

Development of a Statistical Tolerance-Based Fluid Bed Drying Design Space

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Abstract

Introduction The pharmaceutical industry has invested a substantial amount of resources in recent years to develop manufacturing systems that offer improved product quality while limiting costs. The US Food and Drug Administration (FDA) has encouraged the use of the guidelines put forth by the International Conference on Harmonization [ICH-Q8(R2)] that allow for operational flexibility within a validated design space to allow automated systems that incorporate real-time data management. Use of these systems requires substantial process understanding that is typically gained through appropriately developed design of experiments. Appropriate analyses of the data are required to optimize the understanding gained from experiments. Furthermore, these analyses must be combined with existing product specifications to set justifiable operating limits for the process.

Material and Methods Granules containing gabapentin, and hydroxypropyl cellulose were prepared in a high-shear granulator and dried in a fluid bed processing system. The fluid bed dryer was outfitted with near infrared, pressure, temperature, and flow sensors, which were connected to a distributed control system that was used to exercise control of the system. The dried granules were blended with extragranular excipients and then compressed on a rotary tablet press. Designed experimental variations to processing were utilized at each of the manufacturing steps to produce a design space. The outputs of the design (quality attributes) that were considered in this work were the quantity of gabapentin lactam formed during processing, tablet crushing strength, final blend flow properties, and median particle size of dried granules.

Results A tolerance-based design space was constructed for each of the quality attributes considered, and an overall design space was calculated based on the individual unit operations. The overall design space was a combination of process models and was calculated to include the uncertainty (variance) from each of the unit operations and measurements. A tolerance design space was calculated that reflects the probability that a given combination of processing parameters will produce critical quality attributes within specifications.

Keywords Fluid bed processing · Process analytical technology · Multivariate modeling · Feedback control · Design space · Quality by design

Introduction

The pharmaceutical industry has invested a substantial amount of resources in recent years to develop manufacturing systems that offer improved product quality while limiting costs. The US Food and Drug Administration (FDA) has encouraged the use of the guidelines put forth by the International Conference on Harmonization [ICH-Q8(R2)] [1] that allow for operational flexibility within a validated design space which enable fully automated systems that incorporate real-time data management. These systems offer opportunities for continuous improvement of the process and resulting quality improvement through drug product information gained during manufacturing via online process measurements to inform process adjustments to ensure constant product quality [2].

The process set points within the automated control system are optimized using empirical design of experiments to establish the relationship to final product quality metrics called critical quality attributes (CQAs) [1]. The process parameters that are significant predictors of final product CQAs are

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