International Journal of Pharmaceutics 470 (2014) 8–14

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

In-line monitoring of pellet coating thickness growth by means of visual imaging

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ARTICLE INFO

Article history:
Received 14 March 2014
Received in revised form 25 April 2014
Accepted 29 April 2014
Available online 2 May 2014

Keywords:
Coating thickness
Pellets
PAT
Fluid-bed coating
Visual imaging
Quality assurance

ABSTRACT

Coating thickness is the most important attribute of coated pharmaceutical pellets as it directly affects release profiles and stability of the drug. Quality control of the coating process of pharmaceutical pellets is thus of utmost importance for assuring the desired end product characteristics. A visual imaging technique is presented and examined as a process analytic technology (PAT) tool for noninvasive continuous in-line and real time monitoring of coating thickness of pharmaceutical pellets during the coating process. Images of pellets were acquired during the coating process through an observation window of a Wurster coating apparatus. Image analysis methods were developed for fast and accurate determination of pellets' coating thickness during a coating process. The accuracy of the results for pellet coating thickness growth obtained in real time was evaluated through comparison with an off-line reference method and a good agreement was found. Information about the inter-pellet coating uniformity was gained from further statistical analysis of the measured pellet size distributions. Accuracy and performance analysis of the proposed method showed that visual imaging is feasible as a PAT tool for in-line and real time monitoring of the coating process of pharmaceutical pellets.

1. Introduction

Coated pharmaceutical pellets that can be enclosed in capsules or compressed into tablets are increasingly used as controlled-release systems in the production of solid dosage forms (Mayo-Pedrosa et al., 2007; Muschert et al., 2009). In comparison to single-unit dosage forms, pellets offer the advantage of a more predictable gastric transit time and drug absorption, which improves the therapeutic effects of a medical treatment (Bechgaard and Nielsen, 1978). In addition to drug release control, various coatings are being applied in order to mask taste, improve stability of the drug or to physically separate incompatible components of a dosage form. The coating thickness is the most important attribute of coated pellets; with uncontrolled thickness, the end product would not meet the anticipated functionality for sustained release. Coatings that are too thick could result in delayed disintegration or dissolution in case of immediate release dosage forms with protective coating, whereas coatings that are too thin will not assure desired functionality in case of delayed release dosage forms (Knop and Kleinebudde, 2013). Accordingly, coating thickness must be precisely controlled to ensure the quality of solid dosage form products.

Following the process analytical technology (PAT) guidance for pharmaceutical industry (US Food and Drug Administration, 2004), issued by the U.S. Food and Drug Administration (FDA), quality assurance in drug manufacturing is achieved through a systematic approach to pharmaceutical innovation. Development of new in-line, on-line and at-line PAT tools facilitates the implementation of quality by design (QbD) process development introduced in the ICH Q8 guidance, which states that "quality cannot be tested into products; it should be built-in or should be by design" (ICH, 2008; Yu, 2008; Hinz, 2006). In-line monitoring is important, not only for the product quality but also for a better understanding of the manufacturing process. When enough information is collected, PAT can ultimately lead to real-time release approaches wherein end product analytical testing is no longer necessary to ensure product quality, as the real time information gathered already provides a guarantee that the product is acceptable (Vogt and Kord, 2011).

The analytical techniques in use for direct evaluation of the average coating thickness are tests that require the use of spectroscopic methods, often together with separation technique, to determine the amount of coating material in the obtained solution (Joseph and Raghavan, 2013; Duerst, 2013; Ciurczak,

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http://dx.doi.org/10.1016/j.ijpharm.2014.04.066
0378-5173/

2013; Oberdier, 2013). The selection of the specific spectroscopic method is substance-dependent, so that different coating materials require different analytical techniques. The initial pellet core size information is still required and is usually obtained by manually measuring a pellet sample using the microscope or an off-line visual imaging method. The requirement for substance-dependent multivariate calibration methods in spectroscopic analytical techniques further contributes to the complexity of the design and implementation of a quantitative analysis. Consequently, the analytical techniques are time-consuming and the results of the analyses are obtained after the coating process is completed.

A number of analytical tools are being investigated with the aim of improving the accuracy of coating characteristics measurements of pharmaceutical pellets (Andersson et al., 2000a,b; Kennedy and Niebergall, 1997; Kucheryavski et al., 2010; Laksmana et al., 2009; Larsen et al., 2003; Lee et al., 2011; Liew et al., 2010; Možina et al., 2009; Možina et al., 2010; Naelapää et al., 2007; Närvänen et al., 2008; Podczeck et al., 1999), among them, several studies of visual inspection methods (Kennedy and Niebergall, 1997; Kucheryavski et al., 2010; Laksmana et al., 2009; Larsen et al., 2003; Liew et al., 2010; Možina et al., 2009; Možina et al., 2010; Närvänen et al., 2008; Podczeck et al., 1999; Heinicke and Schwartz, 2005). These visual inspection techniques, however, are not designed to give results in real time and under in-process conditions. Under the quality assurance and PAT premise that quality should be "designed into" processes through systematic use of control strategies to continuously ensure quality of the product, the interest for developing PAT tools for in-line, on-line and at-line monitoring of pellet coating process has increased over the last few years (Knop and Kleinebudde, 2013). Studies of in-line monitoring of pellet coating process have been conducted using near-infrared (NIR) spectroscopy (Andersson et al., 2000a,b; Lee et al., 2011) and a combination of NIR and Raman spectroscopy (Bogomolov et al., 2010). The development of new visual inspection techniques for in-line and real time monitoring of the coating process could present many advantages as they offer means of non-invasive, non-destructive, fast and continuous automatic measurements of pellets' coating thickness.

In this study, a visual imaging system was designed and examined for automatic in-line and real time monitoring of pellet coating thickness during the coating process. Image analysis methods were developed for determination of pellets' coating thickness in the in-process visibility conditions. Images of pellets were acquired in-line, in the course of a pellet coating process, through an observation window of a laboratory Wurster coating apparatus. The results for pellet coating thickness growth were obtained in real time and their accuracy was evaluated through comparison with a reference spectrophotometric analytical method. Information about the inter-pellet coating uniformity was gained from further statistical analysis of the measured pellet size distributions. The visual imaging system was also examined in terms of performance and computational efficiency to assess the feasibility of the system for real time monitoring of pellet coating process.

2. Materials and methods

2.1. Materials

A narrow size fraction of microcrystalline cellulose pellets (800–1000 μm, Cellets® 700, HARKE, Germany) was obtained using test sieves (800 μm and 1000 μm) and sieve shaker (Retsch AS 200 basic, Germany).

Pellets were coated with an aqueous solution consisting of 8.08% hydroxypropyl methylcellulose (Pharmacoat 606, Shin-Etsu, Japan), 1.01% polyethylene glycol (PEG 6000, Fluka, Switzerland), and 1.094% tartrazine coloring agent (Sigma–Aldrich, Germany). Tartrazine has a proven stability within the slightly acidic to neutral pH range (Wade and Weller, 1994). Coating solution was prepared by adding the polyethylene glycol and hydroxypropyl methylcellulose to preheated water at 70 °C and then stirred for 30 min. After leaving the solution to cool down to room temperature, coloring agent was admixed and the portion of evaporated water was replaced. In the experiment, 1473.7 g of the coating solution was applied to 1300 g of starting cores (approximately 2,500,000 pellets).

2.2. Coating of pellets

For coating of the pellets, bottom spray fluidized bed coater with a draft tube (GPCG-1, Glatt GmbH, Dresden, Germany, Wurster insert) was used. The coating solution was sprayed using a binary nozzle with tip diameter of 0.8 mm and cap opening diameter of 2.50 mm. Coating process parameters were kept constant throughout the process: inlet airflow rate 130 m^3/h; inlet air temperature 55 °C; spray rate 10.5 g/min; atomizing air pressure 2.0 bar; gap between distribution plate and the Wurster insert bottom edge 20 mm. The spraying-coating process was performed for 140 min. For the purpose of off-line spectrophotometric measurements, periodic samplings of 2 g of pellets were made every 10 min.

2.3. Determination of coating thickness by spectrophotometric measurement of pellet samples

Ten groups of ten pellets were randomly sampled from each pellet sample (2 g) taken during coating. Determination of the amount of coloring agent and corresponding amount of coating material deposited on the pellet cores was conducted via spectrophotometric measurements (UV spectrophotometer HP 8453, Hewlett-Packard, USA) at 425 nm. Groups of ten coated pellets were dispersed in a 6 mL of dihydrogen phosphate buffer with pH 6.5 in order to dissolve coating. After 4 h and prior to UV analysis, each test solution was subjected to filtration (Minisart RC 25 filters, Sartorius AG, Göttingen, Germany). Prior to the sample analysis, a calibration line was constructed ($c = 002064^*A$), where coated pellets without tartrazine served as a blank (c – tartrazine concentration (mg/mL), A – absorbance).

By knowing the coating composition and coating density, determined by helium pycnometer (1.272 g/cm^3), the volume of the applied coating was calculated from the amount of the coloring agent. Calculated coating volumes for ten pellet groups, consisting of ten pellets, were averaged and expressed as per pellet value. Value of the average per particle coating volume was used in a sphere model, a pellet shape approximation, in order to calculate the time specific coating thickness and pellets diameter change. For the pellet diameter estimation, the equivalent spherical diameter (ESD) was used. ESD is calculated from the projected area of a segmented pellet (A) (Jennings and Parslow, 1988):

$$\mathrm{ESD} = 2\sqrt{\left(\frac{A}{\pi}\right)}. \quad (1)$$

Average ESD value for uncoated pellets, determined by an off-line reference visual imaging method (Možina et al., 2009), was used as initial input parameter (882.8 μm).

Values of 10,000 pellet ESDs were used to determine the relative standard deviation (RSD) of the surface area for groups of 100 pellets. Obtained surface area RSD value (2.79%) was used to estimate the standard deviation of the coating thickness,