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Scale-up: Now you know the Critical Process Parameters (CPP) – what do you do with them in pilot and production equipment?

Previous insights have discussed the importance of raw material characterization studies and the use of DoE (design of experiments) to understand the sensitivity of a formulation and process variables. The fluidized bed process has a multitude of variables, most of which are confounding, and several of which will have a strong impact on dosage form performance. What is characteristic is that early stage product development is an 'open door'. Many raw materials and process techniques may be tried, and the number of feasibility trials may exceed 50, even in a relatively short period of time. However, as the product gets closer to the production scale, raw material costs escalate dramatically (due to the increased batch size) and the number of trials run prior to process confirmation and validation is dramatically reduced. It is crucial that the formulators and scale-up and technology transfer personnel have a very good understanding of the robustness of a product and process to avoid failure during process validation or during routine manufacture after the product is approved for marketing.

The use of DoE in small scale trials not only quantifies the impact of the various process variables, but also yields insight into the breadth or narrowness of their domain. For it to be effective, most process variables are fixed and those that are investigated are held at a constant value for as long as possible during a process (from the start to completion is preferred). This information is valuable in identifying the operating ranges experimentally rather than speculatively, which is too often the case.

Interestingly, the first experiment in scale-up may not contain a spraying step. An important consideration is fluidization behavior, particularly for the Wurster process. It is prudent to conduct a 'mass flow study'. Identify a starting and finished batch size and add these amounts to the product container. Begin fluidization and use a variety of conditions (partition height, process air volume, orifice plate configuration). If possible, the ideal fluidization condition should be at a high process air volume for efficiency and total mass balance. It should be satisfactory across the range of starting and final batch weight. Generally the faster the application rate, the better the overall yield (attrition is minimized).

The next step is to conduct a brief series of feasibility batches. The first batch may use ramping of the spray rate to derive a high spray rate without appreciable agglomeration. The second batch should use this value from beginning to end if possible (provided that the substrate is not sensitive to the application medium). Other values for the studied parameters should be selected such that they represent the center point conditions for the DoE.

At this point, the domain for the Critical Process Parameters (CPP) should be identified. As a rule of thumb, the values selected should deviate about 10-20% from the center point for the particular variable. For instance, if the spray rate from the feasibility trials was 500 g/min, the high and low values could be 400 g/min and 600 g/min.

Before running the batches in randomized order, it is prudent to process the 1 or 2 candidates that are most likely to fail. A DoE usually has a limited number of batches and a batch failure (resulting in unusable data) will limit the overall effectiveness of the study. If a batch fails badly, recast the domain slightly and complete the study. A robust process (one that meets CQA for all batches) will yield operating ranges for CPP which have been derived experimentally, not hypothetically.