Research paper

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Raw material variability of an active pharmaceutical ingredient and its relevance for processability in secondary continuous pharmaceutical manufacturing

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ABSTRACT

Active Pharmaceutical Ingredients (API) raw material variability is not always thoroughly considered during pharmaceutical process development, mainly due to low quantities of drug substance available. However, synthesis, crystallization routes and production sites evolve during product development and product life cycle leading to changes in physical material attributes which can potentially affect their processability. Recent literature highlights the need for a global approach to understand the link between material synthesis, material variability, process and product quality. The study described in this article aims at explaining the raw material variability of an API using extensive material characterization on a restricted number of representative batches using multivariate data analysis. It is part of a larger investigation trying to link the API drug substance manufacturing process, the resulting physical API raw material attributes and the drug product continuous manufacturing process. Eight API batches produced using different synthetic routes, crystallization, drying, delumping processes and processing equipment were characterized, extensively. Seventeen properties from seven characterization techniques were retained for further analysis using Principal Component Analysis (PCA). Three principal components (PCs) were sufficient to explain 92.9 % of the API raw material variability. The first PC was related to crystal length, agglomerate size and fraction, flowability and electrostatic charging. The second PC was driven by the span of the particle size distribution and the agglomerates strength. The third PC was related to surface energy. Additionally, the PCA allowed to