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RESEARCH ARTICLE

# Hybrid Controls Combining First-Principle Calculations with Empirical Modeling for Fully Automated Fluid Bed Processing

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**Abstract**
*Introduction* The US Food and Drug Administration has encouraged the use of the guidelines put forth by the International Conference on Harmonization (ICH-Q8) that allow for operational flexibility within a validated design space. These guidelines make possible fully automated control systems that incorporate information about a process back into the system to adjust process variables to consistently hit product quality targets. Traditionally, fluid bed control systems have used either first-principle calculations to control the internal process environment or purely empirical methods that incorporate online process measurements with process models and real-time data management. This study demonstrates the development and implementation of a novel hybrid control system that combines the two traditional approaches.
*Material and Methods* Granules containing gabapentin, and hydroxypropyl cellulose were prepared in a high-shear granulator and dried in a fluid bed processing system (Diosna Minilab). The fluid bed dryer was outfitted with near-infrared (NIR), pressure, temperature, and flow sensors which were connected to a distributed control system (DCS) that was used to exercise control of the system. The control system itself consisted of a Delta V DCS (Emerson Process Management, Equipment and Controls, Inc., Lawrence, PA, USA) that was used to interface the fluid bed dryer with SynTQ (Optimal, Bristol, UK). The dried granules were characterized by median particle size and quantity of gabapentin lactam formed (a chemical degradant).
*Results* Control of a fluid bed dryer utilizing both a first-principle control strategy and empirical model-based controls was demonstrated. First-principle control was based on an environmental equivalency factor model to maintain a constant thermodynamic environment. Empirical models included a pressure drop across the bed and NIR measurement of water content. These systems were combined effectively to consistently dry granules prepared by high-shear wet granulation. Utilization of this system greatly reduced the number of experiments necessary to characterize the performance of the system and facilitated control of the process with respect to the two properties of interest, median particle size and chemical stability during drying.

**Keywords** Fluid bed processing · Process analytical technology · Multivariate modeling · Online monitoring · Real-time data management

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## 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) [1] that allow for operational flexibility within a design space to allow fully automated systems that incorporate real-time data management to be possible. These systems offer the opportunity for continuous improvement of the process and resulting drug product by allowing information gained during manufacturing through online process measurements to inform the process to ensure constant product quality [2].

Fluid bed processing of pharmaceutical powders is an excellent case study for the development of a fully automated control system because of its complexity and the multiple phases that are encountered during a given fluid bed process [3, 4]. A single fluid bed unit operation can take raw