Scale Up of Pan Coating Process Using Quality by Design Principles

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ABSTRACT: Scale up of pan coating process is of high importance to the pharmaceutical and food industry. The number of process variables and their interdependence in a pan coating process can make it a rather complex scale-up problem. This review discusses breaking down the coating process variables into three main categories: pan-related, spray-related, and thermodynamic-related factors. A review on how to scale up each of these factors is presented via two distinct strategies—"macroscopic" and "microscopic" scale-up. In a Quality by Design paradigm, where an increased process understanding is required, there is increased emphasis on "microscopic" scale-up, which by definition ensures a more reproducible process and thereby robust scale-up. This article also reviews the various existing and new modeling and process analytical technology tools that can provide additional information to facilitate a more fundamental understanding of the coating process. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:3589–3611, 2015

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INTRODUCTION

Film coating is a well-established process in pharmaceutical industry. Coating is generally referred to as a process by which a film of solid is applied onto the surface of a tablet or an intermediate (granule or particle). Coatings can be applied by various methods such as spraying a liquid, dipping into a liquid, precipitating from supercritical fluids, or depositing a powder using an electrostatic technique. Aqueous and solvent coating processes are extensively used in pharmaceutical industry to apply functional and/or nonfunctional coats to substrates. The use of solvent-based coatings is reducing significantly in number given various comparative advantages of aqueous-based coatings such as safety, cost, and environment-friendly nature of aqueous coatings. The main advantage of solvent-based coatings is when the substrate or drug is not compatible with water. Challenges associated with aqueous-based coatings pertain mostly to the efficient and balanced removal of water (thermodynamics) during and after the coating process, hence it is important to understand how the thermodynamics of the system can be scaled up accurately. This article will focus mostly on scale-up aspects of aqueous-based pan coating process.

The coating of solid dosage forms, such as capsules, granules, beads, and tablets, provides one or more of the following attributes[1]:

- Improves the aesthetic appearance of the dosage form
- Aids swallowing
- Provides protection from the environment (air, moisture, light, etc.)
- Masks unpleasant odor or taste
- Provides a means of identification
- Facilitates handling (coating eliminates dust)
- Controls site (in the body) of drug release (enteric coating)
- Controls rate of drug release (sustained-release coating)
- Provides an active drug coating layer onto the substrate
- Provides separation of incompatible excipients and drug substances
- Creates a suitable surface for printing (tablet)

Spraying a liquid onto the substrate is commonly carried out either in a coating pan or a fluid bed coater. Generally, if the substrate is around 6.4 mm or less in diameter, then the preferred equipment for coating is the fluid bed coater. However, product movement is generally more aggressive in a fluid bed coater compared to a pan coater, hence tablets of suitable size are commonly coated using a coating pan to minimize mechanical damage to the tablets.[1]

Film coating (polymeric) is commonly conducted in perforated coating pans, whereas sugar coating is traditionally conducted in non-perforated coating pans. A good overview of different kinds of pan coaters is provided by Porter and coworkers.[2,3] Pan coating is simple in operation and offers low mechanical stress to the tablets compared with fluid bed coaters. The main drawbacks of pan coating are relatively longer processing time and higher product variability. In a typical pan coating process, tablets are placed inside a rotating pan. As the pan rotates, the top layer of tablets cascades downwards under gravitational force, thus providing a fresh layer of tablets to come in contact with the spray and get coated with the coating solution followed by drying before moving into the bulk of the tablet bed (Fig. 1). The coating solution is fed through an air-atomizing spray nozzle. After a certain time, defined as circulation time, the tablets re-enter the spray zone and the coating and drying process is repeated. An important objective for the coating equipment is to promote the regular and uniform movement of tablets through the spray zone; however, tablets may bypass the spray as they circulate or enter stagnant or slow moving regions of the tablet bed that reduces the frequency of circulation through the spray zone. Thus, to

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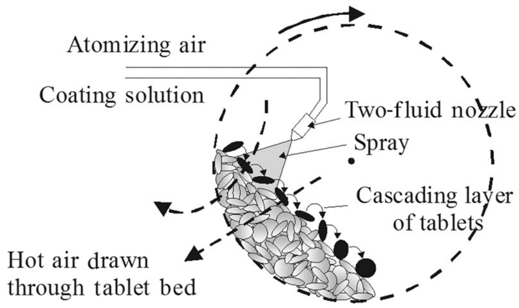

Figure 1. Schematic representation of pan coating process in a perforated coating pan. Reproduced from Pandey et al.[1] with permission from Elsevier.

achieve a uniform coating on each tablet, a relatively long processing time may be required.

The coating process is a unit operation that comprises simultaneous exchanges of heat and mass between inlet air stream, spraying material, substrate, and coating pan. A balance between mass and energy is sought during coating process. Although pan-based coating processes have been used for several decades, the scale-up of this process still remains a challenge. The underlying science of the coating process is complicated and the ability to predict reliably the performance of a coated product *a priori* is often limited. Successful tablet coating requires selecting the appropriate tablet formulation components, tablet properties, coating formulation, coating properties, and coating process conditions. The liquid flow rate (i.e., spray rate) needs to be determined in combination with the appropriate thermodynamic drying conditions (air flow, temperature, and humidity), so that evaporation of the solvent occurs at an adequate rate to achieve uniform (intertablet and intratablet) and aesthetically acceptable film coating.

There have been some efforts in the past to propose scale-up principles for pan coating process. Ding et al.[4] developed scaling relationships for rotating drums by nondimensionalizing the differential equations governing the behavior of solids motion. The analysis did not account for the spray-related process parameters. Qualitative insight into different factors that affect the coating process has been provided by several researchers.[5,6] Researchers have proposed some scale-up rules for pan coating, where parameters such as pan loading, pan speed, number of spray guns and distance between them, coating time, and spray rate were discussed.[7–9] The batch size was scaled on the basis of ratio of pan volumes and the pan speed on linear velocity. Porter[10] has discussed the scale-up problems in more detail. The most common approach used in the industry is to study the effects of coating formulation and process parameters on coating uniformity and other product attributes through a series of designed experiments at various scales with appropriate statistical tools. However, this type of analysis results in information specific to a single formulation/product and equipment with predictive ability restricted only to the studied range of parameters. More recently fundamental studies to understand the physics behind the coating process are being conducted and also fundamental scale-up principles have been proposed.[11,12]

Recent regulatory initiatives require science- and risk-based holistic development of processes and products based on concepts of "Quality by Design" (QbD) and process analytical technology (PAT) as outlined in several guidelines, including ICH Q8, ICH Q9, and ICH Q10.[13–15] By applying QbD approaches, an enhanced knowledge of product performance over a range of material attributes, manufacturing process options, and process parameters need to be demonstrated. To develop and optimize a coated product based on QbD principles, the first step is to establish a Quality Target Product Profile for the core substrate and coated product. The second step is to determine the critical quality attributes (CQAs) of the core substrate and coated product. The third step consists of a risk assessment exercise to identify the critical material attributes (CMAs) and critical processing parameters (CPPs). The final step involves drafting a design of experiments (DOE) to determine the design space of the CPPs for the coating process. The initial risk assessment can be carried out based on historic knowledge and risk ranking/filtering based on data generated from small scale laboratory experiments. The risk assessment is an iterative process and should be updated as more information is generated about process and product at various scales. However, to minimize the iteration and rework during scale-up of coating process, the small-scale experiments should be designed to gain a more fundamental understanding of the coating process based on underlying physics and thermodynamic principles. For example, designing studies to understand the mixing dynamics of the selected core substrate using new advanced modeling and particle tracking tools can assist in defining CMAs, CPPs, and pan coater design. Similarly, a thorough characterization of spray system at small scale using new characterization technologies and modeling techniques will ensure identification of appropriate parameter ranges to achieve similar droplet characteristics and drying during scale-up. Once sufficient fundamental understanding is generated about the coating process, the design space for the CPPs can be identified by conducting smaller DOEs to optimize the coating process. Upon optimization of coating process through appropriate data analysis and modeling strategy, the information generated could enable real-time process decision-making and process control using PAT tools to ensure production of consistent quality product.

A brief overview of coating process parameters that should be considered while conducting risk assessment is provided in the next section. In subsequent sections, current scale-up approaches for pan coating process along with new scale-up methodologies and tools that can be used to assess coating process and coating product quality based on QbD principles are provided.

COATING PROCESS FACTORS

The coating process is a complex process and is not linearly scalable. There are several factors that affect the coating process. It is important to understand the interdependencies of various factors while conducting scale-up studies based on QbD principles. A fishbone diagram of the various coating factors that play an important role in the coating process is shown in Figure 2. While conducting risk analysis and designing studies, the coating factors can be broadly classified into following categories:

- Coating formulation factors—varied to achieve desired drug release, ease of coating application and stability
- Substrate/core factors—affect the attrition, mixing, and coating quality
- Pan coater factors—affect mixing conditions in pan