Department of Pharmaceutical Technology[1], Faculty of Mathematics-Physics-Chemistry,Beuth Hochschule für Technik Berlin-University of Applied Sciences, Berlin, Germany; Department of Pharmaceutical Technology[2], and Pharmaceutical Biopolymer Group (PBiG), Faculty of Pharmacy, Silpakorn University, Nakhon Pathom, Thailand

A burst drug release caused by imperfection of polymeric film-coated microparticles prepared by a fluidized bed coater

P. Sriamornsak[1,2], G. L. Casallas-Hernández[1], S. Manchun[2], M. Kumpugdee-Vollrath[1]

Received February 10, 2011, accepted March 24, 2011

Prof. Dr. Mont Kumpugdee-Vollrath, Studiengang Pharma- und Chemietechnik, Beuth Hochschule für Technik Berlin, Luxemburger Str. 10, 13353 Berlin, Germany
vollrath@beuth-hochschule.de

Pharmazie 66: 576–583 (2011) *doi: 10.1691/ph.2011.1020*

The aim of this study was to investigate the drug release from microparticles coated with various polymeric films. Ibuprofen-loaded microparticles with diameter of 250 and 300 μm were prepared by a fluidized bed granulator. Five polymers were used as coating materials, i.e., ethylene vinyl acetate, ethyl cellulose, ethyl cellulose aqueous dispersion, polyethacrylate or Eudragit® NE 30D, and carnauba wax. The coating was performed with a fluidized bed coater. Afterwards the coated microparticles were characterized in terms of particle size, morphology, and drug content. The drug dissolution was also investigated in pH 7.4 phosphate buffer. In our attempts for production of extended release ibuprofen microparticles coated with polymeric films, it was shown that the coating process had a significant effect on drug release. The undesired burst release of ibuprofen was observed in all film-coated microparticulate formulations, resulting from the imperfection of coating films.

1. Introduction

Recently, there has been an increasing interest in the development of multiparticulate dosage forms for controlled release of drugs. Microparticles have a spherical or irregular shape with the particle size between 1 and 1000 μm (Kutz and Wolff 2007). The potential of microparticles as drug delivery systems has increased since the last two decades and has been useful in terms of flexibility during formulation development and therapeutic benefits to patients. Administration of microparticles offers the advantages of oral multiple-unit dosage forms, e.g., free dispersion in GI-tract to avoid local irritation and dose dumping, and provide uniform absorption and improve bioavailability. Microparticles may be filled into hard-shell gelatin capsules, compressed into tablets, suspended in liquids or packaged in sachets (Ghebre-Sellassie 1994).

Polymeric film coatings have been used in pharmaceutical products for many years to cover taste, protect the unstable or sensitive ingredients from degradation reactions (for example, by light, moisture, air, temperature and oxygen), increase the possibility to swallow the product, and modified release properties to the products (Aulton 2007; Kumpugdee-Vollrath and Krause 2011). Nowadays, the film coatings can be mainly applied on the products by using two different starting materials; film coating materials dissolved in organic solvents or film coating materials as aqueous dispersions (latex). The latter is of interest and increasing importance due to the environmental concern as well as safety and economic reasons (McGinity 1997). The equipment used to apply coatings includes a conventional pan, a perforated pan and a fluidized-bed coating machine. The fluidized-bed technique is suitable for coating small particles such as pellets and granules of active substances due to its drying efficiency and good mixing properties. However, film coating of microparticles and nanoparticles, is a major challenge due to their extremely small size, high surface energy, and high surface area. Thus, agglomeration and deagglomeration can occur and result in surface craters or irreversible agglomeration. Coatings can be applied to fluidized particles by various techniques, i.e., spraying from the top, from the bottom, or tangentially (Jones 1994).

The performance of the coated microparticles fundamentally depends on quality aspects, e.g., microparticle film coating thickness, homogeneity and morphology. Better control of the particle coating process has therefore stimulate the efforts to monitor the coating process by measuring the coating thickness of microparticles. However, this is practically limited for microparticles (Wesdyk et al. 1990). Microscopic techniques, e.g., scanning electron microscopy (SEM) and conventional optical microscopy can be applied to determine coating thickness (e.g., Andersson et al. 2000; Larsen et al. 2003). In previous studies, only the average coating thickness is estimated and no information on the heterogeneity or overall coating quality of coated microparticles is given (Andersson et al. 2000). An exception is the work of Depypere et al. (2009), who performed an analysis of film coating thickness and coating quality of microparticles by confocal laser scanning microscopy. However, the effect of coating quality on drug release has not been observed. Therefore, in our study, the coating thickness and coating quality (or coating deficiency) of polymeric film coated microparticles were observed by SEM. The influence of the coating quality on the drug release was investigated by digital video microscopic technique.

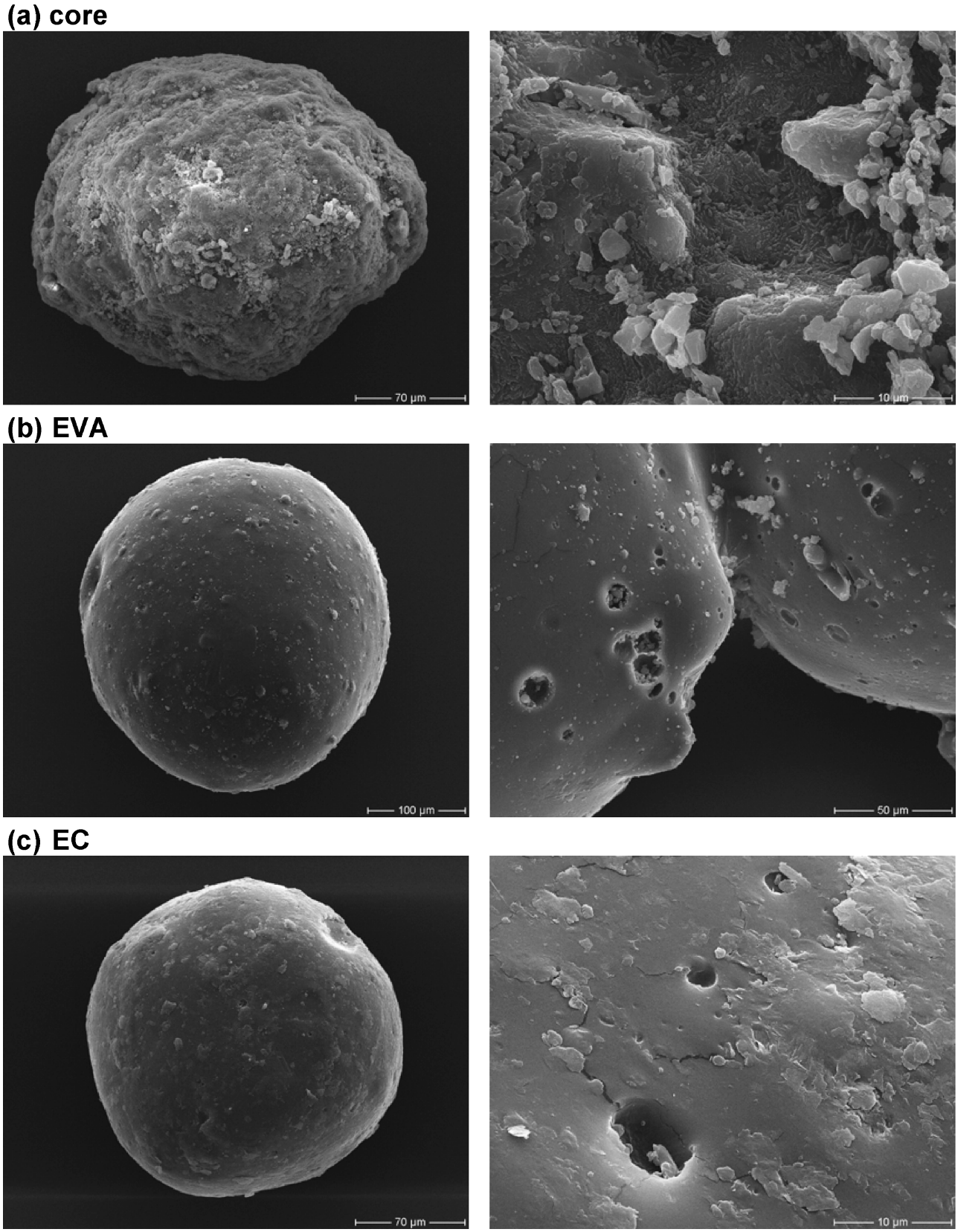


Fig. 1: Scanning electron micrographs showing surface morphology of microparticles; (a) uncoated core, and microparticle coated with (b) EVA, (c) EC, (d) ECAq, (e) EudNE and (f) CW.

2. Investigations, results and discussion

2.1. Manufacture of microparticles and coated microparticles

Ibuprofen (IBP) (Highton 1999) microparticles were produced by granulation using fluidized bed technique. To keep agglomeration to a minimum, it is very useful to have a narrow particle size. In this study, a narrow and uniform particle size distribution within the range was achieved with the mode of 200–250 µm (84% w/w). This fraction was selected as core materials for further coating with different polymers. Polymeric film coating was performed using a bottom-spray fluidized bed technique.

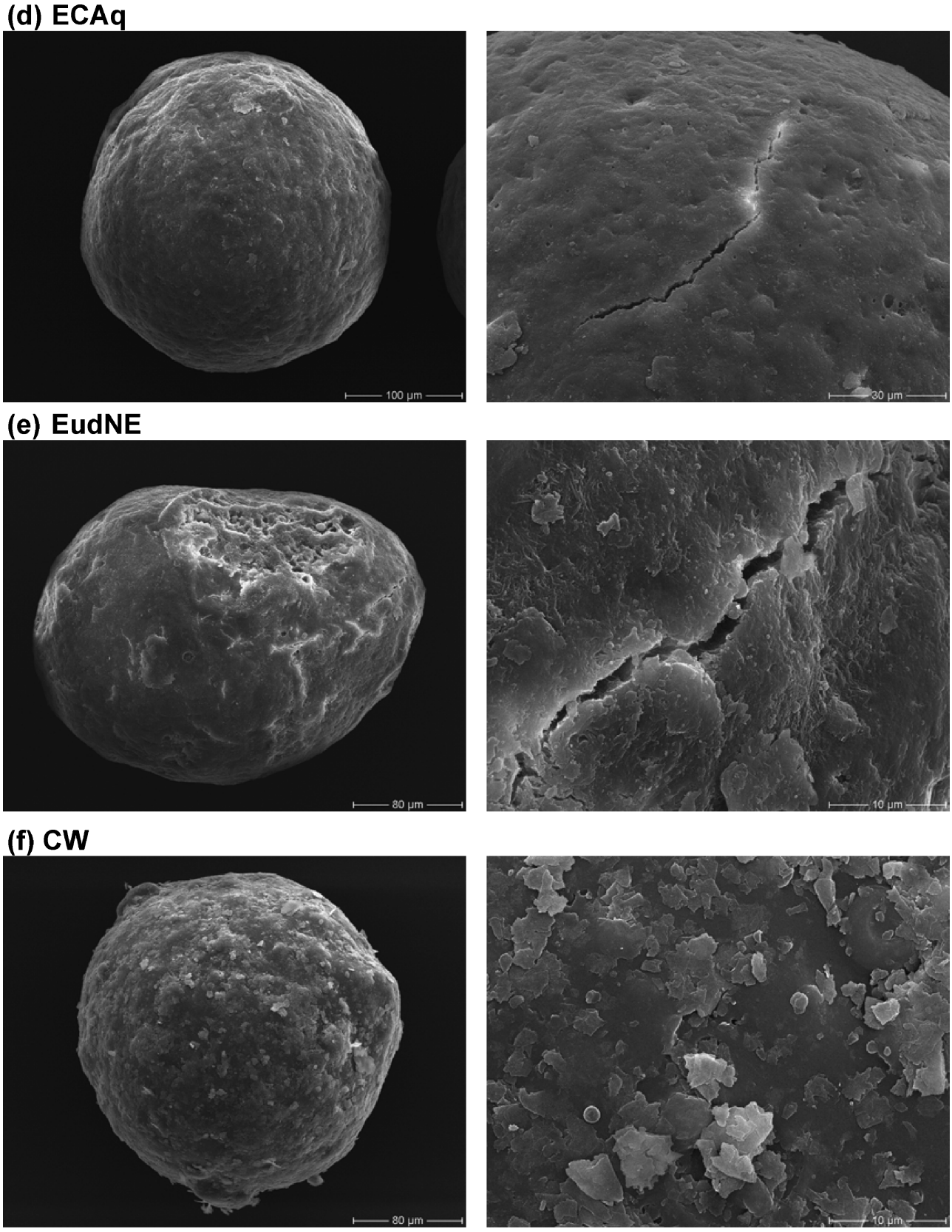


Fig. 1: (*Continued*).

During the coating process, there are several factors that may cause non-uniformity of the coating (Kumpugdee-Vollrath and Krause 2011): (i) particles stick together and create dents on the coating, (ii) stress which develops during the coating process and gravitational forces can result in a thinner coating along the front in the traveling direction and a thicker coating on the opposite side, (iii) if higher rates of evaporation of the solvent are experienced along one side due to the direction of air flow, the reduction in temperature can cause surface tension gradients leading to the surface deflection (Haddish-Berhane et al. 2006). To minimize the difficulty of giving general parameters for the equipment setups according to several recommendations and

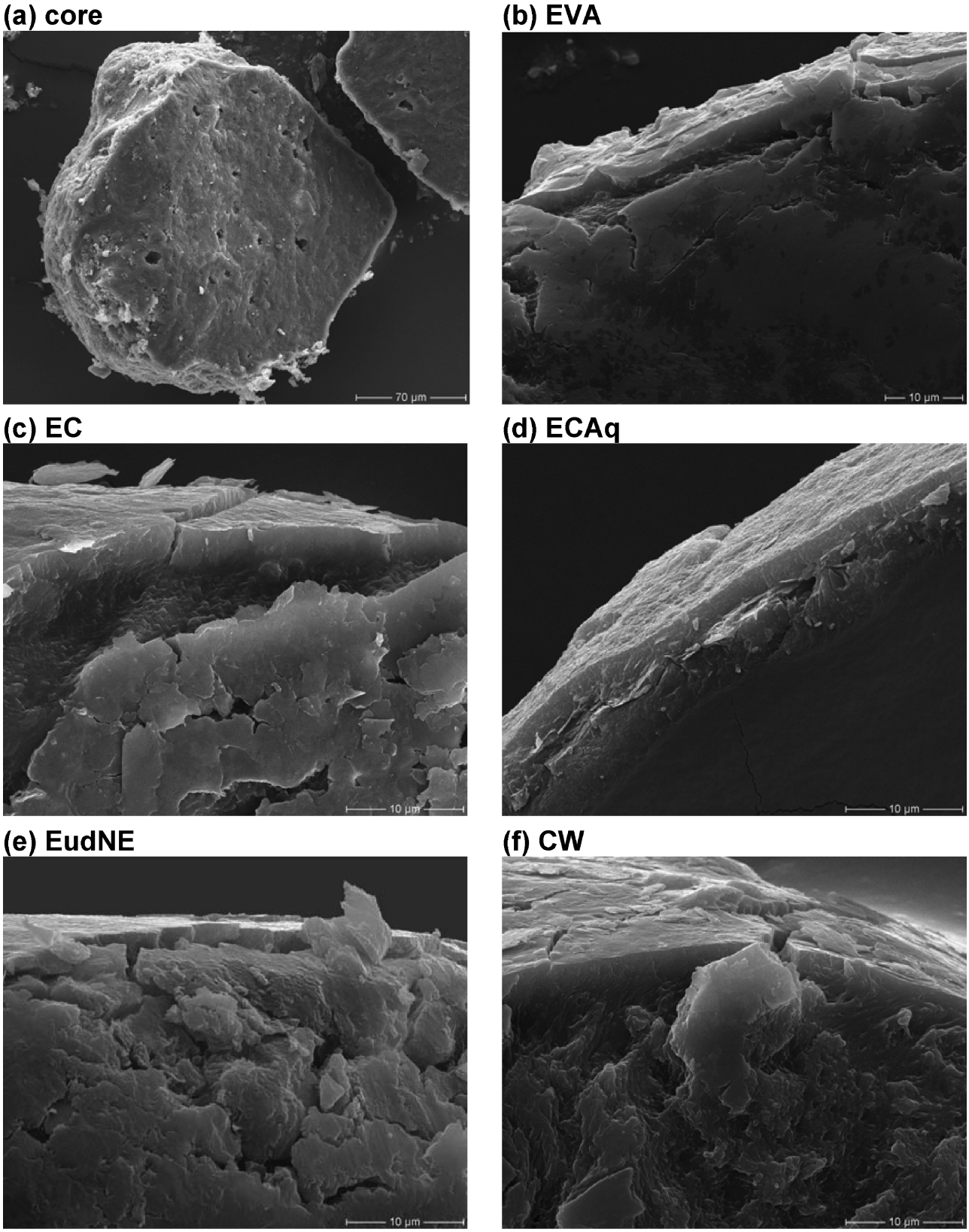


Fig. 2: Scanning electron micrographs showing internal structure of microparticles and the film-thickness; (a) uncoated core, and microparticle coated with (b) EVA, (c) EC, (d) ECAq, (e) EudNE and (f) CW.

experiences used in this technology, it is considered that all parameters relevant to the product quality should be controlled during the spray coating process. The bottom spray method is preferred for the coating of IBP microparticles even though nozzle blockage may happen during the coating process. Werner et al. (2007b) identified several fundamental phenomena that occur during an air-suspension particle coating process. According to their investigation, micro-level processes were analyzed in order to understand how coating quality was influenced by the performed process by a means of the Lödige WFP fluidized bed laboratory unit in this study. The stickiness problems can be found in the air-suspension particles coating because the adhesion of the droplet on the substrate particle surface occurs. Droplets that do not successfully adhere represent as coating pro-

cess inefficiency. For the lipid wax (e.g., carnauba wax) coating that was used in this work, the momentum of the droplet and particles at collision in the adhesion efficiency are factors that play an important role for a good quality coating.

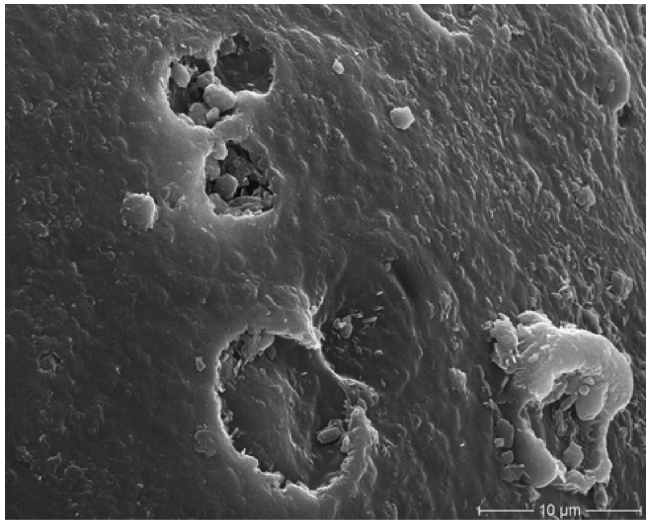
The major particle size fraction of coated microparticles was also in the range of 200–250 μm. The particle size distribution of microparticles coated with different polymers was similar. The fine and coarse fraction increased slightly compared to the uncoated cores (sieve fraction 200–250 μm). An explanation is the occurrence of abrasion and agglomeration during the coating process. Film thickness, as calculated from the increase in diameter, of microparticles coated with ethyl cellulose (EC), ethyl cellulose aqueous dispersion (ECAq), Eudragit® NE 30D (EudNE), ethylene-vinyl acetate copolymer (EVA), and carnauba wax (CW) was 4.0, 4.9, 3.1, 4.0, and 2.8 μm, respectively. It is thought that the film coat was too thin and may not be sufficient to sustain the drug release.

2.2. Morphology of microparticles and coated microparticles

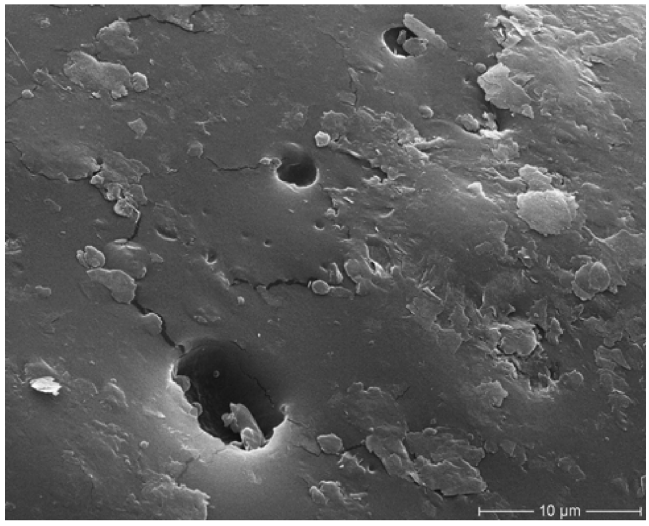
Coating morphology refers to the variation of a given property between particles containing the same amount of coating material. Figs. 1 and 2 illustrate the morphology of the uncoated microparticles and the microparticles coated with different polymeric films, observed by scanning electron microscope (SEM). The uncoated microparticles were irregular in shape with a rough surface (Fig. 1a). Figures 1b-1f show the surface appearance of microparticles with the film coating. The coated microparticles were approximately spherical with a smooth surface. The surface structure of all coated pellets appeared the same irrespective of the type of polymeric film. The coating films prepared by using organic solvents (EVA and EC) showed a smoother surface than those using aqueous dispersions (e.g., ECAq and EudNE). In addition, the minor coating imperfections, e.g., fine cracks of film surfaces were found when the microparticles were coated with ECAq and EudNE. These cracks are not evident in EVA or EC coating. The cracks may result from shrinkage during the drying process, which causes stress fractures in the coating or perhaps during the SEM observation.

Moreover, the inhomogeneous films observed in the formulations using aqueous dispersion coatings may be due to incomplete film formation (Werner et al. 2007a). It is very important when aqueous dispersions are used. It means progressive films formation from these dispersions after coating by coalescence of the latex particles (Steward et al. 2000). High temperatures and high atomizing air pressure were avoided because of incomplete film formation during the coating process. However, it is known that a continuous film is formed when the drying temperature is adjusted to 10 °C above the glass transition temperature (Petereit and Weisbrod 1999), this was not the case in some polymers (see Table 1). In this study, the temperature of 35–50 °C was used for polymer coating but it may not be sufficient.

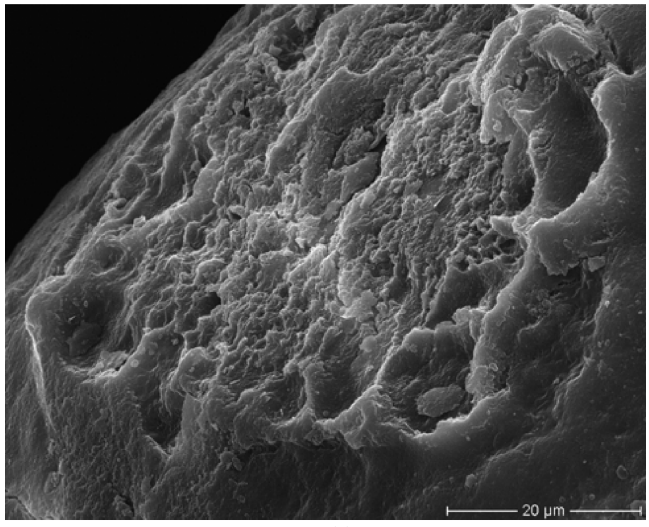
Particle ordering probably took place due to solvent evaporation, but interfacial forces might not strong enough for particles to coalesce, thus yielding a discontinuous and incomplete film (Mendoza-Romero et al. 2009). Obvious imperfections can be caused to the spreading of the droplet on the particle surface because the success of the coating operation depends on it (Werner et al. 2007b). Some possible outcomes of the impact of a droplet on the surface of the microparticles can be assumed. One case in which either the droplet velocity was too high or significant droplet drying has occurred, resulted in droplet rebound. The other case could be that the droplet adhered successfully but did not spread.



(a)



(b)



(c)

Fig. 3: Scanning electron micrographs showing defect of coated microparticles; (a) EVA, (b) EC and (c) ECAq.

Carnauba wax (CW), which is usually used to improve the moisture-barrier ability in formulation of edible films and coatings, showed the potential for coating onto microparticles. The CW in the coating film is responsible for creating uniform layers of large flakes covering the particles (Fig. 1f). Simi-

Table 1: Glass transition temperature of film-forming materials used in this study

Film-forming material	Glass transition temperature (°C)
EVA (Elvax® 40W)	−25 (DuPont 2011)
EC (Ethocel® Standard 40 Premium)	129–133 (Dow Chemical 2005)
ECAq (Aquacoat® ECD)	89 (McGinity 1997)
EudNE (Eudragit® NE 30D)	−8 (Bauer et al. 1988)
CW	Not available

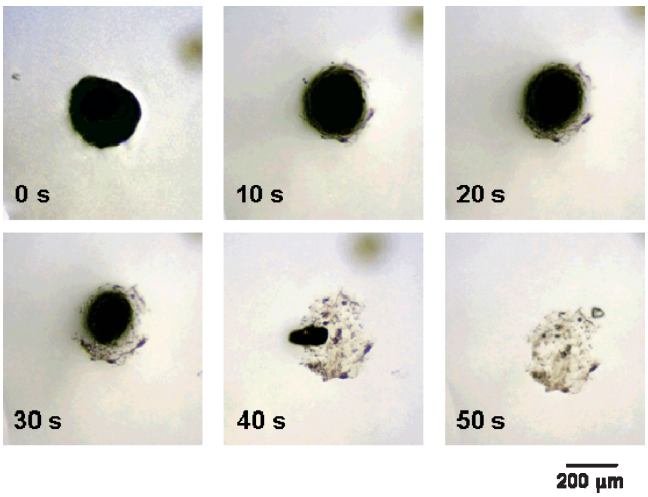


Fig. 4: Video microscopic images of uncoated microparticles in pH 7.4 phosphate buffer.

lar results were reported by Chen and Nussinovitch (2001) in which the CW coating shows the consistent layers of large chips but demonstrates more chaotic, less ordered small flakes when hydrocolloids were added. Fig. 2 shows the cross-sectional view of uncoated and coated microparticles observed by SEM. The thin polymer coats (i.e., 3–5 µm) were seen. This agreed with the film thickness calculated from the increase in diameter, as mentioned above in section 2.1.

The sticking tendency of aqueous dispersions coating (i.e., EudNE and ECAq) was observed. Figures 1e and Fig. 3c demonstrate picking, which is a consequence of the spraying rate exceeding the drying capacity of the process, causing tablets to stick together and subsequently break apart. Another coating process-related problem is orange peel or roughness, which is usually the result of premature drying of atomized droplets of polymer solution. It is considered that the inefficient coating conditions, e.g., low temperature for coating and drying, may play an important role on the coating quality. The possible way to solve of this problem is, e.g., to increase process time, to increase amount of coating material, to increase drying time, to perform curing after the coating or to add plasticizers. The success of these methods has been reported in our previous publications (Heckötter et al. 2011; Ngawhirunpat et al. 2010). Fig. 4 shows video microscopic images of the uncoated microparticles in pH 7.4 phosphate buffer at different times. It is obvious that the particles dissolved quickly, within 50 s, resulting from their small particle size and high surface area. For the film-coated microparticles, the video microscopic images in pH 7.4 phosphate buffer at different times are illustrated in Fig. 5. It is apparent that the microparticles coated with polymeric films dissolved faster (25–30 s) than the uncoated ones. In Fig. 5b, it is visible that the coat was ruptured within a very short time and then the core dissolved. This is probably due to many factors including the poor coating quality as well as the osmotic pressure built up inside the particles.

2.3. Drug release from microparticles and coated microparticles

In general, polymeric coatings were applied to drug-loaded cores to provide a barrier against the diffusion or release. The defects or damages in the coating layer, however, provide pathways by which the dissolution medium may reach the core surface. Fig. 6 displays the dissolution profiles of IBP from uncoated microparticles and microparticles coated with different polymers. The microparticles coated with EVA and EC display an important drug dissolution (more than 95%) in the first 5 min corresponding to a significant IBP initial burst effect followed by a plateau up to 60 min. The IBP dissolved from microparticles coated with other polymers were slightly slower. However, in all formulations, IBP dissolved almost 100% after 20–30 min. Interestingly, IBP dissolved more quickly from the coated microparticles than the uncoated microparticles. A possible explanation might be an increase in the osmotic pressure of the coated cores because of the film as outer layer, resulting in a rupture of the coating film. Furthermore, it is likely that the thin coating films of about 3–5 µm was not sufficient and ineffective to obtain the expected sustained release. It is suggested that the sustained release property of the coated microparticles can be achieved if the coating thickness was increased, the formulation of coating was changed by adding plasticizers or the coating conditions were adjusted (e.g., increase of coating/drying temperature or using curing). This should overcome the problem with the imperfection and inhomogeneity of the films.

3. Experimental

3.1. Materials

Ibuprofen (sodium salt) and maltodextrin were purchased from Sigma-Aldrich Laborchemikalien GmbH (Seelze, Germany). Ethyl cellulose (Ethocel® Standard 40 Premium) and ethyl cellulose aqueous dispersion (Aquacoat® ECD) were supplied from Dow Chemical Company (Michigan, USA) and FMC BioPolymer (Philadelphia, USA), respectively. An aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate (Eudragit® NE 30D) was a gift from Evonik Industries (Darmstadt, Germany). Ethylene-vinyl acetate copolymer (Elvax® 40W) was supplied from DuPont Chemical (Geneva, Switzerland). Carnauba wax was purchased from Ter Hell & Co. GmbH (Hamburg, Germany). All other chemicals were of reagent or analytical grade and used as supplied. Distilled water was used throughout all experiments.

3.2. Preparation of microparticles containing IBP

The microparticles containing IBP (30% w/w) and maltodextrin (70% w/w) were prepared in a fluidized bed granulator/coater (model WFP-Mini 1, Lödige Process Technology, Gebrüder Lödige Maschinenbau GmbH, Paderborn, Germany). Granulating conditions were as follows:
Inlet air temperature 110 °C, Outlet air temperature 85 °C, Inlet air rate 100 kg/h, Spray nozzle diameter 2.5 mm, Spraying rate 19.9 g/min, Spraying time 205 min.

3.3. Coating of microparticles by a fluidized bed coater

3.3.1. Calculation of the coating material required

The amount of coating material required was calculated by using the following equations.

$$M = \rho V \quad (1)$$

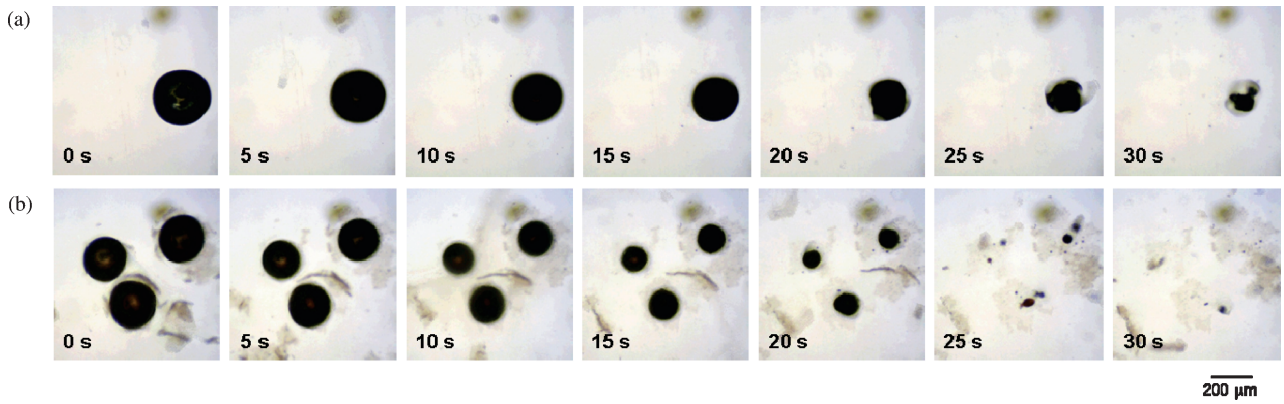


Fig. 5: Video microscopic images of microparticles coated with (a) EVA and (b) ECAq, in pH 7.4 phosphate buffer.

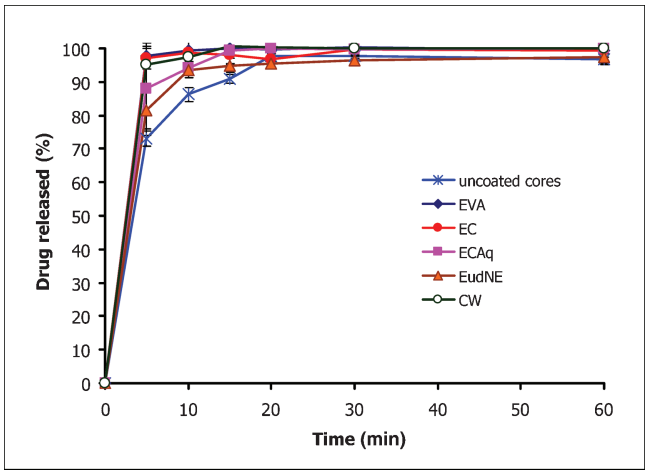


Fig. 6: Dissolution of ibuprofen from uncoated microparticles and microparticles coated with different polymers in pH 7.4 phosphate buffer.

where M is mass or weight of microparticle (g), V is volume of microparticle (μm^3) and ρ is density of microparticle ($g/\mu m^3$). The volume of microparticles can be calculated from the Eq. (2).

$$V = \frac{4}{3}\pi r^3 = \frac{4}{3}\pi r^3\left(\frac{d}{2}\right)^3 \quad (2)$$

where r is radius of microparticle and d is diameter of microparticle. Therefore, the equations for the weight of microparticles before (old) and after (new) the coating process are as follows:

$$M_{old} = \rho V_{old} = \rho\frac{4}{24}\pi d_{old}^3 = \rho\frac{1}{6}\pi d_{old}^3 \quad (3)$$

$$M_{new} = \rho V_{new} = \rho\frac{4}{24}\pi d_{new}^3 = \rho\frac{1}{6}\pi d_{new}^3 \quad (4)$$

where M_{old} is the weight of the microparticles used for one batch, and M_{new} is the weight of the microparticles after the coating experiment. The diameter of the microparticles after coating can be derived from the Eqs. (3) and (4) as follows:

$$\frac{M_{old}}{M_{new}} = \frac{d_{old}^3}{d_{new}} \quad (5)$$

$$d_{new} = 3\sqrt{\frac{M_{new}}{M_{old}}}d_{new} \quad (6)$$

The thickness of the film was then calculated from the increase in diameter of the microparticles after coating as follows:

$$\text{Flim thickness} = \frac{d_{new} - d_{old}}{2} \quad (7)$$

3.3.2. *Coating process*

Coating was performed using a fluidized bed technology. Eight grams of polymer powders or 20 g of polymer dispersion were dissolved or dispersed in suitable solvents (without addition of plasticizer, except ECAq in which triethyl citrate is added, see Table 2) before the coating process was started. In all experiments, 50 g of core particles (200–250 µm in diameter) were processed in a Lödige WFP fluidized bed laboratory unit. The coating solution was fed to the nozzle by a peristaltic pump. Spray rate was regulated with a spray nozzle (0.8 mm in diameter). During the entire spraying process, the spray suspension was continuously stirred and pre-heated at 35 °C (except for CW in which the coating solution was heated to 50 °C). To prevent agglomeration of the coated formulations during drying, talcum powder was added during the manufacture. The general conditions were as follows: Inlet air temperature 50 °C, Outlet air temperature 35 °C, Inlet air rate 27.5 m^3/h, Spray nozzle diameter 0.8 mm, Spraying rate 0.4–0.9 g/min, Spraying time 25 min, Drying time (at 40 °C) 30 min.

3.4. *Characterization of uncoated and coated microparticles*

3.4.1. *Particle size distribution of uncoated microparticles*

A sieve analysis was used to determine the particle size distribution of the microparticles. The sieves used for the analysis contained a nested column of sieves (125, 200, 250, 300 and 355-µm sieves) with wire mesh cloth. The whole batch of microparticles was poured into the top sieve which had the widest openings. Each lower sieve in the column had smaller openings than the one above, the receiver was the base. This column was placed in a mechanical shaker. The column was shaken for 10 min with an amplitude of 1. After the shaking was finished the material on each sieve was visually inspected and weighed.

3.4.2. *Morphology of microparticles*

Morphological examination of the surface of microparticles was carried out using a scanning electron microscope (SEM; model S-4000, Hitachi, Japan) at an accelerating voltage of 15 keV. The samples were coated with gold to a thickness of about 6.5 nm in a vacuum evaporator (model FL-9496 Balzers, Balzers Union, Lichtenstein). For examination of the coating

Table 2: Composition of coating solutions/dispersions

Coating formulation	Polymer powder (g)	Polymer dispersion (g)	Solvent	Amount of solvent (g)
EVA	8	–	Toluene	92
EC	8	–	Ethanol-Toluene	92
ECAq	–	20	Water	80
EudNE	–	20	Water	80
CW	8	–	Chloroform	92

film on microparticle surface and internal structure, the microparticles were crushed in pieces with a steel blade.

3.4.3. Digital video microscopy for measuring of microparticles dissolution

The image acquisition setup included an optical microscope (model BH-2, Olympus, Japan) coupled to a USB video camera (model QX5, Digital Blue, P.R. China). Transmitted light was utilized as well as objective and optical enlargements of 35 × and 10 × , respectively. The movies were recorded at a framing frequency of 5 s, in high-resolution mode. For measuring the dissolution of microparticles, the uncoated or polymer-coated microparticles were placed on glass slide and pH 7.4 phosphate buffer (0.1 ml) at $30.0 \pm 1.0\,^{\circ}C$ was carefully added. The image acquisition was started before the immersion of the microparticles.

3.4.4. Determination of drug content

The drug content in microparticles was experimentally determined. Microparticles (143 mg) were weighed and dissolved in pH 7.4 phosphate buffer in a 50-mL volumetric flask. After dissolving for 30 min in an ultrasonic bath, the solution was filtered through a Millipore filter (pore size 0.20 μm) and analyzed by UV spectroscopy (Specard 40w, Analytik Jena AG, Germany) at the wavelength of 264 nm. The determination was performed in triplicate for each formulation of microparticles.

3.5. In-vitro dissolution studies

The dissolution studies were carried out using USP dissolution apparatus, type II, (model DT 70, Erweka, Germany) equipped with paddles which was operated at the speed of 50 rpm. Nine hundred milliliters of pH 7.4 phosphate buffer, as the dissolution medium, was placed in the glass vessel, the apparatus assembled, and the dissolution medium equilibrated to $37 \pm 0.5\,^{\circ}C$. The amount of drug released was measured at the suitable time interval and was then determined spectrophotometrically (model Lambda 2, Perkin Elmer, Germany) in a 1-cm quartz cell at 264 nm. Each *in-vitro* release study was performed in triplicate.

Acknowledgments: The authors thank Bayer Technology Services GmbH for providing microparticles and assistance with the coating process, Mr. Ulrich Gernert from Zentraleinrichtung Elektronenmikroskopie (ZELMI), Technische Universität Berlin for his assistance with the SEM experiment, and Institut für angewandte Forschung, Berlin for some financial support. PS thanks National Research Council of Thailand and Deutsche Forschungsgemeinschaft for funding of the exploratory visit under NRCT-DFG agreement.

References

Andersson M, Holmquist B, Lindquist J, Nilsson O, Wahlund KG (2000) Analysis of film coating thickness and surface area of pharmaceutical pellets using fluorescence microscopy and image analysis. J Pharm Biomed Anal 22: 325–339.

Aulton ME (2007), Pharmaceutics: The science of dosage form design, 3rd edition. Churchill Livingstone, London.

Bauer KH, Lehmann K, Osterwald HP, Rothgang G (1988) Überzogene Arzneiformen. Wissenschaftliche Verlagsgesellschaft, Stuttgart.

Chen S, Nussinovitch A (2001) Permeability and roughness determinations of wax-hydrocolloid coatings and their limitations in determining citrus fruit overall quality. Food Hydrocolloids 15: 127–137.

Depypere F, Van Oostveldt P, Pierters JG, Dewettinck K (2009) Quantification of microparticle coating quality by confocal laser scanning microscopy (CLSM). Eur J Pharm Biopharm 73: 179–186.

DuPont Company (2011), Internal Information Product-Elvax® 40W, Wilmington, USA.

Dow Chemical Company (2005), Product Data Sheet-Ethocel®, Michigan, USA.

Ghebre-Sellassie I (1994) Multiparticulate oral drug delivery, Volume 65. Marcel Dekker, New York.

Haddish-Berhane N, Jeong SH, Haghighi K, Park K (2006) Modeling film-coat non-uniformity in polymer coated pellets: A stochastic approach. Int J Pharm 323: 64–71.

Heckötter UM, Larsson A, Sriamornsak P, Kumpugdee-Vollrath M (2011) Effect of annealing time and addition of lactose on release of a model substance from Eudragit® RS coated pellets produced by a fluidized bed coater. Chem Eng Res Des 89: 697–705.

Highton F (1999) The pharmaceutics of ibuprofen. In: Rainsford KD (ed.) Ibuprofen: a critical bibliographic review, Taylor & Francis, London, p. 53.

Jones D (1994) Air suspension coating for multiparticulates. Drug Dev Ind Pharm 20: 3175–3206.

Kumpugdee-Vollrath M, Krause JP (2011) Grundlagen und Trends beim Coating pharmazeutischer Produkte. Vieweg + Teubner Verlag, Wiesbaden.

Kutz G, Wolff A (2007) Pharmazeutische Produkte und Verfahren. Wiley-VCH Verlag, Weinheim.

Larsen CC, Sonnergaard JM, Bertelsen P, Holm P (2003) Validation of an image analysis method for estimating coating thickness on pellets. Eur J Pharm Sci 18: 191–196.

McGinity JW (1997) Aqueous polymeric coatings for pharmaceutical dosage forms. Marcel Dekker, New York.

Mendoza-Romero L, Piñón-Segundo E, Nava-Arzaluz MG, Ganem-Quintanar A, Cordero-Sánchez S, Quintanar-Guerrero D (2009) Comparison of pharmaceutical films prepared from aqueous polymeric dispersions using the cast method and the spraying technique. Colloids Surf A Physicochem Eng Asp 337: 109–116.

Ngawhirunpat T, Goegebakan E, Duangjit S, Akkaramongkolporn P, Kumpugdee-Vollrath M (2010) Controlled release of chlorpheniramine from resinates through surface coating with Eudragit® RS100. Int J Pharm Pharm Sci 2: 107–112.

Petereit HU, Weisbrod W (1999) Formulation and process considerations affecting the stability of solid dosage forms formulated with methacrylate copolymers. Eur J Pharm Biopharm 47: 15–25.

Steward PA, Hearn J, Wilkinson MC (2000) An overview of polymer latex film formation and properties. Adv Colloid Interface Sci 86: 195–267.

Werner SRL, Jones JR, Paterson AHJ, Archer RH, Pearce DL (2007a) Air-suspension particle coating in the food industry: Part I – state of the art. Powder Technol 171: 25–33.

Werner SRL, Jones JR, Paterson AHJ, Archer RH, Pearce DL (2007b) Air-suspension particle coating in the food industry: Part II – micro-level process approach. Powder Technol 171: 34–45.

Wesdyk R, Joshi YM, Jain NB, Morris K, Newman A (1990) The effect of size and mass on the film thickness of beads coated in fluidized bed equipment. Int J Pharm 65: 69–76.