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Application of process analytical technology in tablet process development using NIR spectroscopy: Blend uniformity, content uniformity and coating thickness measurements

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Abstract

Near-infrared (NIR) spectroscopy was employed as a process analytical technique in three steps of tabletting process: to monitor the blend homogeneity, evaluate the content uniformity of tablets and determine the tablets coating thickness.

A diode-array spectrometer mounted on a lab blender (SP15 NIR lab blender) was used to monitor blend uniformity using a calibration-free model with drug concentration ranging from 2.98 to 9.25% (w/w). The method developed accurately depicted the changes in concentration of the drug during blending and the positive effect of a delumping step in the production process. Blend homogeneity was reached within 2 min of the blending step post-delumping, with relative standard deviation (R.S.D.) values varying from 1.0 to 2.5% depending on the drug concentration of the blend.

A Fourier-transform spectrometer (Bruker MPA) was used to analyze content uniformity and coating thickness with calibration based models. Prediction of a validation set with tablets compacted at pressures not present in the calibration set yielded an root mean square error of cross validation (RMSEP) of 1.94%; prediction of tablets compacted at pressures present in the calibration set yielded a RMSEP of 1.48%. Performance of the model was influenced by several physical tablet properties, which could be reduced by spectral pre-processing.

A model based on reflectance spectra predicted coating thickness and its variation more accurately than the model based on transmission spectra. Inter-tablet coating variation was predicted with NIR and compared to reference thickness measurements. Both methods gave comparable results. Initial inter-tablet variation of tablets sampled in-process during coating was high, but stabilized after 30 min into the process.

Keywords: Process analytical technology; Blend uniformity; NIR; Tablet coating; Content uniformity

1. Introduction

The process analytical technology (PAT) initiative, started by the FDA at the beginning of this century, has stimulated the pharmaceutical industry to increase its research into new analytical technologies, which enable in-line measurements of critical product parameters. These technologies can be used to "control and understand the manufacturing process" and ensure improved product quality. Moreover, these technologies can be a valuable tool in the development of new products, since "*quality cannot be tested into products; it should be built-in or should be by design*" (CDER PAT subcommittee, 2005). Near-infrared (NIR) spectroscopy is one of the techniques found to be suitable for a variety of PAT applications, and is subject of many studies in the pharmaceutical and nutritional field. Major advantages of NIR spectroscopy are its non-destructive nature and its immediate (real time) delivery of results; drawbacks are the influence of physical properties on spectra and the need for cal-

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ibration using a reference technique, e.g. HPLC. NIR spectra contain chemical as well as physical information therefore pre-processing the spectra is frequently needed before the actual analysis can take place. Physical information originates from differences in packing densities and particle sizes between powder or tablet samples. As a result differences in path length and scatter properties emerge which show as linear and/or non-linear baseline shifts. Light leakage effects (Sparén et al., 2002), instrumental and random noise are further sources of non-chemical information influencing NIR spectra.

Various methods have been developed to pre-process spectra before actual analysis takes place. Most of these methods such as multiplicative scatter correction (MSC), standard normal variate (SNV) and de-trending are specially designed to remove unwanted physical information from spectra leaving behind only the desired chemical or physical information. Older methods such as spectral derivatives are also frequently used. Multiplicative scatter correction, developed by Martens et al. (1983), separate chemical light absorption from physical light scatter and is based on the difference between wavelength dependency of scatter and chemical absorption in NIR spectra. Every sample spectrum is scatter corrected with respect to the average spectrum (the 'ideal sample') resulting in an even amount of scatter in each spectrum. Standard normal variate (Barnes et al., 1989) is a mathematical transformation designed to reduce linear baseline shifts due to non-specific scatter of radiation at the surface of particles and variable spectra path length through the sample. Derivation is often used in NIR spectroscopy to eliminate baseline shifts. The first derivative removes the baseline off-set difference, the second derivative also removes the slope of the spectra. Furthermore, derivation enhances resolution of overlapping bands. In-depth reviews of NIR pre-processing methods are provided by Heise and Winzen (2002).

This article describes the application of NIR as a PAT tool in three steps of the production process of a new potent drug, NIR was used to monitor the active component during blending, to evaluate the content uniformity of tablet cores and to determine the individual coating thickness of tablets. The main goal of the research was to develop and test a blend monitoring method using NIR and to develop/test models for tablet content uniformity and coating thickness measurements.

2. Materials and methods

2.1. Raw materials and process description for manufacturing the tablets

In the preparation of the direct compression mixtures a so-called blend–delump–blend process was used, which consists of a primary mixing step in the NIR SP15 lab blender (GEA Process Engineering Ltd., UK), a delumping step (used to break up agglomerates of the drug) in a Quadro Comil model U10 rotating impeller mill (Quadro Engineering LP, Canada), and a final mixing step in the NIR lab blender. Duration of each mixing step was 25 min; rotational speed was 15 rpm. The primary mixture contains an active component, a filler, a filler/binder and a disintegrant. A lubricant and a flow enhancer were added after the milling (delumping) step. Tablets were compressed at a Korsch XL100 rotating press (Korsch AG, Germany) at a speed of approximately 600 cores per minute and compaction forces of 100, 200, 300 and 400 MPa.

2.2. NIR instruments

The NIR lab blender consists of a Zeiss MCS 511 NIR 1.7 spectrometer (Carl Zeiss, Ltd., UK) and an OMK measuring head mounted on an adapted IBC lab blender from Buck systems. The OMK measuring head is connected via power and optical cables to the spectrometer inside the steel housing of the bin blender. The MCS 511 NIR 1.7 HR spectrometer is a diffuse reflectance InGaAs diode-array spectrometer, equipped with 256 pixels covering approximately 950–1680 nm with a resolution of ~3.0 nm. The OMK measuring head, shown in Fig. 1, has 15 optical fibers placed at 45° for sample observation. The amount of powder sampled during a NIR measurement is approximately 250 mg, depending on the density of the powder. Measurements can be manually, chrono or gravity triggered. Initial processing of light signals from the OMK measuring head is done by a MCS 511 NIR 1.7 spectrometer. A total of 10 scans are averaged into one raw energy spectrum; the resulting raw energy spectra are transported via a radio frequency signal to a nearby computer with Aspect Plus® (version 1.76 Carl Zeiss, Germany), and Process Explorer® software (version 1.1.0.6; Carl Zeiss, Germany). The Aspect Plus® program was used to collect reflection spectra during blending; these spectra were later converted to simulation files which were loaded into Process Explorer® for off-line analysis. Spectrometer calibration was done in the Aspect Plus software using black and white standards.

The Bruker multi-purpose analyzer (MPA; Bruker Optics, Germany) was used in the content uniformity and coating thickness experiments; it is a Fourier-transform spectrometer equipped with both an indium gallium arsenide (InGaAs) and a lead sulfide (PbS) detector able to record reflection and transmission spectra with various sample techniques.

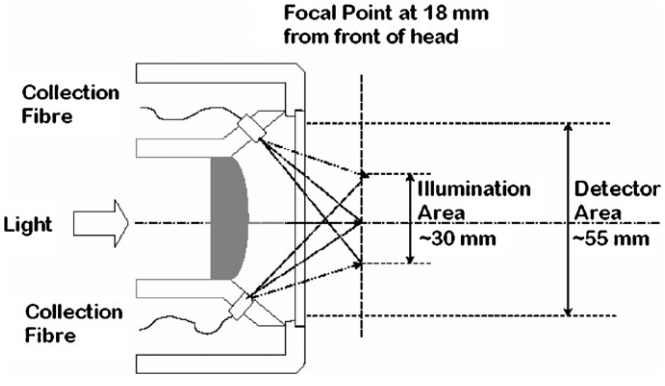

Fig. 1. OMK measuring head of the NIR lab blender (courtesy of Carl Zeiss Inc.).