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Inter-particle coating variability in a continuous coater

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HIGHLIGHTS

- Extended renewal theory for inter-particle coating variability in continuous coaters.
- Particle axial motion is modeled well by an advection-diffusion relation.
- Inter-particle coating variability depends strongly on the axial Peclet number (Pe).
- To obtain a coating variability of less than 1%, *Pe* should be greater than 20,000.
- Long coater lengths are required for typical flow rates and diffusion coefficients.

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ABSTRACT

The influence of particle axial motion on inter-particle coating variability is studied in a rotating drum continuous coater. A mathematical framework based on renewal theory is developed and an expression for inter-particle coating variability is obtained that accounts for the variance in the residence time of particles inside the coater. This model makes no assumptions on the nature of the particle axial motion. Discrete element method simulations have shown, however, that the particle axial motion can be accurately modeled by a combination of advective and diffusive motion characterized by an axial Peclet number. Using this advective-diffusive model, it was found that in order to maintain an inter-particle coating variability of less than 1%, typical of what might be needed for functional pharmaceutical tablet coatings, a Peclet number of 20,000 is required. Such a large Peclet number would necessitate essentially plug flow for typical continuous coater lengths of 1–2 m, or coater lengths of at least 15 m for typical feed rates and spherical particle diffusion coefficients.

1. Introduction

The continuous manufacturing of tableted drug products offers a number of advantages over traditional batch manufacturing, such as better efficiency, reduced processing times, increased throughput, and improved robustness. One component of a continuous pharmaceutical tablet manufacturing operation is continuous coating. In a typical rotating cylindrical drum continuous coater, tablets are fed into the coater at one end, tumble within the drum while being coated by spray nozzles directed at the bed's free surface, nominally move down the length of the drum, and exit from the coater by falling over a weir located at the drum's end. Since the residence time of tablets in the coater, and thus the mass of coating sprayed onto tablets, is dependent on the tablets' axial motion, it is worthwhile to examine this axial motion and its effect on coating variability.

Axial motion of particles has been thoroughly studied for batch coaters. It is well established through experiments (Hogg et al., 1966; Cahn and Fuerstenau, 1967; Parker et al., 1997; Tallon and Davies, 2008) and simulations (Finnie et al., 2005; Cleary, 2006; Third et al., 2010) that the axial movement of particles in a rotating drum can be modeled using a random walk characterized by a diffusion coefficient. Sherritt et al. (2003) provide a detailed review of experimental and simulation studies of particle axial motion in rotating drums.

The axial diffusion coefficient depends on the particle size as well as on operating variables such as drum rotational speed and fill volume fraction. Cahn and Fuerstenau (1967) reported an increase in the axial diffusion coefficient of particles as the drum rotational speed increases. Similar trends were reported by Parker et al. (1997) in their experimental work using positron emission particle tracking. Parker et al. (1997) also observed that most of the particle axial motion occurs in an active layer at the bed's surface.

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Although axial motion was also observed deeper within the bed, this motion was much smaller compared to that within the active layer.

The effect of fill level on the diffusion coefficient reported in the literature is not consistent. Cahn and Fuerstenau (1967) report an increase in the diffusion coefficient as the fill level increases from 30% to 50%, but a further increase in the fill level leads to a decrease in the diffusion coefficient. Rao et al. (1991) found that the diffusion coefficient decreases as the fill level is increased while Finnie et al. (2005) did not observe a significant change in the diffusion coefficient with fill level. These inconsistent trends could be attributed to two competing effects as the fill level is changed. An increase in fill level leads to an increase in the distance over which particle collisions can occur on the bed's surface. Since most of the particle axial motion occurs on the bed's surface (Parker et al., 1997) an increase in the length of the bed surface would lead to an increase in the axial diffusion coefficient. However, an increase in the fill level also leads to a decrease in the frequency with which particles appear on the surface. Different trends could be obtained depending on which of these effects dominate.

The effects of particle size and operating variables on the axial diffusion coefficient have also been studied using computer simulations. Third et al. (2010) used discrete element method (DEM) computer simulations of mono-sized spherical particles to study the effect of particle size and drum rotational speed on the axial diffusion coefficient. They found that particles' axial motion followed a random walk, with the axial diffusion coefficient increasing as the particle diameter or the drum rotational speed increased. Cleary (2006) also report an increase in diffusion coefficient with particle size using results from DEM simulations. Third et al. (2010) also observed a net axial flow of particles in their DEM simulations using periodic boundaries and, thus, performed studies using a cylinder with end walls. The axial motion of particles within a narrow region at the center of the cylinder was used to compute the axial diffusion coefficient. Finnie et al. (2005) found the axial diffusion coefficient to increase linearly with rotational speed.

Axial motion of particles has also been studied for continuous rotary drums with a focus on rotary kilns. It has been found that the motion can be modeled as a random walk characterized by a mean advective velocity and a diffusion coefficient (Abouzeid et al., 1974; Wes et al., 1976; Hehl et al., 1978). The mean and variance of the residence time distribution (RTD) of particles is typically used as a measure of the mean velocity and diffusion coefficient.

Abouzeid et al. (1974) studied the influence of drum speed, feed rate, and particle size on the RTD of particles. The fill level in the drum was dependent on the operating parameters. The variance of the RTD was found to increase rapidly as drum speed was increased due to the increase in collision frequency of the particles. Both the mean and variance of the RTD was found to decrease with feed rate in such a manner that the coefficient of variation (CoV) of the RTD was a constant. The decrease in mean velocity was attributed to an increase in fill level of the drum as the feed rate was increased. Similar findings were reported by Hehl et al. (1978). The Peclet number was also identified as an important parameter affecting the CoV of the RTD.

Although prior research investigating particle axial motion has focused on mixing applications and rotary kilns, many of the results, such as the influence of drum speed, fill level, and particle size, can be directly applied to the tablet coating process. The literature on continuous coating processes, however, is scarce and there are no studies quantifying the effect of axial diffusion specifically on the inter-particle coating variability. There are a few recent studies that investigate inter-particle coating variability more generally for continuous coaters, which are reviewed in the following paragraphs.

Cunningham et al. (2010) studied tablet coating uniformity in a continuous coater. Tablet samples were collected every 10 min during a continuous coating operation and the samples were tested for color uniformity. The color difference of the samples from a target reference was determined by calculating the distance between the sample and target in the color space. A standard deviation of less than two units in the color space over the samples indicated no visual difference in color from the target reference color. Although they did not measure the coating mass on individual tablets, they did note that the tablets had very good color uniformity with the standard deviation of the color difference well within the upper limit of two. They also found that the target weight gain was achieved in significantly less time compared to a batch coater and attributed this reduced time to the shallower bed present in the continuous coater.

Suzzi et al. (2012) studied the effect of tablet shape (round, oval, and biconvex) and fill level on inter-tablet coating variability in a semi-continuous pan coater in terms of the fractional residence time, defined as the ratio of the time spent by a tablet in the spray zone located at the top of the surface to the total coating time. The coater had a series of chambers, each of which performed in a manner identical to a batch coater. The tablets were coated in a chamber for a specified time and were then moved to the next chamber for further coating. They found that for all three shapes, the average fractional residence time decreased as the pan loading was increased due to an increase in the surface velocity. In addition, they found that the average fractional residence time for the biconvex tablet shape was least affected by changes in fill level. The relative standard deviation of the fractional residence time was found to increase with fill level. Again, the biconvex tablets were less affected by changes in fill. Due to the compartmentalized design of the coater, even though axial diffusion was present within each compartment, the residence time within the coater was the same for all tablets.

There have been no previous studies investigating the influence of axial diffusion on inter-particle coating variability in a continuous coater, which is the focus of this paper. A mathematical framework based on renewal theory is developed in Section 2 to account for the effect of non-uniform coater residence times on inter-particle coating variability. The mathematical analysis provides the best inter-particle coating variability that can be obtained in the presence of a distribution of residence times. DEM simulations, validated against published experimental data (Section 3), are used to investigate particle axial motion in a continuous coater to predict residence time distributions (Section 4). Finally, conclusions from the work are presented in Section 5. The ideas presented in this work can be applied to existing continuous coater designs to obtain an estimate of the smallest inter-particle coating variability if the axial diffusion coefficient is known. It should also be noted that in this work the words particle and tablet are used interchangeably and particles do not refer to the individual particles inside the tablet but to the tablet as a whole.

2. Inter-tablet coating variability

Inter-tablet coating variability is an important critical quality attribute during the coating process and is defined as the ratio of the standard deviation, σ_M, to the mean, μ_M, of the total coating mass distribution on the tablets,

$$CoV_{\text{inter}} = \frac{\sigma_M}{\mu_M}. \tag{1}$$

Tablets are typically coated in a rotating drum with a spray located at the top of the tablet bed surface. As the tablets pass