A Commentary on Scale-Up of Pan Coating Process Using Microenvironmental Control

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ABSTRACT: Although significant progress had been made in developing general scale-up rules for an aqueous pan-coating process, there are often scenarios where small-scale experiments are not found to be truly reflective of what may be observed at the large scale. This article reviews some of the methods traditionally used for scale-up, identifies the gaps associated with the traditional scale-up rules, and provides a perspective on a new real-time process monitoring tool that is capable of providing thermodynamic changes taking place in the microenvironment of the substrate being coated. This tool has been used to ensure increased success during scale-up by maintaining environmentally equivalent conditions between the processes, especially for systems that are sensitive to small thermodynamic changes.

Keywords: coating; scale-up; microenvironment; EEF factor; unit operations; quality by design (QbD); process analytical technology (PAT); processing; solid dosage form

INTRODUCTION

A pan coater consists of a rotating perforated pan equipped with spray gun(s) (Fig. 1). The spray gun system is generally a two-fluid nozzle system where the coating suspension is atomized into fine droplets via an air stream (atomization air). These atomized droplets travel through a preheated air stream (inlet air) and impinge on the cascading layer of tablets. These droplets coalesce, spread on the tablet surface, dry and form a thin film on the surface of the tablet.

The thermodynamics of the coating process is governed largely by the factors such as inlet air conditions [temperature, relative humidity (RH)], inlet airflow rate, gun-to-bed distance, heat losses, and spray conditions such as spray rate, droplet viscosity, droplet size, and so on. The thermodynamic conditions inside a coating pan can affect the quality of the film formed on the tablets. For example, a relatively dry environment can result in tablet defects such as surface roughness, whereas a wet environment can cause tablets to stick or pick. Appearance and residual water content of coated tablets have been shown to be a function of coating conditions.[1–4]

Traditionally, the coating process is controlled by maintaining the exhaust air temperature at a predetermined set point by adjusting the inlet air temperature once other independent variables such as spray rate and inlet air volume are fixed. The tablet-bed temperature (T) is assumed to be 2°C–3°C lower than the exhaust temperature, as was measured in certain studies by pointing an IR gun on the surface of the tablet bed (just outside of the spray zone). The inlet air RH (%RH) or dew point is often maintained below a certain set-point in a cGMP (current Good Manufacturing Practice) manufacturing setting. However, in most laboratory and pilot-scale settings, the inlet air %RH is not controlled or monitored. The inlet air is generally obtained from the process room, which may not be well regulated. Additionally, the exhaust air %RH is not controlled or monitored. Clearly, there is incomplete characterization of the process thermodynamics, even at the macroscopic level. Inadequate control of the inlet air %RH has been shown to have a negative effect on the quality of the coated product, with logo bridging tablet defect observed at a high inlet air %RH.[5]

An approach for scaling up the coating process that is most routinely used is to utilize established scale-up rules on individual process parameters.[6–9] The process parameters that play an important role in defining the coating process thermodynamics include inlet and exhaust air conditions, spray rate, airflow rate, gun-to-bed distance, atomization, and pattern air pressure. Other factors such as pan speed (mixing-related) and batch size are important in defining the overall coating operation but do not have a direct role in dictating the process thermodynamics. As discussed before, the exhaust air temperature is assumed to be reflective of the tablet-bed temperature and is therefore maintained constant during scale up. The inlet air temperature is adjusted in order to reach the desired exhaust temperature. Spray rate plays a significant role in defining the thermodynamics of the overall coating process. Spray rate is especially important if the drug product is sensitive or unstable under high moisture conditions, as residual water content in coated tablets can be directly related to spray rate.[1] At fixed formulation factors, the spray rate and the gun-to-bed distance affect the tablet-bed microenvironment significantly, which can impact the final coated drug product quality.[10] During scale-up, it is desired to keep the spray rate as high as possible at the larger scale so as to reduce the process cycle times. In order to compensate for the increased spray rate, the inlet airflow is increased, such that the ratio of inlet airflow to spray rate (drying capacity) is maintained constant across scales. Maintaining drying capacity similar across scales can be effective in keeping the macroscopic environment across scales similar; however, this may not be the case at the tablet-level (microscopic).[2] Alternatively, the inlet air flow is determined first based on recommendations by the manufacturer and equipment limitations.[9] Once inlet airflow is fixed,

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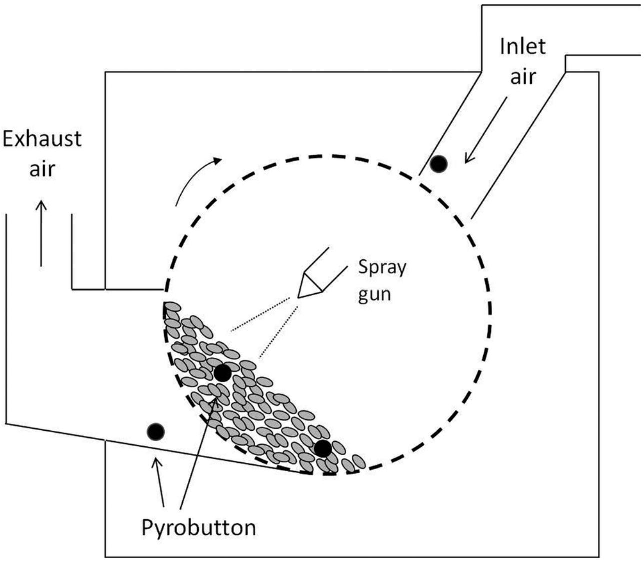

Figure 1. Schematic representation of a pan coater. Also shown in this figure are PyroButton® data loggers that are fixed at different locations inside the coater and also allowed to freely move with the tablets to enable measurement of the microenvironment experienced by the tablets during the coating process (reproduced with permission from John Wiley and Sons).[5]

the spray rate is determined by keeping the ratio of inlet airflow and spray rate constant across scales. There are changes in nozzle sizes and sometimes even spray gun manufacturer during scale up; however, the aim should be to match the average droplet size coming out of the spray nozzle by making spray rate and atomization air pressure adjustments. The atomization and pattern air pressures or flow rates are scaled based on maintaining droplet size distribution similar across scales.[11,12] In absence of droplet size data, as a general rule of thumb, the ratio of spray rate to atomization air flow rate, and atomization air to pattern air ratio can be kept constant across scales.

It is worthwhile to note that all the scale-up factors discussed here are macroscopic factors and do not quantify the changes experienced by the tablets at the microscopic level as they get coated. The fundamental assumption is that changes to the macroscopic parameters at different scales have similar, if not the same, effect on the microenvironment experienced by the tablets. For example, the exhaust air temperature is maintained constant across scales during scale-up with the underlying assumption that by doing so the tablet-bed temperature is maintained constant across scales. Although this may turn out to be a reasonable assumption at certain process conditions, this cannot be generalized. Recent studies have clearly shown that the difference between the exhaust temperature and tablet-bed temperature is a function of the processing conditions, with larger deviation observed between the two for "wetter" process conditions. The difference between the exhaust and the tablet-bed temperature can, in certain cases, be larger than 10°C depending on the process conditions and also on the exhaust temperature measurement location in the coater.[2,13] The difference between the exhaust RH and the tablet-bed RH (or the RH that the tablets experience) can be higher than 20%.[10,14] Such differences between the exhaust air conditions and the conditions experienced by the tablets highlight the importance of characterizing the conditions at the microscopic level (tablet microenvironment). This understanding would be critical for drug products that are sensitive to heat and moisture.

Mathematical models using heat and mass transfer equations have been developed to describe the coating process.[7,15–18] Ebey[15] introduced the concept of using a single value, environmental equivalency factor (EEF), to describe the thermodynamic state of the coating process, with a high EEF value indicating a dry process. EEF number is often used for understanding the effect of changing process parameters at a particular scale and also for scale-up purposes such that it is kept constant during scale up. EEF value accounts for several process parameters including inlet air temperature and RH conditions and also provides the predicted exhaust air T and RH values. However, this approach considers the coating process as a "black-box" and the factors such as gun-to-bed distance, which are well-known to have a significant role in the process,[10] do not appear in EEF calculations. Additionally, the heat losses during the coating process are generally not accounted for in EFF calculations, and therefore, the models tend to deviate from experimental results when used across scales, where heat losses may be different. Some of the newer thermodynamic models have improved upon Ebey's EEF model and accounted for heat losses in their calculations.[16,17,19] However, the approach is still largely macroscopic in nature and such models do not directly address the localized conditions experienced by the tablets. Although the United States Food and Drug Administration's emphasis on process analytical technologies and quality by design stress the importance of a thorough understanding of processes, such a detailed knowledge of the coating process is still incomplete, especially in relation to the thermodynamic conditions in the coating bed.

Recent studies by the authors and coworkers have established the utility of a new real-time monitoring tool (PyroButtons®; Opulus Ltd., Philadelphia, Pennsylvania) that can be used to quantify the microenvironment experienced by the tablets during coating. PyroButtons® are data logging devices that record T and RH data in real-time. These tablet-sized devices (16 mm diameter, 6 mm height) were secured at specific locations in the equipment (e.g., inlet, exhaust, spray gun handle, baffles), and also placed in the tablet bed and allowed to tumble freely along with the tablets (Fig. 1). PyroButtons® that move with the tablets provide information on the thermodynamic conditions (microenvironment) experienced by the tablets during the coating process. There have been a few case studies published recently that show the utility of the information provided by the moving PyroButtons®, where correlations could be established between the measured microenvironment and the coated drug products' critical quality attributes (CQAs) such as appearance, physical, and chemical stability. These case studies can be classified into different categories of drug product CQAs:

1. *Appearance* (logo bridging tablet defect): As part of understanding this CQA, it was shown via a case study that the macroscopic events such as logo bridging coating defect correlated best to tablet-bed RH when compared with the conventionally-measured coating process parameters.[14] It was shown that a process design space can be established based on the tablet-bed microenvironment (RH) where no logo bridging was observed (Fig. 2). A