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COMMUNICATION

Accelerated Fluid Bed Drying Using NIR Monitoring and Phenomenological Modeling

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ABSTRACT

A ''fast-drying'' method to accelerate the fluid bed drying process is presented. It relies on concepts of heat and mass transfer with real-time near-infrared (NIR) monitoring of moisture. Triplicate trials show that fast drying can reduce granulation drying time by half over single-temperature cycles. The product is equivalent in every way tested to material made using a conventional cycle even though the inlet temperature throughout the constant-rate stage was higher than the melting point of the compound. Tablets made from the fast-dried granulation exhibit equivalent physical characteristics to tablets made from granulations dried at a single, lower temperature.

Key Words: *Acetaminophen; Drying; Fluid bed; Granulation; Ibuprofen; Near infrared; NIR.*

INTRODUCTION

Drying of bulk active ingredient and granulations made during processing is often a bottleneck in pharmaceutical manufacturing. This is due to the time it takes to dry, the determination of the end point, and the analysis time for release to the next processing step. The situation is aggravated if the active ingredient is ''low melting'' so that the bed temperature cannot be increased to give faster drying for fear of compromising the granulation.

The fast drying concept developed in our laboratory relies on established principles of both thermodynamics

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and fluid bed dryer dynamics. The evaporation of water during drying requires heat energy to evaporate the water. The water takes this heat from the incoming airflow, which has the effect of cooling the air. When there is little or no water left to evaporate, the air temperature increases, approaching the inlet air temperature, which is the conventional signal for the end of the drying process. During the evaporative cooling or the constant-rate stage, the material in the bed is also cooled. The water evaporates off the surface, reducing the air temperature before the material ''sees'' the higher temperature.

There is, in principle, an opportunity to use a higher inlet air temperature to speed the drying without increasing the bed temperature beyond safe limits (e.g., the melting point of the active ingredient). The practice of only dynamically monitoring the temperatures (inlet, bed, and outlet temperatures), which are essentially constant until the very end of the process, limits the accuracy of determining the end point. Although samples may be taken periodically, it typically requires 20–30 min to determine the moisture content. This can lead to ''overshooting'' the critical point and putting the process at great risk. The near-infrared (NIR) spectroscopic methods developed at Purdue University (West Lafayette, IN) (1) to monitor fluid bed drying makes more accurate monitoring of the process possible.

The intent was to (*a*) use a relatively high inlet temperature until evaporative cooling no longer offers thermal protection to the bed; (*b*) then decrease the inlet temperature to a known ''safe'' level to finish the process; and (*c*) reduce the process time relative to the traditional single, low-temperature process.

There are basically two ''stages'' during the fluid bed drying process for typical pharmaceutical granulations. These are defined by the rate-limiting process involved with the loss of water (2). The first stage is heat transfer limited, which occurs throughout the period when surface or loosely associated water is evaporating from the surface of particles. The second stage is diffusion limited, which occurs as the water internal to the granules must diffuse to the surface of the granule before it can be lost. Each of these processes is characterized by different time dependencies.

The dependence of moisture content M with time during the first stage is linear:

$$M = M_o - KT$$

where K is a constant at a given temperature, gas density, bed height, and heat of vaporization. The dependence during the second stage is exponential (for spherical particles):

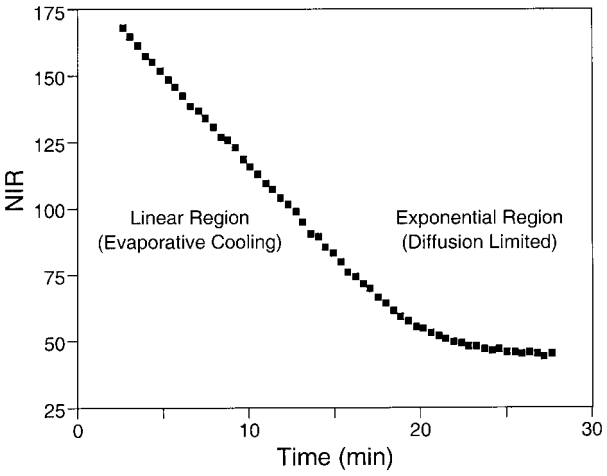

Figure 1. Fluid bed drying curves for APAP granules at 60°C.

$$M = M_o' k \cdot \exp(-k'T)$$

where k and k' are geometric constants summed over n terms in an infinite series, and is the moisture content at the beginning of the diffusion-limited phase.

This dual-drying behavior, linear followed by exponential, is present in most of the NIR curves generated in our recently completed drying project. An example curve for an acetaminophen (APAP) granulation dried at 60°C illustrates the point (see Fig. 1).

The temperature during drying is, as expected, relatively constant during the evaporative cooling region and rises as diffusion becomes limiting (Fig. 2). The point at which the drying process changes from linear to exponential (evaporative to diffusion limited) can be found by curve fitting the linear region to the proper equation point by point until the correlation coefficient starts to decrease

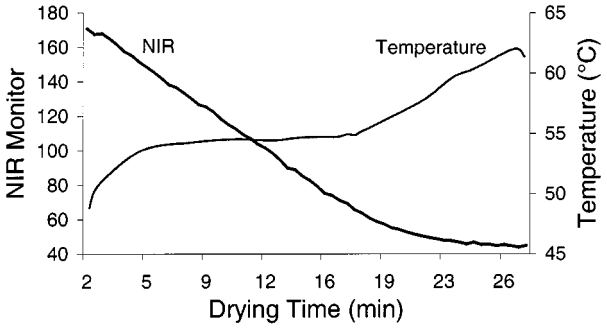

Figure 2. Comparison of NIR readings and exit temperature for an APAP granulation.

Table 1

Detection of End of the First Stage of Drying, Linear Regression Analysis

Points	r^2	NIR Value
1–37	.9992	61.0
1–38	.9991	59.0
1–39	.9988	57.4
1–40	.9985	55.2

(Table 1). (The exponential region may also be fitted until the coefficient increases to a maximum.)

Therefore, there is a method of determining the maximum time available for evaporative cooling for a given inlet temperature, dryer, and formulation.

EXPERIMENTAL

Chemicals

Racemic ibuprofen was a gift from BHC Industries (Bishop, TX). NF starch 1500 was a gift by Colorcon, Incorporated (Indianapolis, IN). Polyvinylpyrrolidone (PVP) K90 (BASF, Parsippany, NJ) at 5% was used as the binder solution.

Equipment

Granulations were carried out in a planetary mixer (Hobart Corp., Troy, OH). Fluid bed drying was performed in a Uni-Glatt (Glatt Air Products, Ramsey, NJ). NIR monitoring was accomplished with an MM55 gauge (NDC Infrared Engineering, Maldon, Essex, UK) using the appropriate cutoff filters and algorithms for water monitoring. The gauge was positioned to monitor the bed continuously through a lower inspection window. X-ray powder diffraction (XRPD) was determined on a Shimadzu XRD 6000 (Kratos Analytical, Chestnut Ridge, NJ). Differential scanning calorimetric (DSC) analysis and thermogravimetric analysis (TGA) were performed on a TA instrument 2900 DSC (Rheometrics Scientific, Epsom, Surrey, UK). Tablets were pressed on a Carver® press (Carver, Inc., Wabash, IN) at 2500–3000 ft-lb with a 5-sec dwell. Dissolution was performed using the USP ibuprofen dissolution testing conditions.

Method

The ibuprofen-starch granulation used in the drying project was dried at approximately 70°C, which is 7°C below the melting point of racemic ibuprofen. This was performed in triplicate to establish the critical NIR reading and provide XRPD/DSC samples to check for melting.

The fast-drying runs began with an 80°C–90°C inlet air temperature, which was maintained until approximately 90% of the critical NIR readings were reached (approximately 115 MM55 units). At that point, the temperature was reduced to 40°C to complete the run. This process was repeated three times. All samples were analyzed by XRPD and DSC to determine any melting that might have occurred. Tablets were pressed on a Carver press to determine hardness, weight, and dissolution characteristics of the products.

RESULTS AND DISCUSSION

Fast-drying trials were conducted in triplicate on an ibuprofen granulation in a Uni-Glatt equipped with the NIR unit. Figure 3 shows the results of these trials. These triplicate trials show that fast drying dries the granulations in roughly half the time of conventional drying.

The DSC and XRPD patterns of the ibuprofen granules prepared by fast drying and those prepared using conventional conditions were determined (Table 2 and Fig. 4). The results show that the fast-dried granulations are physically equivalent to the conventionally dried material. The heats of fusion of the materials are the same within experimental error, and the XRPD patterns show no increase in amorphous content between the treatments.

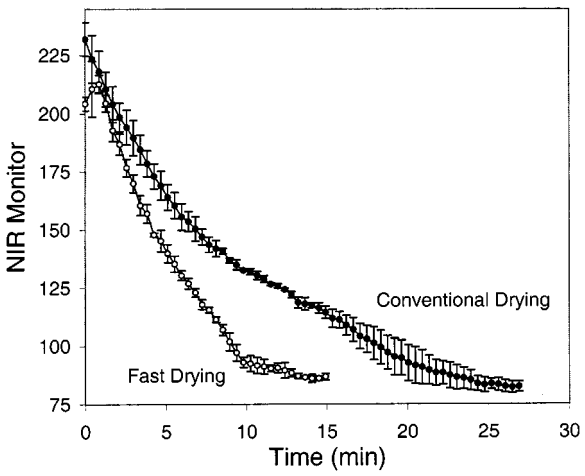

Figure 3. Drying trials of an ibuprofen granulation (error bars were determined from three repetitions).

Table 2

Differential Scanning Calorimetry Data for Granulations and Pure Ibuprofen

Sample	Onset Melting Point (°C)	ΔH_f (J g^{-1})
Conventional drying	74.0 ± 0.19	78.4 ± 4.07
Fast drying	74.2 ± 0.29	82.7 ± 5.97
Pure ibuprofen	74.8	135.0

In addition, the tablets made from these granulations were tested for dissolution. The dissolution rate and profile of the tablets from the fast-dried granulation were equivalent to those of the tablets made from conventionally dried granulation (Fig. 5). This confirms that the granulations have similar compression characteristics on the Carver press and produce equivalent tablets. Insufficient tablets were produced for full content uniformity determination, so 100% was taken as the theoretical from the batch record.

CONCLUSION

A fast-drying method to accelerate the fluid bed drying process was developed. The method relies on traditional concepts of heat and mass transfer coupled with the ability of real-time monitoring of moisture using NIR. Triplicate fast-drying trials on a Uni-Glatt show fast drying can dry a granulation in approximately half the time as drying with a single, lower temperature. The big win is the ability of the method to safely dry formulations containing problematic low-melting active ingredients, which typically have slow-drying formulas. The resulting product from our studies is equivalent in every way tested to material made using a traditional cycle even though the inlet temperature through the constant-rate stage was higher than the melting point of the compound.

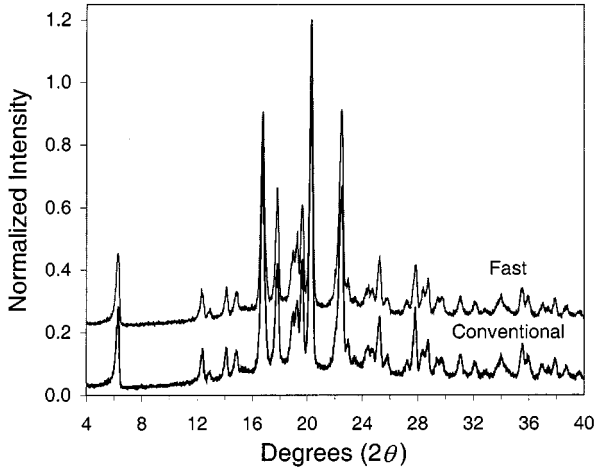

Figure 4. Overlay of the X-ray powder diffraction patterns of conventional and fast-dried ibuprofen granulations.

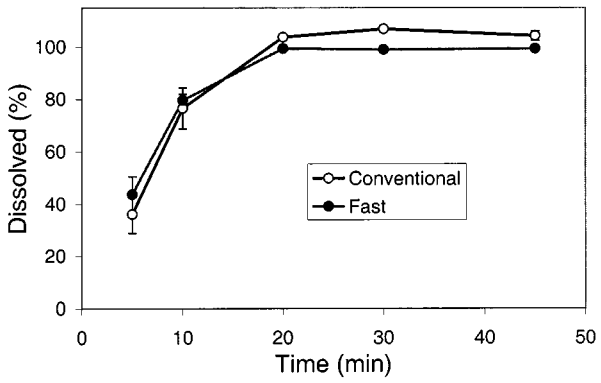

Figure 5. Comparison of dissolution profiles of tablets prepared from conventionally dried and fast-dried ibuprofen granulations.

The fast-drying strategy is to identify the critical NIR readings corresponding to the end of the evaporative cooling and to use this as a temperature-independent end point. During the process, this is the signal to lower the inlet temperature to complete the drying process safely. The method is real time and noninvasive and requires little or no modification to existing equipment. It is also applicable to other methods of drying, such as tray or conveyer drying.

ACKNOWLEDGMENT

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