RESEARCH ARTICLE

Drying Process Optimization for an API Solvate Using Heat Transfer Model of an Agitated Filter Dryer

NANDKISHOR K. NERE, KIMBERLEY C. ALLEN JAMES C. MAREK, SHAILENDRA V. BORDAWEKAR

Process Research and Development, Global Pharmaceutical Research and Development, Abbott Laboratories, North Chicago, Illinois 60064

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ABSTRACT: Drying an early stage active pharmaceutical ingredient candidate required excessively long cycle times in a pilot plant agitated filter dryer. The key to faster drying is to ensure sufficient heat transfer and minimize mass transfer limitations. Designing the right mixing protocol is of utmost importance to achieve efficient heat transfer. To this order, a composite model was developed for the removal of bound solvent that incorporates models for heat transfer and desolvation kinetics. The proposed heat transfer model differs from previously reported models in two respects: it accounts for the effects of a gas gap between the vessel wall and solids on the overall heat transfer coefficient, and headspace pressure on the mean free path length of the inert gas and thereby on the heat transfer between the vessel wall and the first layer of solids. A computational methodology was developed incorporating the effects of mixing and headspace pressure to simulate the drying profile using a modified model framework within the Dynochem software. A dryer operational protocol was designed based on the desolvation kinetics, thermal stability studies of wet and dry cake, and the understanding gained through model simulations, resulting in a multifold reduction in drying time. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: desolvation; drying; mixing; kinetics; solvate

INTRODUCTION

Drying of an active pharmaceutical ingredient (API) is an important unit operation in the pharmaceutical industry as it is used to control residual solvent content, in addition to preserving or producing the right crystal form. Drying operation is often time consuming, and may turn out to be a bottleneck in the overall process cycle time. Many APIs are potent compounds that require filtration and drying to be done in a single contained vessel, known as a filter dryer, to minimize operator exposure. The present work focuses on the agitated filter dryer wherein the dryer is equipped with an agitator for mixing the solids and promote better heat transfer. Given a fixed geometric configuration of an agitated filter dryer, there exist several parameters that can be varied to achieve optimal drying performance, including the extent and intensity of mixing, headspace pressure, jacket temperature, inert gas temperature, and flow rate. Nevertheless, there is no universal drying protocol applicable to all pharmaceutical compounds, due to variations in physicochemical properties of the wet cake and the desired dried product attributes. Because of these challenges, modeling can be of great utility in designing dryer operating conditions. Insights from the modeling can reduce experimental efforts, thereby saving expensive material required to understand the drying process at bench scale and also ensure predictable robust performance on scale-up.

In the present paper, we demonstrate an approach that was used for a significant reduction in drying time of an API ethanol bis-solvate. We will refer to ethanol as “solvent” and the bis-solvate as “solvate” in the discussion. In an early pilot plant campaign (batches I and II), the drying process took nearly a week to achieve an acceptable solvent content of less than 0.1% (w/w). The dryer was operated at a nominal jacket temperature of 50°C, which resulted in a maximum internal temperature of about 40°C. The outline

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Correspondence to: Nandkishor K. Nere (Telephone: +91-22-2740-3140; Fax: +91-22-2740-3140; E-mail: nandkishor.nere@adityabirla.com)

Nandkishor K. Nere's present address is Aditya Birla Science and Technology Company Ltd., Panvel, Maharashtra, India.

Kimberley C. Allen is currently not affiliated with Abbott Laboratories.

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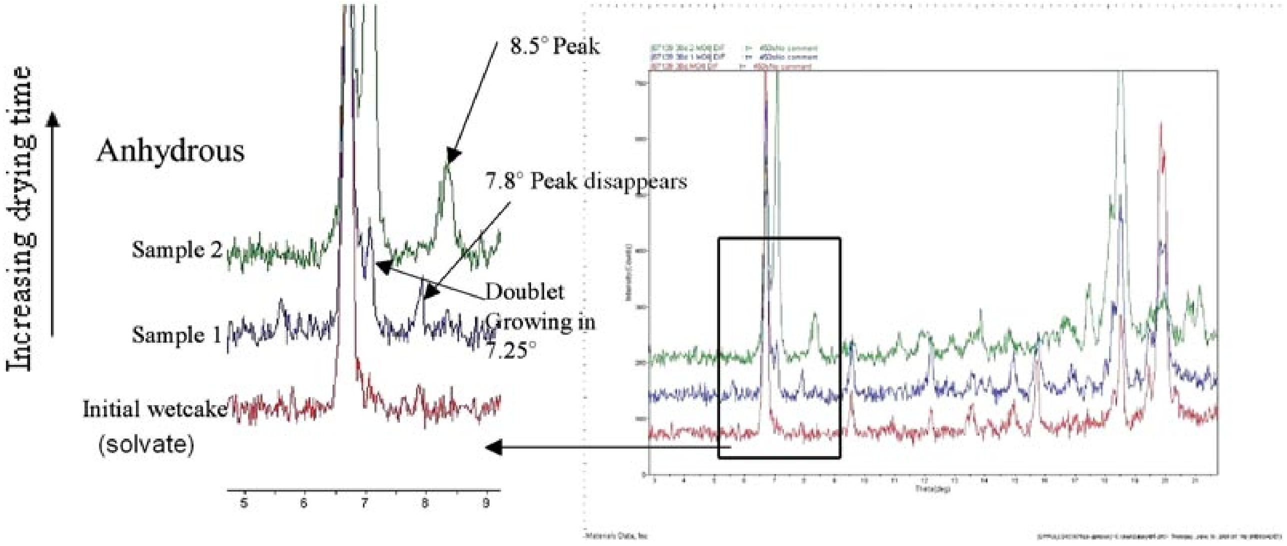

Figure 1. PXRD patterns indicate the form conversion from solvate to anhydrous form during the course of drying. Red line, initial wet cake; blue line, partially converted solvate; green line, anhydrous form.

of this paper is as follows: We present a brief analysis of the drying using powder X-ray diffraction (PXRD) patterns of solids and monitoring of the exit gas using mass spectrometry, followed by the estimation of intrinsic desolvation kinetics. We describe the various transport processes, and their interactions during the course of drying, that were used to guide development of a composite model. A heat transfer model similar to that of Tsotsas and Schlünder[1] is described, which is followed by the algorithm for simulating the drying profile in a filter dryer. Prediction of past drying performance is presented, followed by optimization of the drying process and the subsequent verification. Finally, we propose general guidelines to operate filter dryers for efficient drying.

Process Description

A typical agitated filter dryer is equipped with a heated agitator in addition to the heated jacket. Internal diameter of the pilot plant filter dryer is 0.6 m and the agitator diameter is 0.58 m. The maximum possible agitator speed in the filter dryer is approximately 20 rpm. Because of hydraulic controls, start-up speed generally goes high and settles on the control speed after few seconds. Besides raising or lowering the agitator to the desired axial location, the direction of agitator rotation can also be changed to achieve either cake mixing or smoothing of the cake surface. Nitrogen gas can be purged through the cake at a desired flow rate and vacuum can be applied below the bottom filter plate. Headspace pressure and solids temperature can be monitored online. Total heat transfer area provided by the filter dryer includes the surface area provided by the heated agitator, in addition to the jacketed surface in contact with the cake. In the case under consideration, the dryer was operated at maximum fill capacity, thereby utilizing the entire heat transfer area afforded by the jacket.

Desolvation Kinetics

Before describing the modeling of the drying process, it is of interest to briefly discuss relevant studies carried out using a process analytical technology tool to understand the drying process at laboratory scale. Figure 1 shows the PXRD patterns that demonstrate crystal form conversion (from solvate) to anhydrous API during the course of drying. The analysis of crystal structure obtained using a single solvate crystal identified it as a bis-solvate of API. Online mass spectrometry analysis of the exit gas from the dryer operated at two different temperatures showed significant enhancement in the solvent removal rate at 60°C compared with 40°C. This also indicates that the desolvation is accelerated beyond a certain temperature, which is certainly above the nominal internal drying temperature of 40°C observed in the early pilot plant campaign. Intrinsic kinetics of desolvation was obtained by tracking the solvent content as function of time in dynamic vapor sorption (DVS) experiments carried out at three different temperatures under nitrogen purge. In the DVS experiment, 50 mg of material was placed in a pan as a thin layer and kept at a constant temperature of 40°C. The loss of weight was tracked as a function of time to calculate the rate of solvent loss, which is readily related to the rate of desolvation. The dynamic desolvation data were then fitted to first-order kinetics to extract the rate