Layering an API onto tablets using a perforated-drum coater: A case study

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Controlling weight gain is an important factor when applying any coating, but it becomes absolutely critical when the coating contains an API. This article presents a case study that identifies the critical process parameters for developing a consistent and robust coating process that provides in-range results.

Innovators continue to seek drug products that can deliver multiple active pharmaceutical ingredients (APIs) in a single tablet or capsule. Among the approaches used are biphasic tablets, multi-particulate tablets, and controlled-release matrix systems. Applying an API in layers over placebo tablets or over tablets that include an API are other approaches. The latter method—which can employ an aqueous or non-aqueous coating—enables formulators to combine incompatible APIs into a single dosage form [1, 2]. API layering can also be used to overcome patent restrictions and is suitable for manufacturing high- and low-dose drug products, although manufacturing high-dose products is simpler because content uniformity across the batch is less of an issue. In the case of low-dose products, process optimization becomes critical to ensure quality and consistency. The two major factors are machine design and controlling the process parameters that most influence the quality of the finished product.

Key aspects of machine design

Baffle design, mixing pattern, spray pattern, spray consistency, drying efficiency, turbulence in the coating zone, temperature consistency, airflow, and differential pressure are among the factors that affect the quality of the finished product. But baffle design, spray pattern, and airflow pattern are three that have a major effect on the coating process.

Baffles. Many types of baffles are available, including tubular, ploughshare, rabbit ear, shark fin, spiral, and...
Fischer designs. The rabbit-ear baffles provide gentle mixing and are suitable for friable tablets, but their mixing efficiency is poor. Tubular baffles provide good mixing of round tablets but have limitations when it comes to friable tablets and tablets of other shapes. Fischer and spiral baffles are more useful overall since they provide gentle and efficient mixing and handle all tablet shapes and sizes.

Spray nozzles. Two basic types of nozzles are available: the horn design and the anti-bearding design. A major disadvantage of horn-type nozzles is that spray-dried coating (dust) deposits on the air cap, causing clogs and disturbing the spray pattern. As a result, many manufacturers favor anti-bearding caps, some of which include a self-cleaning provision.

Airflow pattern. The turbulence from the hot air in the process zone—the airflow pattern—varies from manufacturer to manufacturer. The most common and traditional is diagonal flow, with the air entering at the chamber’s top and exiting at a diagonal through an exhaust shoe at the bottom. This pattern causes the hot air to pass through the coating zone, which leads to spray drying and formation of a beard on the nozzle, eventually reducing coating efficiency. The diagonal pattern also disturbs the spray pattern, leading to non-uniform coating. In other flow patterns, including the within-bed and horizontal, the path of hot air is separated from the spray zone, which eliminates spray drying and thus minimizes the chance of spray-pattern deviations. This leads to a more consistent and uniform distribution of the API on the tablets.

In addition to these design factors, the coating system must offer a means to control—as Quality by Design (QbD) requires—all the critical parameters (airflow, temperature, differential pressure, spray rate, atomization pressure, etc.) within a specified range at all times. This is often done through automation.

Key process parameters

It is important to understand the critical process variables and how they interact when layering an API onto tablets because they directly affect the assay and content uniformity of the final unit dose. First, examine the coating uniformity by determining the assay value of the coated tablets. According to USP guidelines, API variation must not exceed 6 percent relative standard deviation (RSD) [3].

Variation is of two types once the process reaches the commercial stage: batch-to-batch and tablet-to-tablet. In some cases, manufacturers analyze the batch for the assay and, if required, perform additional coating to save the batch. But that practice is not acceptable to many manufacturers or regulators, who insist on a robust process that ensures the product meets the specification on the first attempt. Another major challenge is achieving content uniformity across the batch. There have been many instances of batch failures due to a high RSD value of intra-tablet assay, in which case the batch had to be discarded. Such cases raise a question about the robustness of the manufacturing process for the particular product. If the out-of-spec assay goes undetected, it could lead to a market recall that would damage the brand and entail a severe financial loss.

Case study

This article discusses how to identify and optimize the critical process parameters (CPPs) using a QbD approach. The first step was to conduct a risk assessment to select the process parameters that had the most effect on the product’s critical quality attributes (CQAs). A full factorial design was employed as a statistical model to optimize the process variables, which included pan speed, spray rate, atomizing-air pressure, and nozzle-to-bed distance. Paracetamol (acetaminophen) was selected as the model API. Numerical and graphical optimization techniques that employed a design-space approach were used to understand the critical process and machine parameters by setting a constraint on the dependent and independent variables.

The results revealed the interaction of the parameters and highlighted the CPPs that were critical to monitor when layering an API onto tablets using a perforated pan coater. The experimental values of percentage assay and RSD of content uniformity for an optimized batch were found to be in close agreement with those predicted by the mathematical model, thus confirming the validity of the coating process.

Materials and methods

Formulating the tablet using layering. Placebo granules comprising mainly starch and lactose were manufactured using a top-spray granulation technique with PVP K30 as a binder. The granules were compressed into tablets using a 9-millimeter round, standard punch. The tablets, which would serve as the substrate for API layering, were seal-coated to 2 percent weight gain using HPMC E5. The model API, paracetamol, was combined with HPMC E5 (binder) and PEG 6000 (plasticizer). Table 1 lists the composition of the API coating solution.

Risk assessment of CQAs. The ICH Q9 guidance outlines the concept of quality risk management in terms of assessing, controlling, communicating, and reviewing the risks to the “quality target product profile” (QTPP) over a product’s lifecycle, and optimization of the coating process was critical to the QTPP. The risk assessment for

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Milligrams per tablet</th>
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<tbody>
<tr>
<td>Paracetamol</td>
<td>9.8</td>
</tr>
<tr>
<td>HPMC</td>
<td>5.0</td>
</tr>
<tr>
<td>PEG 6000</td>
<td>1.6</td>
</tr>
<tr>
<td>Ethanol and purified water (30:70)</td>
<td>As needed to 12%</td>
</tr>
<tr>
<td>Total weight of API-layered tablet</td>
<td>322.4</td>
</tr>
</tbody>
</table>

Table 1 Composition of layering solution
loading the API on the core tablets was carried out, and the CPPs that could affect the CQAs were identified and their associated risk was evaluated. As it was not feasible to conduct a Design of Experiment (DoE) to evaluate all the variables, they were ranked as low-, medium-, and high-risk during the assessment (Table 2). The parameters ranked as low and medium risks were set as fixed values. The high-risk variables were evaluated by conducting DoE studies to gain process understanding.

Equipment and formulation. An R&D coating system [4] equipped with a 2-liter perforated pan was used to conduct basic and DoE trials. It was equipped with Fischer baffles and a spray nozzle fitted with an anti-bearding nozzle and a 0.8-millimeter insert. In the preliminary trials, weighed amounts of paracetamol, HPMC 5, and PEG 6000 were dissolved in a mixture of ethanol and purified water (solvent ratio = 30-to-70) that was sprayed on the tablet cores as the parameters were monitored.

DoE. A full factorial DoE was conducted, with pan speed, spray rate, atomizing-air pressure, and nozzle-to-bed distance used as independent variables. Assay and RSD of content uniformity were chosen as dependent responses. Table 3 lists the factors and responses.

Table 2

<table>
<thead>
<tr>
<th>CQA</th>
<th>Pan speed</th>
<th>Spray rate</th>
<th>Atomization air pressure</th>
<th>Nozzle-to-bed distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay</td>
<td>Low</td>
<td>High</td>
<td>Medium</td>
<td>Medium</td>
</tr>
<tr>
<td>Content uniformity</td>
<td>High</td>
<td>Medium</td>
<td>Medium</td>
<td>High</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Formulation variables</th>
<th>Levels</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan speed (rpm)</td>
<td>-1</td>
<td>12</td>
</tr>
<tr>
<td>Spray rate (g/min)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Atomizing air (bar)</td>
<td>+1</td>
<td>1.2</td>
</tr>
<tr>
<td>Nozzle-to-bed distance (cm)</td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>

The purpose of the design was to evaluate the effects of process variables on the responses and provide guidance on optimal process conditions to achieve the desired API content uniformity. The experimental design and analysis of the effect estimates and response surface were conducted using Design Expert 9.0.1 software (Stat-Ease, Minneapolis, MN). All other process parameters, such as exhaust temperature, airflow, and differential air pressure, were kept constant in the feasibility study. Based on the number of variables, their levels of study, and the type of study, a 24 factorial design with four factors and two levels (i.e., 16 runs) was selected for optimization of the process parameters of the paracetamol-loaded tablet to meet the required QTPP.

Results and discussion

A risk assessment was conducted as shown in Table 2, and high-risk parameters—based on their strong correlation to the CQAs and the QTPP—were considered for the DoE to ensure product quality was pre-defined.

Input variables (pan speed, spray rate, atomization-air pressure, and nozzle-to-bed distance) contribute interactively to the equilibrium between assay and content uniformity. These potentially high-risk process variables, as identified during the initial risk assessment, were investigated next.

Effect of process variables on assay. All batches demonstrated acceptable assay, which was well within the specification limits (95.0 to 105.0 percent w/w). As the half-normal plot in Figure 1 shows, spray rate, atomizing-air pressure, and nozzle-to-bed distance have a significant effect on assay value, whereas the effect of pan speed was minimal. The assay was found to increase with an increase in the spray rate, and it was highest at the shortest nozzle-to-bed distance. This was mainly because the short distance minimized spray drying. An inverse effect on assay was seen when coating at a low spray rate and long nozzle-to-bed distance, as the 3-D surface-response and contour plots show (figures 2 and 3).

Effect of process variables on RSD of content uniformity. As the half-normal plot in Figure 4 shows, spray rate, atomizing-air pressure, and nozzle-to-bed distance significantly affected the RSD of content uniformity. It increased as the spray rate increased at the minimum nozzle-to-bed distance. This is mainly because, at a higher spray rate, the process finished faster and because the shorter distance decreased the spray's bed coverage. The
result was poor distribution of the coating on the tablets. When the spray rate was reduced, thereby extending the process time, the RSD of content uniformity decreased, and API distribution over the tablet mass improved (Figure 5). Figure 6 illustrates how spray rate and pan speed affected the RSD of content uniformity.

Based on the results of the screening DoE studies, the spray rate and nozzle-to-bed distance were identified as CPPs. The design space was determined from the common region of successful operating ranges for multiple CQAs at the 1.5-kilogram scale. The overlay plot (Figure 7) indicates that the process parameters within the overlap region gave an assay within the target range of 97 to 103 percent and good process efficiency. They also allowed the maximum range of operation to achieve the desired quality attributes.

Thus spray rate and nozzle-to-bed distance level had significant impacts on tablet assay. Curvature effects were
observed for all responses studied, and the main effect and interaction effects were identified using a full factorial DoE. The DoE models were used to establish acceptable ranges for formulation variables. Figure 7 shows the overlay plot of all responses, and the yellow zone indicates that all the responses were achieved simultaneously. The combination of a higher spray rate and shorter nozzle-to-bed distance enhanced assay because spray drying was minimized.

References

4. Quest TCM from ACG Pharma Technologies, Mumbai, India.

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