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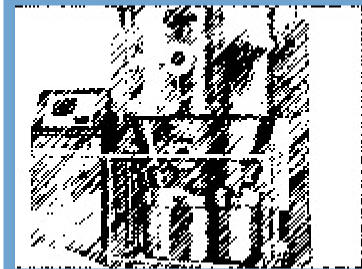

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Quality By Design: Incorporating DOE (Design of Experiments) Throughout Product Development

A comment often heard when discussing formulation and product development is: "DOE? We don't have the time or the resources to do it." A consequence is that all too often a product that is successful in the clinic is a menace on the manufacturing floor. When used effectively in small scale batches, DOE is a learning tool – it helps identify critical process variables. The selected response variables may extend well beyond the critical quality attributes, sometimes teaching you things you didn't expect. At the pilot scale, successful experimentation in a broadened domain establishes the operating limits for the critical process parameters. Finally, a limited number of early production scale batches should confirm the results of the pilot scale DOE.

As an example, suppose a target product is comprised of drug layered pellets, coated for sustained release. A good candidate for the Wurster process, the variables that a formulator must consider for laboratory scale development include insert configuration (orifice plate and retention screen selection; partition height); process air volume, temperature and dew point; atomizing air pressure (and volume); spray rate; solution concentration and product temperature during spraying. At first glance, the list is long and it is understandable that using DOE to quantify their impact would be a time consuming task, even for a screening study. This is compounded by the likelihood that process variables are confounding – change one, and there is an impact on others. For instance, process air volume is a multi-tasking variable: it delivers heat for vaporization of the application media, carries away the vapor and impacts the product temperature. It also governs the fluidization pattern and for this reason a 'mass flow study' is conducted to identify the best combination of partition height, orifice plate configuration and process air volume to optimize the fluidization pattern (prior to running any batches). When this is finished, these values are fixed for the duration of development, and three variables are 'removed from the list'. Values for 'global' parameters may be identified based on prior knowledge of the attributes of the spraying materials (temperature sensitivity, viscosity, etc.). In this manner, process air dew point and solution concentration may at least temporarily exit the list as well. The list has now been narrowed to spray rate, atomizing air pressure (and volume) and product temperature during spraying (actually a dependent variable, but one controlled by process air temperature in response to evaporative cooling via the application media). First experiments are conducted using conservative parameters. Experimental batches will approach or achieve the desired critical quality attributes. Subsequent batches should be processed using a pre-determined 'experimental domain' – high and low values for the three remaining process variables (in some cases, one or more of the conservative parameters may ultimately represent the 'low' values in the DOE). Within 8 batches, you have sufficient data to evaluate the significance of impact of three process variables in a center composite design. Three replicate 'center point' batches will reveal the repeatability of the process, and you are then ready for scale-up.

It is reasonable to expect that larger batch sizes in pilot equipment will exhibit behavior not seen in lab machines. Bed depth is greater, substrate flight is elongated, the nozzle is larger and the kinetic energy produced at its tip (from the volume and velocity of atomizing air) is considerable. Additionally, relative to the size of the 'coating zone' (interaction of droplets with substrate), the particle size is much smaller in the pilot equipment in comparison to the lab machine. So-called coating 'efficiency' may change. However, the process variables found to be the most significant in the lab will still apply to the pilot scale, and only the range or breadth of the domain may change.

The next 'Insight' will discuss methods for identifying the domain in pilot scale and how the results will apply to the next step – 'Scale-OUT' (if the spray zone geometry is replicated) in production equipment.