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Research paper

In-line spatial filtering velocimetry for particle size and film thickness determination in fluidized-bed pellet coating processes

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ABSTRACT

A spatial filtering velocimetry (SFV) probe was applied to monitor the increase in particle size during pellet Wurster coating processes in-line. Accuracy of the in-line obtained pellet sizes was proven by at-line performed digital image analysis (DIA). Regarding particle growth, high conformity between both analytical methods (SFV/DIA) was examined for different coating processes. The influence of ring buffer size and the process of filling the buffer were investigated. With buffer sizes of 30,000–50,000 particles best results were obtained in this study. Investigated process parameters, such as inlet air volume and spray rate, had different effects on the impact of the SFV probe. While the particle rate (the number of particles detected by the SVF probe per second) was highly dependent on the inlet air volume, different spray rates of up to ±1 g/min did not affect the detected particle growth. Artefacts and delays in SFV particle sizing appeared especially at the beginning of the coating processes. The slope of the particle growth during the final spraying period was therefore used to determine coating thickness.

1. Introduction

Multiple unit dosage forms often consist of spherical drug containing pellets filled into capsules or compressed into tablets. By coating pellets, enteric, sustained or controlled release, taste masking, improved stability or esthetic appearance [1] can be achieved. Pellet coating processes are usually performed in fluidized bed coaters [2,3]. Different types of fluid bed equipment exist for batch processes, such as top spray, bottom spray or rotor with tangential spray system. Most frequently used in pharmaceutical industry is the so called Wurster coater, which is an insert bottom spray coater. This system has been applied in the food industry [1,4], but was originally developed as pharmaceutical technique to coat powder particles, granules, tablets or capsules [5,6]. Due to the controlled particle circulation, which increases the drying rate and reduces undesirable agglomeration during coating, it is an efficient batch fluid bed coater [7].

The film thickness and the coating uniformity strongly affect the properties of coated pellets [8,9]. In different studies image analysis was applied to evaluate the film characteristics, such as film thickness or integrity [10–17]. The often applied dynamic image analysis measures the particle size of a high number of particles, which are detected as a particle flow passing through a measuring field [18–21]. It was observed that the DIA method can directly measure the increase in coating thickness down to 2% of added polymer coat weight [19]. The method was even discussed to serve as surrogate dissolution test for coated pellets [20]. In-line pellet sizing during fluid bed coating processes by image analysis based methods have recently been introduced [22,23]. However, a high optical contrast between the core and the coating material is necessary to successfully determine the film thickness by these in-line methods.

The modified spatial filter velocimetry (SFV) is a technique that provides chord length values of moving particles by calculating their velocity and time of flight while passing through a laser array. To enable particle size determination in-line, this technique can be implemented into a stick probe of a manageable size. The modified SFV technique relies on the conventional velocimetry by a fiber optical spatial filtering velocimeter. Aizu and Asakura classified spatial filtering velocimeter based on their configuration in four typical groups: the transmission grating type, the detector type, the spectral grating type and the optical fiber type [24]. The optical fiber type was described to be beneficial due to the flexibility and stability of the optical and mechanical system. The SFV technique was further modified to determine the particle size by a technique called fiber optical spot scanning (FSS) [25,26]. The time of flight of a moving particle passing through a single optical fiber is observed

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by the FSS technique and the particle chord length is calculated from this single impulse time and the particle velocity.

The Parsum® SFV probe is equipped with a disperser which encloses the measuring gap, dilutes the incoming particle stream and centers the particle flight path [27]. However, the particle trajectory can still be positioned randomly in relation to the fixed single fiber. The distribution obtained by the SFV probe is thus a chord length distribution (CLD) and the chord length is a random cut across the particle. Considering this fact, Petrak calculated the possible chord density distribution detected by the SFV method on narrow-sized glass beads and found a good agreement between the calculated and the measured distribution [25]. In another study the characteristics of the chord length were observed and it was pointed out that a CLD does not clearly reflect the underlying particle size distribution (PSD) [28]. Therefore, a mathematical approach to transform the SFV-CLD into a PSD was performed by Fischer et al. [29]. The individual values detected by the SFV probe are written continuously into the flexible storage system. It was mentioned in the literature that the selected size of this particle ring buffer influences the latency of the probe and observations on the optimal buffer size were made in preliminary investigations [29].

Plitzko and Dietrich focussed on the in-line SFV detection of pellet agglomeration during Wurster coating [30], while SFV has recently been established for in-line particle size monitoring in fluidized bed granulation [27,31–36]. The obtained SFV data improved the understanding of the impact of process variables by using model-based process control approaches, such as DoE, univariate and multivariate PLS. In these studies, the SFV probe was placed into a granule side-stream.

Aim of the present work was to determine the increasing film thickness in-line by applying a SFV probe in fluidized bed coating processes. To prove reliability of the results (1) the accuracy of the in-line obtained particle sizes during the coating processes should be confirmed, (2) the influence of the particle buffer size on the results should be assessed and (3) effects on particle sizing based on process parameters, such as inlet air volume or spray rate should be evaluated. Finally, findings should be applied to present a suitable method to determine film thickness during coating (4).

2. Materials and methods

2.1. Core and coating materials

HCT layered pellets (hydrochlorothiazide layered on Cellets®500 (IPC, Dresden, Germany) [37]) (Fig. 1c) black curve) or theophylline pellets (Temmler Ireland Ltd., Killorglin, Co Kerry, Ireland) (Fig. 1c) gray curve) were used as core materials. Basic butylated methacrylate copolymer (Eudragit® EPO), Ammonio methacrylate copolymer type A (Eudragit® RL 30D), Ammonio methacrylate copolymer type B (Eudragit® RS 30D) and PlasACRYL® (a ready to use mixture of glyceryl monostearate, triethyl citrate, polysorbate 80 and water) were received by Evonik Industries AG (Darmstadt, Germany). Sodium lauryl sulfate and titanium dioxide were purchased from Caeser&Loretz GmbH (Hilden, Germany), stearic acid from Baerlocher (Lingen, Germany), triethyl citrate from Merck KGaA (Darmstadt, Germany) and talc from C.H. Erbsloeh (Krefeld, Germany).

2.2. Coating dispersions

Coating dispersions for *trial 1–4* were prepared based on the excipients summarized in Table 1. To prepare the dispersion of trial 1, water was heated up to 50 °C and 100 g less than the required amount was weight into the preparation vessel. Stearic acid and sodium lauryl sulfate were stirred into the warm water until the solution was clear. Eudragit® EPO was added and the slurry was stirred, until a slightly yellow, light turbid solution emerged. Talc was added to the omitted 100 g of water (room temperature) and homogenized using an Ultra Turrax for 10 min. The talc water mixture was poured slowly to the turbid solution while stirring continuously.

For *trial 2*, triethyl citrate and talc were homogenized in water for 10 min. The Eudragit® RL30D and RS30D dispersions were combined at a four-to-six ratio and stirred. Both suspensions were combined by slowly pouring the first suspension into the Eudragit® mixture while stirring gently. PlasACRYL® was shaken manually and stirred using a dissolver plate for the preparation of the dispersion for *trial 3*. The Eudragit® RL30D and RS30D dispersions were combined and added to the PlasACRYL® suspension. Water

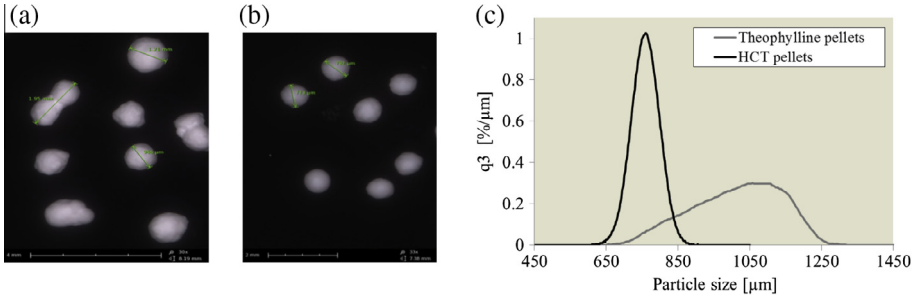

Fig. 1. Core material: (a) theophylline pellets, (b) HCT layered pellets (light microscopic pictures), (c) volume density distributions (q3 [%/µm]) measured by the dynamic image analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Composition of the coating dispersions, quantity based on the solid fraction [% (w/w)] is given.

	Core	Eudragit® EPO	Eudragit® RL 30D	Eudragit® RS 30D	Sodium lauryl sulfate	Stearic acid	Triethylcitrate	PlasACRYL®	Talc	Titanium dioxide	Total solid content (%)
Trial 1	HCT layered cellets	57.13	–	–	5.73	8.6	–	–	28.53	–	15
Trial 2	Theophyllin pellets	–	25	37.49	–	–	6.26	–	31.25	–	20
Trial 3	Theophyllin pellets	–	34.79	52.17	–	–	4.33	8.67	–	–	20
Trial 4	Theophyllin pellets	–	29.64	44.46	–	–	3.71	7.37	–	34.8	23.48