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Research paper

Quantitative on-line vs. off-line NIR analysis of fluidized bed drying with consideration of the spectral background

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ABSTRACT

Quantitative dehydration studies of dibasic calcium phosphate anhydrous (DCPA) in a small-scale cold-model fluidized bed dryer with process air control were conducted. Near-infrared spectroscopy (NIRS) with partial least squares regression (PLSR) was used to predict DCPAs' residual moisture content. Loss-on-drying (LOD) was employed as a reference method and confirmed the actual moisture content of DCPA. First, dynamic PLSR modeling was carried out, i.e., the NIR spectra were on-line recorded and predicted throughout the drying process. Secondly, PLSR off-line modeling was performed, i.e., samples were consecutively thief-probed from the processor, put into glass vials and analyzed off-line. Furthermore, two background spectra were collected prior to the in- and off-line measurements in an attempt to increase the method's sensitivity, i.e., (i) dry DCPA that was fluidized at respective process air velocity (on-line) or inside a glass vial (off-line) and (ii) Spectralon® – a highly reflecting standard reference material made of fluoropolymer. Benefits and drawbacks of the in- and off-line approaches with different spectral backgrounds are discussed in detail. The results indicated that (i) the thief-probed sample amount from the processor and thus the sample weight and (ii) the downtime between thief-probing a sample and its actual analysis via NIRS and LOD can bias the moisture content predictions.

1. Introduction

Drying is a crucial unit operation in the manufacture of pharmaceutical solids to remove water or other solvents, e.g., after filtration following crystallization, after wet milling and wet granulation [1], or to stabilize the state of the drug prior to further processing, such as lubrication, compression or coating. During drying, the heat transfer may take place by convection, i.e., hot gas is flowing through the solid or fluidizing the solid, or by conduction, when the energy is transferred to the wet material via a hot surface [2–5]. In such a case, the surface is heated by hot steam, water, or oil. For example, fluidized bed dryers, if available, are used if easily dispersable particles are dried with a typical particle diameter in the range of 0.1–2 mm [6,7]. In general, during fluidization a bed of solid particles is converted into an expanded, suspended mass showing liquid-like behavior, excellent mass and heat transfer characteristics as well as good mixing of the solid phase. Thus, it allows efficient drying of various materials and high rates of heat exchange at a high thermal efficiency [8,9].

Fluidization is a process that is caused by air flowing around particles while suspending the particles in the air stream. In a fixed bed a fluid passes through the gaps between the stationary particles. If the flow rate increases, some particles begin to move apart (referred to as an expanded bed). With a further increase in the flow rate, the bed reaches its minimal fluidization velocity, i.e., the drag force between the particles and fluid counterbalances the weight of the particles. At higher flow rates, bubbling and channeling of gas occurs, the movement of solids becomes more vigorous and the bubbles coalesce and grow as they rise. Slugs start to form where the bed is continuously pushed upward above the bubbles leading to an unstable oscillatory motion of the bed. Slugging is especially observed in long, narrow systems. As soon as the maximal fluidizing velocity exceeds the critical limit, i.e., terminal velocity, particles begin to entrain [10]. The fluidization ability of the particles strongly depends on their solid material properties, e.g., fine or sticky powders lead to a cohesive bed that tends to channel instead of fluidize. Large or coarse particles often lead to spouted bed operation, i.e., a bed in which the air forms a single opening through which particles flow up and fall to the outside region [11].

As mentioned above, fluidization is characterized by high mass and heat transfer coefficients of the individual particles, leading to very high drying rates. The effectiveness of fluidization for the

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drying of pharmaceuticals was already reported in the early 1950s, and Scott et al. studied the first practical application of fluidized bed drying of granules in the early 1960s [12,13]. In general, the goal of any drying process is to reach optimal product moisture. If the product is over-dried (e.g., if a solvate is the desired form of the API), it might not be suitable for sale or further processing, and energy would have been wasted on the drying process. In the case of under-drying, the dryer may need to be stopped and re-started several times to sample for moisture verification [14]. A poorly controlled drying end-point can also affect downstream processability, tablet dissolution characteristics and long-term chemical stability. Moreover, characteristics of a drying process can considerably affect material properties, micro-structure and possibly lead to phase transitions of the material, e.g., transformation of polymorph or desolvation of solvates, affecting the bioavailability of the final product [15,16]. Pharmaceutical hydrates may undergo several solid-state phase changes during drying. The solid-state form of an active pharmaceutical ingredient (API) may change depending on the drying conditions, which may lead to therapeutic failure [17].

Due to the importance of precise monitoring of key pharmaceutical processes, such as drying, granulation and coating the food and drug administration (FDA) has issued a process analytical technology (PAT) guidance to encourage the pharmaceutical industry to apply (at best non-invasive) real-time techniques on a routine basis for process and product monitoring [18]. In the case of fluidized beds, several approaches have been suggested over the years, e.g., radiation absorption imaging techniques [19], particle image velocimetry (PIV) [20] and microwave resonance technology (MRT) [21]. Recently vibrational spectroscopic techniques, such as Raman-, mid-infrared (MIR) and near-infrared (NIR) spectroscopy (NIRS), became widely accepted for real-time process monitoring due to non-contact sample characterization and the lack of preparation required, as well as due to flexible process implementation via fiber optic probes [22–25]. In general, there is a current shift from off-line analysis toward on-line and on-line monitoring of batch and continuous unit operations [26–30], in which NIRS has repeatedly been applied to determine moisture content and especially to monitor wet granulation procedures [31–33] and fluidized bed drying [34–47].

Raman spectroscopy and NIRS are complementary in nature and can detect various drug hydration states [48,49]. NIRS is most suitable for tracing moisture content as many solvents (and specifically water) show strong absorption bands in the NIR region. Thus, water content can be monitored by NIRS, while Raman spectroscopy has less sensitivity toward water. Since there has been a growing tendency to use water as a solvent, as it is environmentally friendly and eliminates explosion risk compared to organic solvents, monitoring of water content has become an important task for on-line control systems. For example, as early as 1968 Sinsheimer and Poswalk utilized NIRS for residual water analysis of pharmaceuticals [50].

Generally, water can be present in pharmaceutical solids in at least two thermodynamic states: (i) free water, i.e., water molecules adhere to the surface and interstitial spaces of the particle matrix by London dispersion forces and (ii) bound water, i.e., water molecules are retained inside individual crystals and integrated in the lattice. The level of free and bound water has a major influence on the dosage form's stability, solubility and bioavailability. Generally, the NIR absorption spectrum of liquid water at room temperature shows five distinct bands at 760, 970, 1190, 1450 and 1940 nm that are the characteristics of overtones and combinations of fundamental stretching bands in the mid-IR. Moreover, NIRS can be used to distinguish between free and bound water, since the level of hydrogen bonding and the intermolecular distances differ [51]. Free surface water shows a band at a shorter wavelength at around 1905 nm, whereas bound water shows a band at around 1936 nm.

In order to achieve consistent product quality, the method for dryer monitoring and end-point control needs to be highly accurate. To ensure high precision of the real-time monitoring method, it is essential to compare a precise analytical method or reference method, such as loss-on-drying (LOD, a gravimetric technique) with the relative method (NIRS). To identify and extract useful analytical information in a spectrum and to further correlate this information with the reference data (LOD), typically multivariate data analysis (MVDA) is used, for which partial least squares regression (PLSR) is commonly applied [52–56]. In the PLSR method two blocks of data, generally denoted **X** (spectral data, i.e., wave numbers or wave lengths) and **Y** (reference data, such as LOD) that are used to predict **Y** from **X** are processed. PLSR incorporates the information contained in **X** and **Y** into a linear multivariate model. After a calibration stage with subsequent model validation, the PLSR model can be used to predict unknown sample properties within the respective calibration range.

In our work we used an atmospheric lab-scale fluidized bed processor made of poly-methylmethacrylate (PMMA) to dry dibasic calcium phosphate anhydrous (DCPA) at room temperature. Thereby, NIR spectra were consecutively recorded either on-line with a fiberoptic probe outside the processor (through the PMMA wall) or by off-line analysis, where thief-probed samples were filled into glass vials and analyzed with an integrating sphere device. First, Spectralon® (a highly reflecting standard material made of fluoropolymer) was taken as a background spectrum prior collecting the on- and off-line spectral data. As expected, PMMA from the processor (on-line approach) and glass from the vials (off-line approach) caused considerable interference with NIR bands of the residual water signals. Thus, spectra of dry fluidized DCPA measured from outside the processor (on-line approach) and dry DCPA inside a glass vial (off-line approach) were taken as a background prior to collecting the on- and off-line spectral data. Thereby, a zero baseline was established for ready-dried material. Hence, the dry DCPA was either static (off-line approach) or dynamic (on-line approach) and spectra may therefore differ marginally. It is hence of interest to compare those two approaches. PLSR with LOD (as a reference method) was then utilized to develop calibration models, whose performance with regard to predicting the residual water content during fluidized bed drying was evaluated and compared.

The effect of sampling is an important and perhaps underestimated aspect prior to calibration. Green et al. demonstrated that sampling during fluidized bed drying at various scales may have a significant effect on the apparent error, total analytical error and multivariate modeling error [57]. Thus, in this study we investigated the influence of sampling effects on the PLSR models' prediction accuracy. In summary, our goal was to develop a robust method for monitoring a fluidized bed drying process. As such, we first compared the prediction performances of the two PLSR models either developed with on-line recorded NIR spectra or off-line recorded NIR spectra. Secondly, two different spectral backgrounds were collected prior to process monitoring to correct for interfering bands and to eventually increase the sensitivity of the NIR method, i.e., to lower the detection limit for the residual water. Finally, we identified potential effects of the sampling procedure on the prediction accuracy of the developed PLSR models.

2. Materials and methods

2.1. Material

Dibasic calcium phosphate anhydrous (DCPA, Emcompress®, JRS Pharma GmbH & Co. KG, Rosenberg, Germany) was sieved with