Powder Technology 283 (2015) 373–379

Contents lists available at ScienceDirect

Powder Technology

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

Passive acoustic emissions monitoring of the coating of pellets in a fluidized bed—A feasibility analysis

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ARTICLE INFO

Article history:
Received 17 December 2014
Received in revised form 7 March 2015
Accepted 1 June 2015
Available online 9 June 2015

Keywords:
Fluidization
Top spray coating
Acoustics
Monitoring
Pellets

ABSTRACT

Pharmaceutical pellets are small spherical particles that contain the active ingredient or drug. They are often film coated and packed into capsules as a multiple unit dosage form to provide modified drug release. Conventional methods used to evaluate pharmaceutical film coatings require invasive sampling and off-line testing, which are time consuming, disruptive to the process and often non-representative of the pellet bed indicating the need for developing more reliable monitoring methods. Passive acoustic emissions measurements have shown potential as a monitoring tool due to the non-invasive nature and real-time means of collecting process information. The goal of this study was to assess passive acoustic emission monitoring of the coating of pellets in a fluidized bed. Microphones were attached to the exterior of a top spray fluidized bed reflecting local fluidization conditions and information on nozzle performance. Decreased fluidization conditions were identified from acoustic emissions acquired at the interface of the liquid spray and fluidized pellet bed, influencing the distribution of the coating spray throughout the bed and drying of the film coat around the pellet core. Acoustic emissions acquired from the exhaust of an air outlet at the top of the column showed potential application for the detection of nozzle clogging. Continued research regarding the development of passive acoustic emissions monitoring would provide important information about fluidized bed coating of pellets and potentially improve process control for the determination of an optimum coating end-point.

1. Introduction

Pharmaceutical pellets are small, spherical particles between 100 and 1000 μm in diameter that contain the active ingredient or drug. These pellets are film coated to control the release rate of the active ingredient, as well as to protect the drug from heat, moisture and light, provide mechanical stability and improve appearance of the dosage form [1]. The coated pellets are packed into capsules to create a multiple unit dosage form to be taken orally. The release rate of the active drug is dependent on the uniformity, thickness and overall quality of the coating film on the pellets [2–4]. Capsules containing coated pellets are a relatively new multiple unit dosage form. This form has advantages over conventional tablets of reducing variations in gastro intestinal transit time and minimizing the potential of dosage dumping [5], which are significant factors for potent drugs with critical dosages and delivery.

Coating processes are performed in either a rotated drum pan coater or a fluidized bed coater of the top spray, bottom spray or rotating configuration. For larger solid dosage forms such as tablets pan coating is preferred [6], while fluidized bed coating is better suited for the lighter, smaller dosage forms such as pellets. These particles are easier to fluidize resulting in good particle mixing. An atomized liquid spray consisting of a solute and solvent is sprayed onto the fluidized pellet bed. The heated fluidizing air evaporates the solvent, leaving behind the solute to form the coating film around the pellet core [1].

Fluidized bed coating is a complex process. A variety of parameters must be taken into consideration to ensure that the desired end-product is achieved, including the inlet/outlet temperature, inlet/outlet humidity, superficial gas velocity, atomizing air pressure, spray rate and droplet size [7]. Due to the interdependence of these parameters, an on-line and real-time monitoring technique is required to provide further insight into process dynamics and to improve process control. A top spray fluidized bed has exceptional need for the development of process monitoring and control, as these coating processes are associated with random particle flow, non-uniform coating and a high risk of bed defluidization [1,8,9].

Pressure measurement analysis is the most common technique for monitoring fluidization. These measurements have been used to detect bed defluidization, evaluate regime transitions and to provide insight into fluidization phenomena [10–12]. Pressure fluctuation analysis may provide general information about fluidization behavior of fluidized bed coating, but provides no information about the film coat.

Conventional techniques used to evaluate the film coat of tablets require sample acquisition for the theoretical determination of film

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http://dx.doi.org/10.1016/j.powtec.2015.06.004
0032-5910/

thickness based on coating mass and for dissolution or disintegration testing [13]. These techniques have many drawbacks especially for pellet coating: (i) the weight gains of the pellets are small and difficult to accurately measure, (ii) variations between pellets are not considered, (iii) measurement of weight gain does not account for any loss of the core pellet due to attrition, (iv) disintegration and/or dissolution testing provides only an indirect measurement of coat thickness and does not evaluate coat uniformity, and (v) sampling and measurements are time consuming and therefore cannot provide real time information that is critical for process control. Techniques that are being developed to improve measurement of coating include a variety of imaging and spectroscopic methods [2,3,14,15]. These methods, however, still involve in-process sampling and off-line testing, which are disruptive to the process, time-consuming and inaccurate.

Research has shifted towards the development of on-line, non-invasive monitoring tools for process control, due to the Food and Drug Administration's initiative to implement process analytical technologies (PATs) for the improvement of pharmaceutical manufacturing, development and quality assurance [16].

Techniques that have been investigated for on-line and real-time monitoring and control of fluidized bed coating of pellets include near infrared spectroscopy [4], combined near infrared and Raman spectroscopy [17] and passive acoustic emission monitoring [9]. Raman and near infrared spectroscopy both require a window or port into the process vessel which necessitates equipment modifications and can also lead to inaccurate measurements if the window or probe interface becomes fouled. In addition, Bogomolov et al. [17] found that over wet process conditions interfered with the measurements, as the wet pellets changed light propagation conditions, which affect the intensity of the spectra. Depypere et al. [2] further argued that near infrared spectroscopy does not have the required spatial resolution to enable accurate measurements of the pellet coating as the pellets themselves are small and the coating is thin, about 25 to 75 μm.

Acoustics, defined as the generation, transmission and reception of energy in the form of vibrational waves [18], have shown potential as a basis for the development of on-line monitoring and control systems. As a monitoring technique, it has been explored in various industries, such as the chemical, biochemical and food industries, to provide insight into the physicochemical changes that occur within a process [19]. Specifically, in the pharmaceutical industry, passive acoustic emissions have been used to monitor high-shear and fluidized bed granulation processes, as well as fluidized bed drying [20–25]. A major advantage of acoustic emissions monitoring is the non-invasive nature and real-time means of collecting process information.

Passive acoustic emissions from a fluidized bed, described by Tsujimoto et al. [20], are generated as a result of (i) particle-particle or particle-equipment collisions, (ii) friction from these collisions, and (iii) air turbulence generated by the fluidizing air passing through the particle bed. One study, conducted by Naelapää et al. [9], highlighted the possibility of applying passive acoustic emissions monitoring for the coating of pellets in a fluidized bed. Four accelerometers were used to measure the vibrations from the passive acoustic emissions during the coating of potassium chloride crystals and the signals were compared to samples tested for dissolution and to the theoretical amount of film applied. The technique appeared promising, but many of their results were inconclusive due to: (i) differences in the signals from repositioning the sensors between batches, (ii) samples were not representative of the entire batch as only limited samples were extracted and (iii) the amount of applied coating was estimated from the volume drop in coating solution rather than direct measurements of the actual coated pellets.

Our research builds from the work by Naelapää et al. [9] carefully considering the factors that led to their inconclusive results. Due to limited research on the development of monitoring methods for fluidized bed coating of pharmaceutical pellets, the objective of our research was to assess the possibility of applying passive acoustic emissions monitoring to the coating of pellets in a fluidized bed.

2. Materials and methods

2.1. Fluidized bed

A schematic of the top spray fluidized bed is shown in Fig. 1. The air entered a wind box and is then distributed into the conical bed through a polyethylene distributor plate with a pore size of 75 μm.

A differential pressure transducer (Omega Model 163PC01D36 and Model 142PC15D) recorded pressure data using a National Instruments data acquisition system and LabVIEW software. The transducer measured the pressure drop across the bed (one port located 0.050 m above the grid and a second port located 0.100 m above the grid) at a sampling rate of 1000 Hz.

Three piezoelectric microphones (PCB Piezotronics Model 130P10) were used to record passive acoustic emissions. The data was recorded using a National Instruments data acquisition system and LabVIEW software. Microphone 1 was suspended in the exhaust of one of the air outlets located at the top of the column. Microphones 2 and 3 were attached flush to the exterior of the column 0.150 m and 0.025 m above the grid, respectively. This allowed for measurements to be obtained at the interface of the fluidized pellet bed and liquid spray, and at the grid. All three microphones recorded data at a sampling rate of 40 000 Hz to allow full reconstruction of the audible frequency range (20–20 000 Hz) without aliasing. Statistical and frequency signal analysis was performed off-line using Matlab version 7.10 in 10 second consecutive chunks.

A sampling port with a side sampling thief, located 0.057 m above the grid, allowed for samples to be withdrawn during trials. An atomizing spray nozzle (John Brooks Company Limited, Reference #: 1/8 PRJJB 0.0390) was located at the top of the column. The spray tip was 0.559 m above the distributor. The top of the column contained four filtered air outlets.

2.2. Coating experiments

Glass beads, 1000 μm in diameter and a density of 2.4 g/cm^3, were coated with a 5% (*w*/*w*) sugar solution. These materials were selected as a reusable, model pellet system comparable to microcrystalline cellulose starter cores, Cellets®, that have a diameter of 1000 μm and a density of 0.8 g/cm^3, and are often coated and used in multi-particulate dosage forms. For each trial approximately 2 kg of glass beads was coated.

The inlet air temperature was heated to 35 °C with a humidity of approximately 15%. A superficial gas velocity of 1.85 m/s was used to fluidize the pellets. An atomizing spray pressure of approximately 40 psi was used to spray the coating solution, corresponding to a spray rate of approximately 20 mL/min.

Coating was performed over four 2-minute intervals, with a total coating time of 8 min (Fig. 2). Approximately 10.0 g of pellets was removed periodically using the sampling port during each trial. Samples were removed before and after each coating period (S1, S2, S3, S4, S6, S7, S9, S10) and throughout the drying period (S5, S8, S11, S12, S13). From each sample, 100 pellets were carefully counted, weighed, washed with 1000 mL of warm water at 35 °C, dried on trays for about 20 h at a temperature of 20 °C and humidity of 10%, and re-weighed once dry. The coat thickness per pellet was calculated based on the coating mass per 100 pellets, assuming the film coat was perfectly uniform and evenly distributed among the 100 pellets. This allowed for the film coat thickness to be directly measured for each sample.

Acoustic and pressure measurements were recorded during each trial. The measurements were started prior to the first coating period to ensure measurements taken under initial stable operating conditions. Preliminary trials were conducted to assess the sampling and passive