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Investigation of factors affecting isolation of needle-shaped particles in a vacuum-agitated filter drier through non-invasive measurements by Raman spectrometry

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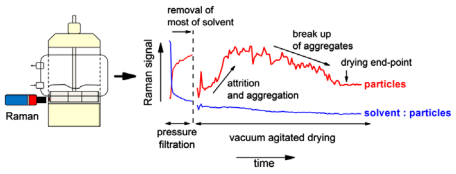
HIGHLIGHTS

- Full particle filtration–drying process monitored non-invasively by wide area Raman spectrometry.
- Allows simultaneous monitoring of solvent removal and effect on particle bed.
- Off-line dynamic image analysis used to assess factors affecting particle attrition.
- Relationship between starting wetness, agitation time and extent of attrition examined.
- Real-time Raman measurements can be used to better control particle properties.

GRAPHICAL ABSTRACT



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ABSTRACT

The effects of pressure filtration and vacuum agitated drying on cellobiose octaacetate (COA) particles in methanol slurries were studied by making Raman measurements through the glass wall at the side of a filter drier beneath the oil jacket. The change in intensity of methanol peaks in the spectra allowed the removal of the solvent from the particle bed to be monitored. Also, drying curves for COA generated from the Raman measurements gave an indication of the changing physical status of the particle bed during continuous or intermittent agitation. The intensity of the Raman signal for COA depended on the bulk density of the particle bed, which changed due to aggregation and attrition that occurred during solvent removal and particle motion induced by agitation during vacuum drying. Loss on drying (LOD) measurements of samples removed at the end of the pressure filtration and vacuum agitated drying stages established the degree of wetness and confirmed the end point of drying ($< 0.5\%$ w/w solvent), respectively. Dynamic image analysis confirmed that minimum attrition of COA was achieved when (a) the majority of the methanol was removed during pressure filtration at 0.5 bar N_2 and (b) intermittent agitation was applied during the vacuum drying stage.

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1. Introduction

The use of agitated filter driers is popular for isolation of active pharmaceutical ingredients (APIs) following crystallisation, as filtration and drying can be completed in a single vessel (Kougoulos et al., 2011). Industrial filtration is often performed under a positive pressure of an inert gas, typically N_2, to remove excess solvent from particles before drying is conducted under vacuum to remove the remaining residual solvent. The impact of the isolation process on particulate properties, especially during the drying phase, may determine the success of an API manufacturing campaign; however, the effects of particle isolation are often not well understood and poorly controlled.

There are a growing number of examples in the literature where the influence of agitated drying on particulate properties has been investigated (Hare et al., 2009; Kom et al., 2011; Kougoulos et al., 2011; Lamberto et al., 2011; Lekhal et al., 2003, 2004). The processes that lead to particle attrition have been studied extensively by Ghadiri et al. (2000, 1991), Ghadiri and Zhang (2002), Subero and Ghadiri (2001), and Zhang and Ghadiri (2002). Lamberto et al. (2011) reported the development of a laboratory method to rank qualitatively six pharmaceutical materials on a breakage scale (hard, medium or easy to break) that allowed recommendations for processing conditions at a larger scale. In contrast, there have been few published studies of the combined effects of filtration and agitated drying on particulate properties. Recently, however, needle breakage has been reported at the end of filtration of needle-shaped particles, owing to the stress caused by the positive pressure applied to the particles exceeding that of the critical stress required for needle breakage (MacLeod and Muller, 2012).

Process analytical technologies (PAT) are currently being implemented across a wide range of unit operations in the pharmaceutical industry to improve process understanding and control. Various spectroscopic techniques have been applied successfully to monitor unit operations such as crystallisation (Cornel et al., 2008; Kougoulos et al., 2005; Larsen et al., 2006; Liu et al., 2011; O'Grady et al., 2008), granulation (De Beer et al., 2011; Tok et al., 2008; Walker et al., 2009) and blending (El-Hagrasy et al., 2006a, 2006b; El-Hagrasy and Drennen, 2006). Drying processes have also been studied either through analysis of the off-gas or the particle bed directly. For example, optical spectroscopic techniques such as mid infrared (MIR) (Tewari et al., 2010) and near infrared (NIR) (Coffey et al., 1998; Harris and Walker, 2000; Parris et al., 2005) have been used to monitor the solvent concentration in the off-gas of tray and rotary driers by insertion of a gas cell into the vacuum line. On-line mass spectrometry has also been used to measure the moisture content in the off-gas for microwave assisted vacuum drying (Hettenbach et al., 2004). The solvent content of the particle bed in filter, paddle and spherical driers has been monitored in situ using an in-line NIR probe (Burgbacher and Wiss, 2008). In-line NIR spectrometry has also been used to monitor the progress of fluidised bed drying processes (Demers et al., 2012; Green et al., 2005; Peinado et al., 2011). In all of the above studies, the extent of drying was monitored on the basis of the solvent content of either the off-gas or powder bed. However, in one study the drying of molecular sieves in a rotary drier was monitored using acoustic emission generated from the impact of the particles with the vessel wall (Briens et al., 2008). The effects of the drying conditions on the particles themselves are rarely considered and the physical effects that occur during drying are still relatively unstudied. Spectra obtained with NIR or Raman spectroscopy are known to be affected by the physical properties of samples and have been used in powder blending (Bellamy et al., 2008a, 2008b) or wet granulation (Walker et al., 2009) to study physical changes to the material. Raman spectrometry can offer advantages over NIR spectrometry including narrower spectral features and easier interpretability of the spectra (Allan et al., 2013). For isolation processes, Raman spectrometry provides opportunities to monitor directly and simultaneously both the solvent and powder. Drying end-point is currently determined by off-line measurement of the solvent content of the powder bed, which is sampled periodically during the process. Consequently, in situ measurements eliminate the need for sampling and also allow identification of the drying end-point in real-time; the ability to monitor both solvent removal and the physical state of the powder bed allows better control of particle properties. Benefits of implementation of PAT for drying processes include a reduction in drying time, elimination of over-drying, and lower energy consumption and costs (Parris et al., 2005).

In a preliminary study (Hamilton et al., 2011), methods were investigated for monitoring needle-shaped cellobiose octaacetate (COA) particles directly in a laboratory scale vacuum agitated drier using non-invasive Raman spectrometry. A design of experiments approach was used to investigate the effects of three process variables (mode of agitation, % solvent loss on drying, and jacket temperature) on the drying time, with off-line particle size analysis by laser diffraction employed to determine the extent of attrition. Subsequent research compared the efficacy of three commonly used particle size analysis techniques for quantitative assessment of the extent of attrition that occurs during the drying of needle-shaped particles (Hamilton et al., 2012). It was found that the Feret Max diameter obtained from dynamic image analysis provided the best indication of changes in needle length; although qualitative trends could be obtained from laser diffraction or focused beam reflectance measurements.

In this study, the full isolation process for filtration and drying of COA particles in a vacuum agitated drier was investigated. Slurries of COA particles and methanol were subjected to different periods of pressure filtration before vacuum agitated drying was performed using either continuous or intermittent agitation. Raman measurements were collected in situ throughout each experiment and samples were collected at the end of each stage for measurement of loss on drying (LOD) and particle size using dynamic image analysis. In contrast to the preliminary study (Hamilton et al., 2011), Raman measurements were made from the side of the vessel towards the bottom of the packed bed rather than from the top, which allowed a better assessment of the impact of the filtration/drying conditions on the particles during processing. By interpretation of the Raman profiles it was possible to monitor in real time the removal of the solvent and changes to the physical status of the packed bed, and hence determine the end point of drying. Further, the particle size analysis allowed the relationship between starting wetness (LOD), agitation time and extent of attrition to be examined. The study illustrates for the first time the potential of non-invasive Raman spectrometry to monitor the full filtration-drying isolation process, which will be particularly beneficial when optimising conditions for fragile particles.

2. Materials and methods

2.1. Materials

Cellobiose octaacetate (COA) was obtained from GSK (Stevenage, Hertfordshire, UK). COA has a needle-shaped crystal habit with a high aspect ratio and does not exhibit polymorphism. COA was selected as a model compound to study as it has similar physical characteristics to many pharmaceutical active compounds (e.g. the dry powder has a low bulk and tapped density and the crystals are needle-shaped), without being biologically active and therefore requires no specific controls for handling in a laboratory.