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Development of a two stage batch fluid bed drying process to minimise impact of entrainment on product quality and drying endpoint determination

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ABSTRACT

Control over batch fluid bed drying processes is important to assure product of uniform moisture content as the level of residual moisture can impact further processing and final product performance and stability. Entrainment during batch fluidised bed drying can potentially result in non-uniformity of the product moisture content and impact reliability of the process endpoint. A two stage inlet air flow batch drying process was defined to minimise the impact of entrainment on product uniformity. The two stage batch fluid bed drying process reduced the level of entrainment observed. This enables the implementation of a relatively straightforward differential temperature technique based on a temperature sensor only to reliably indicate drying endpoint.

1. Introduction

Wet granulation is a key unit operation used in the pharmaceutical industry to improve powder flow, facilitate metering in tabletting, improve uniformity in the product, and compressibility. Fluid bed drying is integral to granulation as the interparticle liquid bonds between active drug(s) and pharmaceutically inert excipients formed in wet granulation are converted to permanent bonds. This bond is often a polymeric bond or may be the result of re-crystallisation of a dissolved excipient, e.g. lactose. The interparticle bond strength is important to withstand the drying process and preserve the granule structure in fluid bed drying. Process control for fluid bed drying is important to assure that the product is of acceptable uniform moisture content as the level of residual moisture can impact compressibility, tabletting, dissolution, drug stability and product stability [1–7].

Near infra-red spectroscopy (NIRS) and microwave resonance technology (MRT) have been investigated to improve monitoring and control of the fluid bed drying process [8–12]. In practice, use of this technology in a pharmaceutical commercial operation can be impacted by the drying process as well as fluidisation and may increase complexity and cost. An alternative ΔT method has been reported [2,4,13,14] utilising a temperature sensor only. This technique is based on the product temperature increase in the falling rate drying period above its equilibrium value in the constant rate drying period, ΔT, and the simultaneous reduction in moisture content. The drying curve, describing moisture content with ΔT, is a function of inlet temperature, inlet humidity and may be impacted by formulation and fluidisation. For inlet humidity controlled fluid bed drying processes, the variation in temperature in the constant rate drying period can often be considered negligible. The drying curve may then be based on moisture content and product temperature only, rather than use of ΔT.

The drying curve may be used to establish a pre-defined product temperature or ΔT criteria indicative of the required moisture content. This is used to indicate completion of the fluid bed drying process and avoids laborious in-process sampling and testing. In industrial practise, straightforward use of a product temperature based endpoint indication only is preferred over use of ΔT.

The formulation can impact the drying curve [1,11,13,15], as the rate of drying in the falling rate drying period is dependent on physicochemical properties and may limit the applicability of the ΔT method, e.g. for precise moisture control or for powders with a large resistance to internal mass transfer [17]. The batch drying process and fluidisation hydrodynamics are interrelated and may impact product quality [1,6,15,16]. After initial start-up, fluidisation becomes progressively easier with reduction in moisture content, and this may result in vigorous fluidisation behaviour and powder flux away from the fluid bed to the filter sock (entrainment) towards the end of drying. The rate of entrainment may be exacerbated by attrition of the granule, e.g. due to particle–particle collisions and low mechanical resistance of the granule due to

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weak interparticle bond strength. Because of often rapid product drying, entrainment may lead to a level of non uniformity in moisture in the batch dried product. Product in the fluidised bed will dry at an accelerated rate, while product in the filter sock will dry at a reduced rate. This may result in significantly different moisture levels for the fluidised bed mass and the mass retained in the filter sock.

Excessive entrainment and/or attrition, potentially in combination with entrapment in fluid bed dryer filters, is therefore likely to impact the uniformity of the dried product and will equally impact the reliability of NIR sensor or temperature based endpoint indication. While exhaust temperature rather than fluidised bed product temperature can be used as endpoint indication, to assure better moisture uniformity in the dried product, it is likely to impact responsiveness due to size of drying equipment and limits ability to control moisture.

A two stage process can be defined, utilising the difference in driving force for the constant and falling rate drying period. An example of a two stage process strategy based on inlet temperature for use with a low melting point drug has been reported [8].

For processes used in the pharmaceutical industry, entrainment is often observed at production scale only. Drying time at the production scale can be up to three to five times the drying time observed at laboratory scale. A two stage drying inlet air flow rate was evaluated to minimise entrainment and potential for attrition on product quality and uniformity on a commercial production scale dryer with a high value pharmaceutical product. A number of batches were used to obtain data for evaluation and address limitations in the ability to collect data on this industrial dryer. These data were used to construct a drying curve and assess the impact of a two stage drying process on entrainment.

For the constant rate drying period, the inlet air flow rate was maximised while achieving acceptable fluidisation to rapidly convert the granule liquid bridges to more permanent bonds. In the falling rate period the inlet air flow rate was reduced to reduce the superficial velocity to minimise potential for attrition. Minimising or prevention of entrainment is a key factor in assuring product of uniform dried quality. This is an important consideration in pharmaceutical product Quality by Design.

2. Material and methods

2.1. Materials

Each batch of 163 kg powder of a pharmaceutical formulation, predominantly consisting of active pharmaceutical ingredient and lactose monohydrate, microcrystalline cellulose, and hydroxymethylpropylcellulose (HMPC) was high shear granulated with 48.9 kg water. The granulated agglomerates, when dried, obtained are of a mass median particle size of approximately 110 μm by sieve size analysis and a bulk tapped density of approximately 0.55 g/cm^3.

2.2. Drying experiments

Each batch of wet granule (211.9 kg) was dried in a single filter sock chamber batch fluid bed dryer (Glatt GPCG 200), fitted with a Conidur® 10 mesh plate. The fluid bed dryer consists of a bowl of base diameter is 1000 mm, bowl height of 610 mm, and top bowl diameter of 1400 mm. Above the bowl, a straight chamber of 1000 mm was fitted leading to the filter sock housing. The product temperature was measured with a PT-100 temperature probe (TC Ltd., Uxbridge, United Kingdon) at a height of 225 mm from the bowl base plate. The differential pressure over the bowl was measured from just below the bowl mesh plate to the top of the straight chamber with a differential pressure transmitter (Rosemount Model 1151 DP, Emerson Process Management GmbH, Germany).

The inlet air temperature used was 70 °C and the inlet air humidity controlled to ≤5 g/kg dry air. The sock shake interval used was 5 min. The drying air flow rate for the standard fluid bed drying process was set to 2400 m^3/h based on visually acceptable initial fluidisation throughout the fluid bed drying process. For the two stage fluid drying process the drying air flow rate was set initially to 2400 m^3/h and reduced to 1800 m^3/h at 50 min into the fluid bed drying process, near the transition of the observed start of the falling rate drying period. The reduced drying air flow rate in the two stage drying process of 1800 m^3/h was based on the minimum fluidisation air flow rate required on initial start-up to avoid the potential for bed collapse; this resulted in visually acceptable fluidisation on the change in drying air flow rate. The total drying time was approximately 60–70 min.

To construct the drying curve, samples were collected during, and on completion of the fluid bed drying process. Immediately after collection, the residual moisture content for the granules was determined via loss on drying (LOD) using a Computrac® Max® 1000 moisture analyser (Arizona Instruments LLC, USA) at an operating temperature of 110 °C. The corresponding fluidised bed product temperature was recorded. The fluidised bed temperature and moisture content (LOD) data were used to construct the drying curve.

The data for a number of drying batches for the standard drying process (18 batches) and two stage drying process (11 batches) were combined to enable evaluation of the drying curve and the impact to the level of entrainment observed.

The pressure drop over the fluidised bed is proportional to the pressure drop over the Conidur® 10 mesh plate and the weight of the batch. The industrial dryer used is of a single sock chamber design. The difference in the differential pressure over the fluidised bed, just before and just after a sock shake, assuming minimum drying, can therefore be taken to be indicative of powder mass returned from the filters to the fluidised bed. This was used as an approximate measure for the level of entrainment observed. The level of entrainment, $\Delta m_{,entrainment}$, from the difference in differential pressure over the fluidised bed, on a filter shake, $\Delta p_{,fluidised\ bed}$ is then:

$$\Delta m_{entrainment} \approx \frac{\Delta\Delta p_{fluidised\ bed,shake} \cdot A_{bowl}}{g} \quad (1)$$

The pressure drop over the Conidur 10® mesh plate was determined with the machine empty at 2400 m^3/h and 1800 m^3/h and was found to be 0.30 kPa and 0.16 kPa. The average level of entrainment for the standard drying process (18 batches) and two stage drying process (11 batches) was computed from obtained process data.

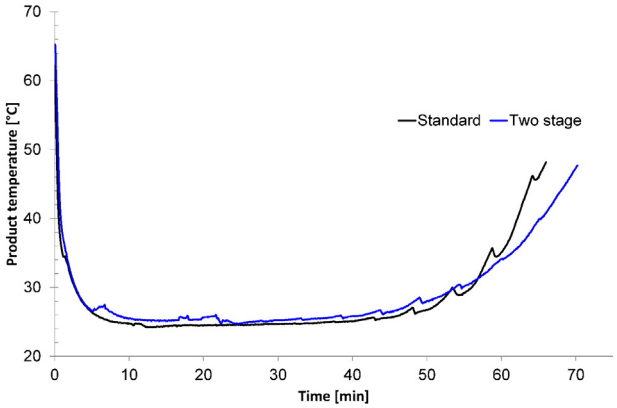

Fig. 1. Temperature profile for standard and two stage batch fluid bed drying process.