%	20%	55.2%	4.3%
	Triethylcitrate	–	30%	20%	66.0%	1.4%
	Glycerol	–	30%	20%	45.4%	0.5%
	–	Myvacet®	30%	20%	67.7%	1.7%
HPMCAS	Isopropyl myristate	–	30%	20%	85.5%	0.4%
	Myvacet®	–	30%	20%	85.7%	0.6%
	Cocoyl caprylocaprate	–	30%	20%	81.8%	0.9%
	Triacetin	–	30%	20%	77.2%	0.6%
	PEG 200	–	30%	20%	77.7%	0.6%
	Glycerol	–	30%	20%	64.4%	0.8%

* $n = 1$.

capillary bridges during the coating process and thus to an increase in coating efficiency. However, in most cases it is difficult to detect the velocity and amount of liquid absorption. As this was not investigated and quantified in this study, it cannot be excluded, that the velocity of liquid absorption may play a role as well. However, the results reveal that contact angle measurements can be used as a predictive tool to identify liquid additives leading to high coating efficiencies.

Similar observations are reported for wet granulation processes where the role of the spreading coefficient λ in the selection of suitable binders was examined (Rowe, 1990; Iveson et al., 2001; Tuske et al., 2005). The spreading coefficient λ is a measure of the tendency of a liquid and a solid to spread over each other and is related to the works of cohesion and adhesion:

$$\text{Work of cohesion} \quad W_C = 2\gamma_L \tag{6}$$

$$\text{Work of adhesion} \quad W_A = \sigma_S + \gamma_L - \gamma_{SL} \tag{7}$$

$$\text{Spreading coefficient} \quad \lambda_{LS} = W_A - W_C \tag{8}$$

σ_S is the surface free energy of the solid, γ_L the surface tension of the liquid, γ_{SL} the interfacial tension between the solid and the liquid and λ_{LS} the spreading coefficient of the liquid over the solid. A positive spreading coefficient of the binder over the substrate leads to reproducible and less fragile granules (Iveson et al., 2001). However, if the spreading coefficient is negative, granulation still occurs but with another growing mechanism (Rowe, 1989) resulting in weaker agglomerates. Another possibility to calculate the work of adhesion described in literature is derived by substitution of the Young–Dupré equation:

$$W_A = \gamma_L(\cos\theta + 1) \tag{9}$$

Using this equation, the maximum achievable value of the spreading coefficient is zero meaning the closer to zero, the better the spreading. In contrary to Eq. (7) it is not necessary to determine the polar and disperse fractions of surface energies of the solid and the liquid but to investigate directly the interactions between them by measuring the contact angle.

To further investigate the role of spreading behavior in dry powder coating both mathematical approaches were tested to calculate the work of adhesion between ethylcellulose and the different liquid additives used for the coating procedures. The surface energy of ethylcellulose for Eq. (7) was determined on films and tablets to evaluate if the sample preparation has any impact on the work of adhesion. The contact angle of the various liquid additives on ethylcellulose films measured after 10 s was used to calculate the

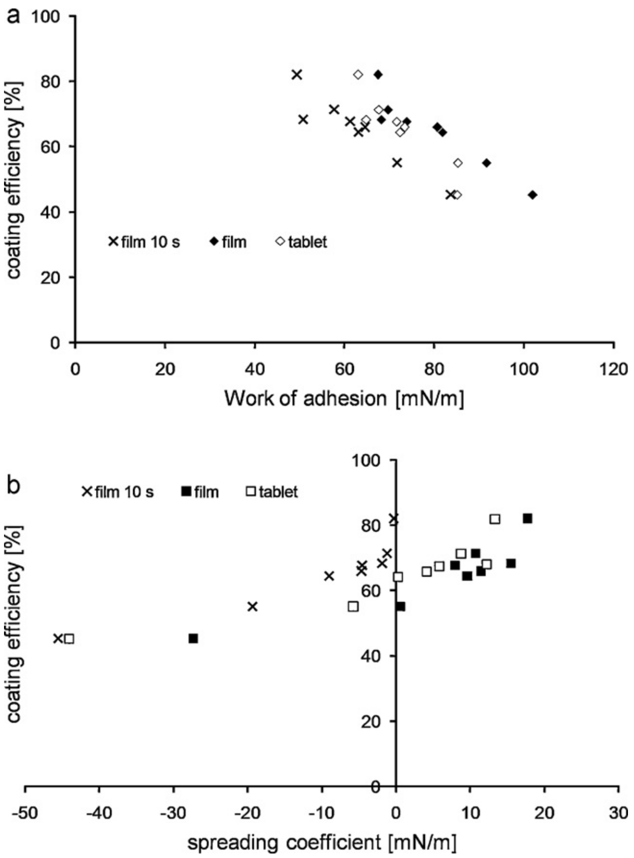

Fig. 7. (a) Calculated values of work of adhesion between liquid additives and ethylcellulose versus coating efficiency ($n = 3$, mean value ± standard deviation). "Film 10 s" was calculated using Eq. (9) with contact angles measured on ethylcellulose films after 10 s. "Film" and "tablet" were determined using Eq. (7), surface energy data were obtained from either ethylcellulose films or tablets. (b) Calculated spreading coefficients of liquid additives over ethylcellulose versus coating efficiency.

Table 3
Correlation coefficients of different methods and sample preparations correlated with the coating efficiency.

Correlation	Sample	R
CE versus contact angle	Ethylcellulose film	0.974
	HPMCAS film	0.951
CE versus work of adhesion	Ethylcellulose film 10 s	0.940
	Ethylcellulose film	0.937
	Ethylcellulose tablet	0.923
CE versus spreading coefficient	Ethylcellulose film 10 s	0.904
	Ethylcellulose film	0.890
	Ethylcellulose tablet	0.890

work of adhesion with Eq. (9). In Fig. 7a the coating efficiency is plotted against the work of adhesion calculated by means of Eq. (7) (film and tablets) and Eq. (9) (contact angle measured on films after 10 s). A similar trend is obvious although the values obtained by the various methods differ. With decreasing work of adhesion the coating efficiency increases regardless of the determination method or sample form. The results of the calculated spreading coefficients are shown in Fig. 7b. The higher the spreading coefficient calculated using Eq. (7), the higher the coating efficiency obtained. Data derived from Eq. (9) show that high coating efficiencies were obtained with spreading coefficients close to zero. These results clearly indicate the importance of spreading of the coating liquid additive over the polymer powder during dry powder coating. In contrast to wet granulation processes in which granulation even feasible with negative spreading coefficient, powder adhesion seems to be strongly impaired in dry powder coating.

In comparison to the contact angle measurements, the correlation coefficients of spreading coefficients and works of adhesion are slightly lower (Table 3). One possible explanation can be the fact that surface energy values depend on the determination method used and can differ when using other theories (Zenkiewicz, 2007). Therefore, these values should be seen considering their determination method and not as true values. Nevertheless, the results indicate that applying the Owens–Wendt approach for surface energy determination, the calculated works of adhesion and spreading coefficients can be used as predictive tools as well without the need to conduct additional contact angle measurements. However, contact angle determinations show a better correlation and are probably less error-prone.

3.1.3.2. Influence of viscosity. The viscosity of a liquid can affect the spreading velocity although it does not have an influence on the contact angle. Furthermore it is reported in literature that viscous forces can have an effect on granule consolidation in wet granulation processes (Iveson et al., 2001). Therefore it was of interest to evaluate the impact of liquid additive viscosity on the coating efficiency. The results are shown in Fig. 8. The viscosity of the tested liquid additives was relatively low ranging from 4.9 mPa s to 77.2 mPa s except for glycerol with 744 mPa s. The correlation between viscosity and coating efficiency is poor (R = 0.771). Thus, the viscosity of the liquid additives alone cannot be used as screening tool.

However, viscosity also affects the spray generated by pneumatic atomizers and thus the quality of the liquid distribution during the coating. In order to quantify the influence of the viscosities on the sprays, the droplet sizes were measured. These measurements could not be carried out during the coating process, but externally under spraying conditions according to the process. Table 4 demonstrates the results of these determinations. Comparable mean droplet sizes in the range of 16.7 μm to 21.3 μm of the sprays were found for all additives except for glycerol. The mean droplet size of glycerol was found to be about 220 μm. Additionally, the atomization performance of glycerol was poor, as pulsation of the spray was observed. This may lead to insufficient glycerol distribution during the coating process and can be an additional reason for the weak powder adhesion when using glycerol.

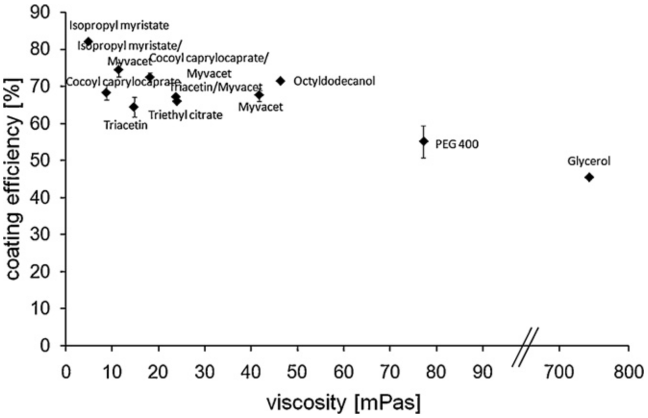

Fig. 8. Viscosity of liquid additives versus coating efficiency (n = 3, mean value ± standard deviation).

3.1.3.3. Influence of plasticizing activity. The plasticizing activity of the liquid additives on ethylcellulose was examined by means of thermomechanical analysis. An efficient plasticizer may have a good solubility within the polymer and thus might be quickly absorbed impairing liquid bridge formation on the powder surface possibly decreasing the coating efficiency (Kablitz et al., 2008; Klar and Urbanetz, 2009). Another possible impact can be a higher stickiness occurring during the process when using a liquid additive with high plasticizing activity. This can lead to a desired increase of material adhesion on the one hand but also to undesired agglomeration

Table 4
Evaluation of mean droplet sizes of the liquid additives at an atomizing air pressure of 1.5 bar and a spray rate of 3.2 g/min and the surface tensions measured with a tensiometer.

Liquid	Mean droplet size d_{50} [μm]	Surface tension [mN/m]
Triethyl citrate	16.7	34.65
Triacetin	17.0	36.10
Isopropyl myristate	17.6	24.85
Cocoyl caprylocaprate	17.8	26.36
Octyldodecanol	18.2	29.45
Myvacet®	18.4	32.91
PEG 400	21.3	45.53
Glycerol	220	64.63

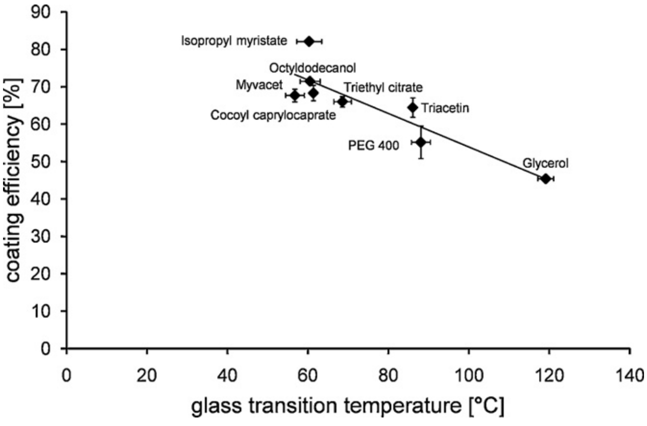

Fig. 9. Glass transition temperatures of plasticized ethylcellulose films measured with thermomechanical analysis (n = 3, mean value ± standard deviation) versus coating efficiency (n = 3, mean value ± standard deviation).

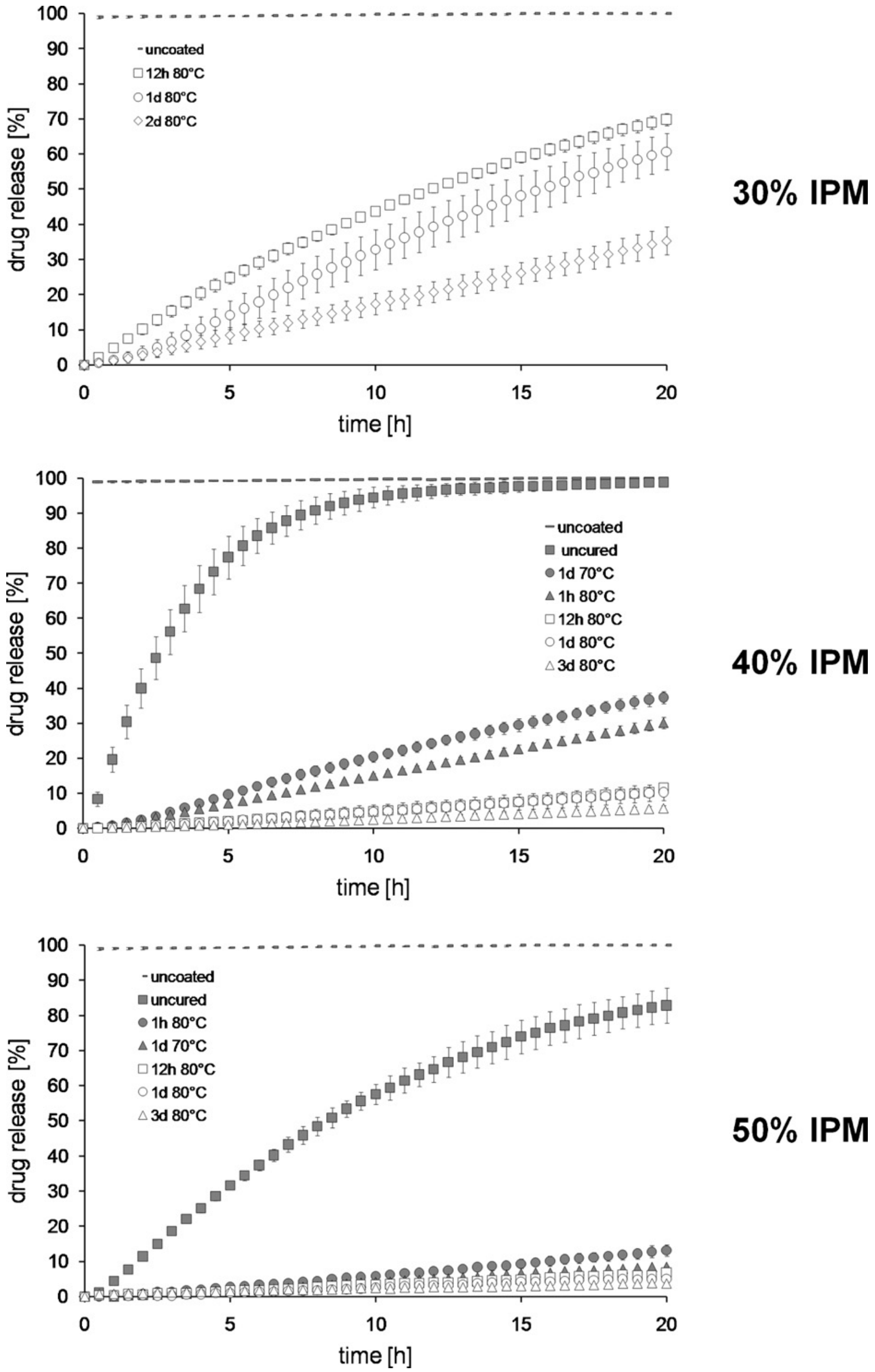

Fig. 10. Dissolution profiles of uncoated theophylline pellets and dry powder coated with ethylcellulose and different amounts of isopropyl myristate in dependence on curing conditions ($n = 3$, mean value ± standard deviation).

of pellets and sticking to container walls on the other hand. Fig. 9 exhibits the interrelationship between the glass transition temperature of plasticized ethylcellulose films and the coating efficiency. With lower T_g coating efficiency tends to higher values but it is not possible to choose liquid additives leading to sufficient material adhesion only relying on T_g measurements since there are too many values deviating from the regression line ($R = 0.88$). The liquid additive providing the highest coating efficiency, isopropyl myristate, also exhibits a plasticizing effect on ethylcellulose ($T_g = 60.3\,°C$). Hence, it is possible to use it without an additional plasticizer. For further investigation, the T_g of plasticized ethylcellulose films with varying isopropyl myristate contents were measured (Table 5). With increasing plasticizer content the T_g decreases till 46.3 °C with 50% isopropyl myristate. The influence of the various isopropyl myristate amounts on the coating efficiency is shown in Table 2, it increases from 82.1% (30% isopropyl myristate) to 87.4% (50% isopropyl myristate).

3.1.3.4. Multiple linear regression. The coating efficiency was correlated with the contact angle between liquid additives and

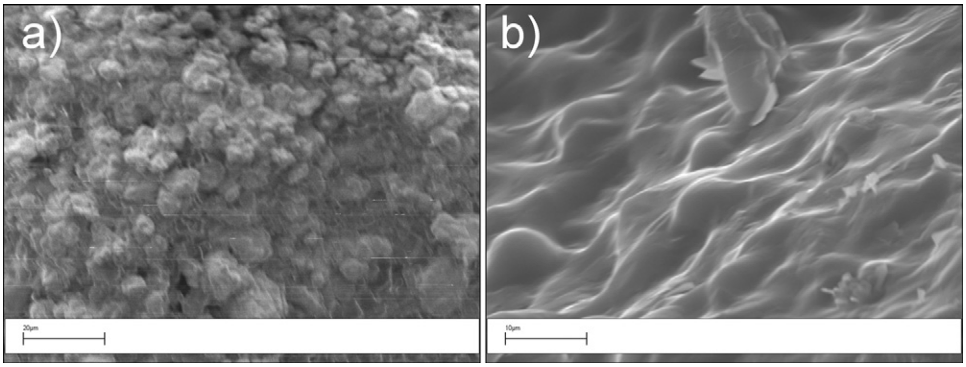

Fig. 11. SEM images of pellets dry powder coated with ethylcellulose: (a) uncured and (b) cured (80 °C for 1 day in an oven).

Table 5
Glass transition determinations on ethylcellulose films containing different amounts of isopropyl myristate via thermomechanical measurements, $n = 3$, mean value ± standard deviation.

Plasticizer amount (rel. to polymer weight)	T_g [°C]
Isopropyl myristate 30%	60.3 ± 0.8
Isopropyl myristate 40%	51.1 ± 0.2
Isopropyl myristate 50%	46.3 ± 0.1

ethylcellulose films, the viscosity of liquid additives, the glass transition temperature of plasticized ethylcellulose films and the droplet sizes of the liquid additives using multiple linear regression. Only the contact angle has a significant influence ($\alpha = 0.05$) on coating efficiency, the other variables do not reveal a significant effect. These results confirm those obtained by the univariate linear regressions that contact angle measurements have the most predictive power regarding the coating efficiency.

3.1.4. *Evaluation of film formation*

The dry powder coating process can be roughly divided into a material application phase, the coating phase, and into a film forming phase in which the polymer particles coalesce to form a film. Whether both occur simultaneously during the process depends on the polymer's glass transition temperature and rheological characteristics and on the process parameters used. To evaluate the effectiveness of film formation, dissolution testing is an appropriate tool. A dense ethylcellulose film should reveal a considerable retard effect if no pore forming agents are used and should not change its dissolution characteristics when exposed to elevated temperatures and/or humidity (Siepmann et al., 2007). This can be simulated by curing steps at different temperatures, times and humidities.

Fig. 10 shows the results of the dissolution testing of the formulations with 30%, 40% and 50% isopropyl myristate, which is the liquid additive leading to the highest coating efficiency among the tested liquid additives and exhibiting also plasticizing activity. The release behavior of the formulation with 30% isopropyl myristate was not stable after curing for 1 day at 80 °C and the release rate decreased further after 2 days of curing. Since the active substance theophylline is thermically stable up to a temperature of 250 °C, degradation did not take place at these curing conditions. Therefore, the changes in the release profiles are due to further coalescence of the polymer particles (Schnitzler et al., 2004). Curing at 80 °C for 1 day did not result in complete film formation, therefore, the dissolution behavior of uncured pellets or cured at lower temperature was not evaluated. Using 40% isopropyl myristate the dissolution profile did not change anymore upon further treatment after curing for 12 h at 80 °C. This indicates complete film formation. Shorter curing times and lower temperatures were insufficient and may lead to changes in the release characteristics after storage. The

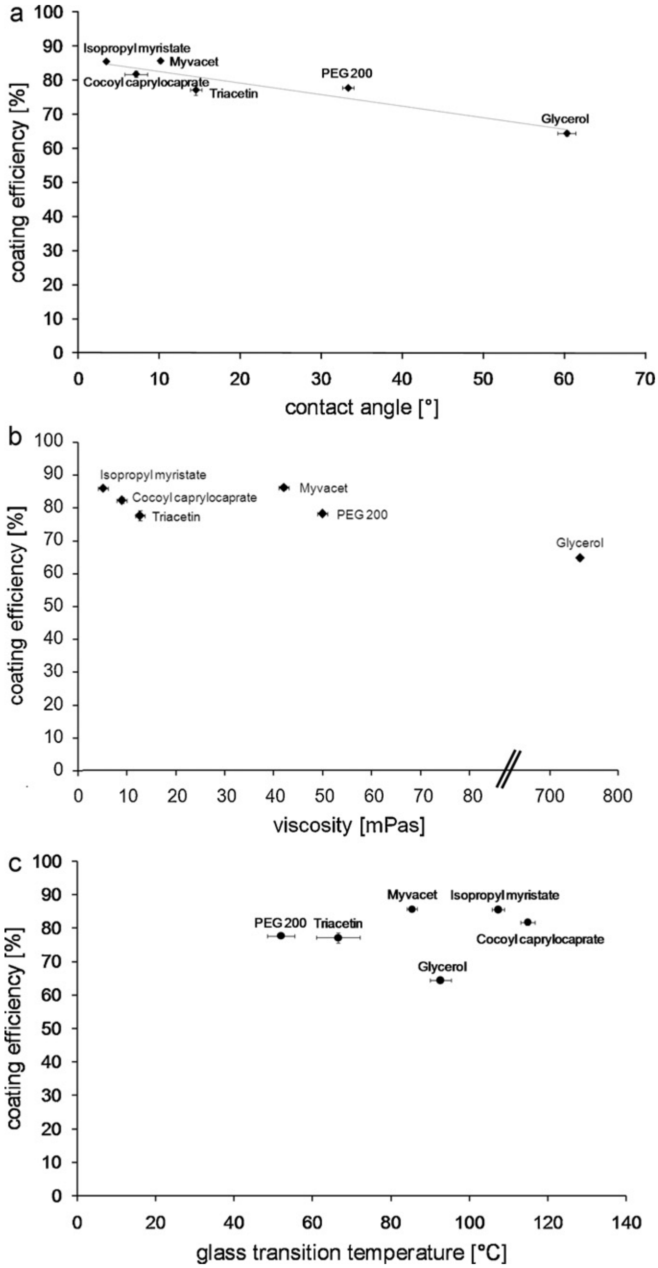

Fig. 12. (a) Contact angles measured after 10 s on HPMCAS films ($n = 4$, mean value ± standard deviation) versus coating efficiency ($n = 3$, mean value ± standard deviation). (b) Viscosity of liquid additives versus coating efficiency. (c) Glass transition temperatures of plasticized HPMCAS films ($n = 3$, mean value ± standard deviation) versus coating efficiency.

formulation containing 50% isopropyl myristate did not change its release behavior after curing at 80 °C for 1 h ($f_2 = 69.5$ for 80 °C/1 h and 80 °C/12 h and $f_2 = 61.6$ for 80 °C/1 h and 80 °C/3 days). Curing at 70 °C for 1 day also led to successful film formation. These results demonstrate the impact of plasticizer concentration on the curing conditions required.

Although thermomechanical investigations exhibited glass transition temperatures of 46.3–60.3 °C for the different formulations (Table 5), it was necessary to cure at higher temperatures to achieve sufficient polymer coalescence within a reasonably short time. This is in contrast to the findings of Kablitz and Urbanetz (2007) that curing at the glass transition temperature leads to adequate film formation within less than 1 h when using HPMCAS as coating polymer. This emphasizes the impact of the polymer used. Ethylcellulose is known for its brittleness and its poor film formation properties even in aqueous coating in which film formation is enhanced by water acting as temporary plasticizer and by capillary forces arising through evaporation of dispersion media. Koerber et al. (2010) found that storage stability at accelerated conditions of 40 °C and 75% relative humidity with an aqueous ethylcellulose/hydroxypropyl methylcellulose formulation containing 25% (w/w) triethyl citrate was only possible with curing at 60 °C and 75% relative humidity or 80 °C at ambient conditions.

SEM images of cured and uncured pellets were taken to evaluate visually the film formation. Uncured pellets revealed a rough surface with visible single polymer particles whereas pellets cured at 80 °C for 1 day exhibited a smooth and coalesced one (Fig. 11).

3.2. HPMCAS

To examine the applicability of the results obtained with ethylcellulose to other polymers, the impact of contact angle, viscosity and plasticizing activity of liquid additives on coating efficiency using HPMCAS was investigated. The results are demonstrated in Fig. 12. Viscosity ($R = 0.89$) and T_g ($R = 0.209$) measurements alone are not appropriate as screening tool for choosing liquid additives whereas contact angle determinations exhibit a correlation between low values and high coating efficiency ($R = 0.951$). Thus, the data gained using ethylcellulose seems to be applicable on other coating systems as well.

4. Conclusion

The results demonstrate the impact of liquid additives, like plasticizers, on the coating efficiency of a dry powder coating process. Spreading behavior of liquid additives on the polymer was identified as a key parameter influencing powder adhesion. Contact angle measurements on polymer compacts and films proved to be a successful screening tool to choose liquid additives leading to high coating material adhesion and thus coating efficiency. Calculated values for works of adhesion and spreading coefficients exhibited also potential for use as predictive tools. Determination of surface energy of the coating polymer used can help to optimize the formulation and to save experiments and material. Viscosity data of the liquid additives and evaluation of their plasticizing activity on the polymer used are not adequate to be used as predictive tools solely.

Finally film formation of ethylcellulose with isopropyl myristate exhibiting good spreading on the polymer as well as plasticizing activity at the same time was successful resulting in stable release profiles.

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