Improving Process Validation for Dry Granulation, Solid Dosage Form Unit Operations

Effective process validation contributes significantly to assuring drug quality. The FDA defines process validation "as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product". Process validation establishes the elasticity and restrictions within the manufacturing process controls to deliver upon the specified attributes of the dosage form while preventing undesirable out-of-specification results.

Roller Compaction is a continuous dry granulation process to increase the bulk density and uniformity of powders into free flowing granules used in downstream manufacturing operations. Many researchers and process engineers have stated that within roller compaction operations that the physical and the mechanical properties of produced granules have direct influence to the solid dosage form's physical stability as well as the accuracy of desired patient dosage

The densification of powders blends in Roller Compaction unit operations is a complex procedure due to the diversity of available powder blends and the control and adjustment parameters involved in the process. The character and homogeneity of the produced ribbon is controlled by a number of factors, such as the properties of the individual powders themselves, roll speed, roll gap/nip angle, and feeding speed; all of which subsequently determine the character of the produced granules (size distribution, density, and flow behavior).

It is critical to produce uniform and specified ribbon densities throughout the process, as well as throughout the ribbon itself. This is important in order to achieve analogous tensile strengths and desired particle size distributions of the milled materials. Specified ribbon densities can be achieved by maintaining equivalent compaction pressure applied by the rolls on the ribbon for a specified gap distance and speed.

In pharmaceutical operations, the Roller Compaction process has significant effect on particle size distribution, porosity, flowability in downstream operations, homogeneity, compactability and compressibility of the API, additives/ excipients. These factors influence dissolution profiles, disintegration time, and hardness of the produced solid dosage form.

Within compaction operations, roller pressure, roller gap, speed and mill screen orifice size can be identified as critical process parameters (CPPs) for the roller compaction and integrated milling process step.

In many cases higher roller pressures will result in higher shear stresses, increased ribbon density, coarser granules, higher bulk-tap densities and lower tablet tensile strength. In regard to roll gap, as roll gap increases, the constant force from the roller is applied through a thicker ribbon. The produced ribbon will have a lower strength that may result in smaller, weaker granules. Roll speed also affects granule hardness. At low roll speeds granule hardness is increased due to the formation of hard ribbons; conversely; finer granules are produced at higher roll speeds due to softer ribbons.

Ribbons with suitable solid fraction are preferred since under-compacted ribbons can disintegrate back to the original primary powders of the individual blended components. Excessively compacted ribbons will lead to hard and brittle granules that prevent reprocessing.

The need for advanced technologies for monitoring and evaluating roller compaction processes had led to the development of some novel new systems. A desire for in-process, on-line monitoring is used by spectroscopic/ microscopic methods, such as near infrared (NIR), acoustic emission, focused beam reflectance measurement (FBRM), and particle video measurement (PVM). These methods hold promise but are still being evaluated as robust and rugged solutions. Some of these systems are costly to implement and have been shown to require a learning curve with detailed operator training to be successfully employed in a production environment.

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A well-documented and widely accepted approach for process validation in roller compaction operations is to monitor the process by using a target Solid Fraction to ensure reproducible and consistent ribbon quality. Solid Fraction can be used as an indicator of the desired downstream processing character of the produced granules and their eventual influence to final dosage form performance.

Solid Fraction, determined through data driven instrumental methods, is an excellent path to achieve Roller Compaction operations that incorporate a QbD approach to process validation. Solid Fraction can be used as an important Critical Process Parameter (CPP) and is determined using the following formula:

$$SF = \frac{\rho_e}{\rho_o}$$

SF= Solid Fraction (relative density)

Pe = envelope density of the ribbon

Po = true density of the granules

A Helium pycnometer, for example the AccuPyc from Micromeritics Instrument Corp., is used to determine the true density of a sample. It is a fully automated instrument that can be placed at-line or within a supporting lab operation for manufacturing control. Gas pycnometry is recognized as one of the most reliable techniques for obtaining true, absolute, skeletal, and apparent volume and density. This technique is non-destructive as it uses the gas displacement method to measure volume and analysis is accomplished in minutes. Rugged and simple, the helium pycnometer requires very little training or user expertise making it a good choice for at-line validation control.

For envelope density, Micromeritics has developed the automated GeoPyc envelope density analyzer. The instrument employs a unique, non-destructive, fast displacement measurement technique that uses Dry Flo, a quasi-fluid composed of small, rigid spheres having a high degree of flowability. The sample is placed in a bed of Dry Flo which is agitated and gently consolidated about the sample. The GeoPyc collects the displacement data, performs the calculations, and displays or prints the results.

While skeletal and envelope volume measurements are significant in their importance as individual measurements, their combination permits the pharmaceutical scientist or process engineer to also accurately calculate percent porosity and total pore volume. With this data a quality assurance scientist or manufacturing engineer can have greater knowledge of their process for improvements in both quality of product and optimization of the manufacturing process. Employed in tandem, these two instruments can achieve data driven, instrumental analysis to employ Solid Fraction as a process validation, CCP in pharmaceutical densification operations.