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Passive acoustic emission monitoring of pellet coat thickness in a fluidized bed

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ABSTRACT

Pharmaceutical pellets are often packed into capsules as a multiple unit dosage form. The small, spherical particles contain the active ingredient or drug and are film coated for modified drug release. Evaluation of pellet film coatings requires invasive sample acquisition and extensive off-line testing leading to inaccurate results non-representative of the pellets, identifying the need for a more reliable monitoring and control method. Passive acoustic emissions have been proven as a useful non-invasive monitoring tool with the ability to provide on-line and real-time measurements. The goal of this study was to assess the potential of passive acoustic emissions to monitor the pellet coat thickness of sugar coated glass pellets in a fluidized bed. A microphone attached to the exterior of a fluidized bed reflected changes in the signal amplitude corresponding to increases in pellet film coat thickness. Additional experiments showed that an increase in pellet mass produced larger acoustic emission amplitudes. Simulated pellet–wall collisions identified the sensitivity of the acoustic emission measurements to detect differences in pellet collisions, necessary for monitoring thin film coatings. Overall, changes in the acoustic emission amplitude were shown to reflect the film coating, provided the pellets were sufficiently fluidized, indicating the potential for applying passive acoustic emission monitoring for the determination of a desired coating end-point. Additional research to continue the development of passive acoustic emission monitoring is necessary for industrial fluid bed coating applications, with the potential to improve overall product quality and process cost-effectiveness.

1. Introduction

Pharmaceutical pellets are often coated and packed into capsules as a multiple unit dosage form for oral consumption. The active ingredient is usually contained within the pellets, which are spherical in shape and range in size from 100 to 1000 μm in diameter. Coating is performed to provide a variety of functions including modified drug release, mechanical integrity, to protect the active ingredient, and to provide a more aesthetically appealing dosage form [1]. The coating film thickness, uniformity and overall quality are significant factors to the function of modified drug release and behavior of the dosage form *in vivo* [2–4]. Coated pellets packed into a capsule have various advantages over the conventional tablet, including minimal variations in gastro intestinal transit time, the ability to minimize dosage dumping and an increased flexibility in drug formulation and design [5]. Potent drugs with critical dosages rely heavily on these factors for accurate and safe delivery.

Pharmaceutical coating is achieved in either a rotated drum pan coater or fluidized bed coater equipped with a top spray, bottom spray or rotating spray nozzle. Large particles, such as tablets, are typically coated in a rotated drum pan coater [6], while smaller particles, such as pellets, are better suited to be coated in a fluidized bed. The pellets are lighter and easier to fluidize resulting in good particle mixing, ideal for fluidized bed coating. An atomized liquid solution is sprayed onto the pellet bed, while the heated fluidizing air evaporates the solvent allowing for the solute to act as a coating medium around the pellet core [1].

Fluidized bed coating is characterized by the complex interaction of gas, liquid and solid phases. It is important to find the appropriate balance between operating parameters to ensure that the final product meets the desired design specifications. This includes monitoring and/or controlling the inlet/outlet air temperature, inlet/outlet air humidity, superficial gas velocity, atomizing air pressure, spray rate and droplet size [7]. The difficulty associated with the complex interaction of these parameters highlights the need for developing an on-line, real-time monitoring system to improve process control and to provide additional insight into process behavior. Top spray fluidized beds are typically associated with random particle flow resulting in non-uniform coating and an increased potential for bed defluidization [1,8,9]. Such issues identify the need for developing new process monitoring and control techniques for top spray fluidized beds.

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Evaluation of the film coating involves sample removal to estimate the film coat thickness based on a difference in mass or through dissolution and/or disintegration testing [10]. These methods are typically used to evaluate coated tablets and are associated with many weaknesses when applied to the evaluation of coated pellets: (i) it is difficult to accurately measure the small differences in weight, (ii) no variations within or between pellets are considered, (iii) attrition and loss of coating are not accounted for, (iv) indirect measurements are provided when performing disintegration and/or dissolution testing, and (v) no information about coat quality is given. Overall, these techniques require invasive sampling and time-consuming measurements and therefore, are unable to provide real-time information necessary for process control.

A variety of imaging and spectroscopic methods have been explored to improve these measurement techniques and to evaluate pellet film coatings including fluorescence microscopy [11], digital imaging [10], confocal laser scanning microscopy (CLSM) [2,12], X-ray micro tomography [3] and Raman spectroscopy [13]. Conventional image analysis techniques, such as fluorescence microscopy, are typically limited to the pellet surface preventing a full analysis of the film coat, or require slicing of the pellet into segments destroying the pellet completely [2]. CLSM in combination with other image analysis techniques has been explored by both Depypere et al. [2] and Laskmana et al. [12] as a non-destructive imaging technique. The described methods required invasive sampling, fluorescent labeling, off-line analyses and extensive image processing, limiting industrial applications. Perfetti et al. [3] studied the feasibility of X-ray micro-tomography and was able to non-destructively produce high resolution 3-D images but required complex mathematical algorithms for image reconstruction, as well as expensive X-ray equipment and technology. Sovány et al. [13] encountered issues with the use of Raman spectroscopy due to the weakening of the Raman signal from scattered light and the difference in size between the pellet and large laser spot. As well, the characteristic peaks of the active ingredient overlapped with peaks of the coating material leading to inconclusive results [13]. Overall, these studies have led to important discoveries regarding fluidized bed pellet coating, but still require disruptive in-process sampling or invasive measurement acquisition, as well as time consuming off-line testing and analyses.

The pharmaceutical industry has been moving towards the development and implementation of process analytical technologies (PATs) for the improvement of pharmaceutical manufacturing, development, and quality assurance in accordance with the Food and Drug Administration's ICH guidelines Q8 [14]. The objective of these efforts is to develop more robust manufacturing that applies an increased understanding of the science behind each process, improving the overall cost-effectiveness and minimizing loss of product or failed batches with better process control.

PAT techniques that have been explored for pellet coating in a fluidized bed include near infrared spectroscopy [4], near infrared spectroscopy combined with Raman spectroscopy [15] and passive acoustic emission monitoring [9]. Both spectroscopic methods require an invasive measurement probe or window into the unit leading to inaccurate measurements and contamination issues, as well as the need for equipment modifications. Bogomolov et al. [15] found wet pellets to influence light propagation, interfering with the measurements; a high level of moisture corresponded to lower spectra intensity due to increased incident light penetrating the coating material. A study by Kato et al. [16] identified different coating formulations, variations in coat thickness and the amount of coating applied to influence the accuracy of NIR spectra. Furthermore, Depypere et al. [2] identified NIR to have a limited spatial resolution, unable to obtain accurate measurements of thin coating layers in the range of 25 to 75 μm.

The application of acoustic emissions as an on-line monitoring and control technique has been proven useful in the chemical, biochemical and food industries [7]. In general, acoustics is characterized as the generation, transmission and reception of energy in the form of vibrational waves [17]. When applied as a monitoring tool, passive acoustic emissions provide a non-invasive and real-time means of collecting information about the physicochemical changes that take place within a process [18]. Pharmaceutical applications of acoustic emission monitoring have been shown to be useful for high-shear and fluidized bed granulation, fluidized bed drying and mixing processes [19–25].

In the 1970s, Leach and Rubin studied passive acoustic emissions produced from the interaction between different sized particles [26–30]. This work led to the theory of passive acoustic emissions to be generated as a result of (i) particle–particle or particle–equipment collisions, (ii) friction from these collisions, and (iii) air turbulence from the fluidizing air [19]. In the case of fluidized bed coating of pellets, one study by Naelapää et al. [9] assessed the possibility of using passive acoustic emission monitoring. Vibrations produced during the coating of potassium chloride crystals were measured at different locations on the column using four accelerometers. The measurements were compared to an estimated coat thickness based on a theoretical amount of film coating applied and samples tested for dissolution. Although the technique showed promise, some issues with the experimental procedure were identified leading to inconclusive results: (i) repositioning of the sensors between batches led to signal differences, (ii) limited samples were removed and did not represent the entire batch and (iii) the amount of film coating applied was calculated based on a volume drop in coating solution and therefore indirectly estimated the film coat thickness.

Our previous work assessed the feasibility of using passive acoustic emissions to monitor pellet coating in a fluidized bed, building from the study by Naelapää et al. [9]. It was concluded that passive acoustic emission profiles could indicate local fluidization conditions and were also able to provide information about the spray nozzle performance. To our knowledge, there is limited research that focuses on the application of passive acoustic emissions to monitor specific properties of the film coating, such as the film coat thickness. The goal of this study was to expand on our previous work and to assess the possibility of determining a coating end-point related to the pellet film coat thickness using passive acoustic emission monitoring. Additional insight into the effect of the coating solution on the fluidized bed coating process was also explored.

2. Materials and methods

2.1. Fluidized bed

Coating was performed in a conical top spray fluidized bed, shown in Fig. 1. Heated fluidizing air entered a wind box, before passing into the unit through a polyethylene distributor plate that had a pore size of 75 μm. The unit was equipped with an atomizing spray nozzle (John Brooks Company Limited, Reference #: 1/8 PRJJB 0.0390) located at the top of the column, 0.559 m above the distributor plate. The top of the column was equipped with four filtered air outlets.

2.2. Coating experiments

Glass pellets, 1000 μm in diameter, were used as the solids for the coating experiments. These solids were easily reusable and, as shown in Table 1, had diameters similar to microcrystalline cellulose starter cores, called Cellets®. Cellets® are often commercially coated and used in pharmaceutical multiple unit dosage forms for modified drug release. Approximately 2 kg of glass pellets were coated during each trial.

The inlet air had a superficial gas velocity of 1.82 m/s to fluidize the pellets and was heated to a temperature of 35 °C with a humidity of approximately 15%. A 5% w/w sugar solution was used for coating. This coating solution was applied using a pressurized atomizing spray nozzle at a rate of approximately 15–20 mL/min, summarized in Table 2. Each coating stage consisted of a 2–4 minute coating spray period to ensure a