An examination of dynamic and static near infrared measurements of pharmaceutical blends

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Introduction

The process of blending pharmaceutical raw materials is critical to manufacturing solid dosage products. Because of this, there is interest in the mixing process, which ensures even distribution of the ingredients throughout the blend.

Traditionally, blend samples are thieved from the mixing vessel and tested by UV-vis spectroscopy or HPLC. Adequate mixing of a pharmaceutical blend is demonstrated from statistical uniformity calculations of the active concentration in the blend. Shortcomings of the sample thief method include the labour intensity needed to sample the blend and the lack of timeliness in receiving results to make decisions (i.e. stop the blender, thieve samples, wait for analytical results and, possibly, continue mixing). In addition, the thieved blend uniformity results often do not reflect the content uniformity results for the tablets.[1] Because of its rapid and non-destructive nature, near infrared (NIR) spectroscopy has attracted much attention in the pharmaceutical industry as a technology to examine the pharmaceutical mixing process.[2–10] The advantage of using NIR for powder samples, such as pharmaceutical blends, is that no sample preparation is needed and, thus, measuring NIR spectra during the mixing process is feasible.

A feasibility study was performed in which NIR spectra of mixed caffeine/Avicel® blends were measured as the mixed blend flowed between the hopper and the feedframe of a Manesty™ Betapress. These measurements could, potentially, help to understand mixing processes that might affect the blend homogeneity in the hopper as the powder flows from the hopper to the tablet press. Moreover, information about the blend closer to the actual tableting process may give a better representation of the final tablet uniformity. Additional NIR measurements of flowing blends containing 2, 5, 10, and 15% caffeine in Avicel® with 1% magnesium stearate, as a lubricant, were performed to assess sensitivity of this method.

Before the first "flowing blend" NIR measurements were performed, the mixing process was characterised with static measurements by probing a 15% caffeine in Avicel® blend containing 1% magnesium stearate manually in a 12-L Matcon Buls cube with a fibre optic probe. During this mixing process, thief samples of the blend were drawn and examined by NIR with a sample desk attachment. In addition, prepared solutions of the blend samples were analysed using UV-vis spectroscopy. In this static measurement work, the blend was characterised by calculating the standard deviation from the spectra collected at each mixing timepoint for each of the spectroscopic methods.

Percentages on a weight/weight basis.

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Experimental

Materials

Caffeine, USP, anhydrous, Avicel® (microcrystalline cellulose) PH102 and magnesium stearate were obtained from Aldrich, FMC Corporation and Harcross Chemical Group, respectively. The caffeine was passed through a 20-mesh screen prior to blending to break up any large agglomerates.

Manufacturing equipment

A 12-L Matcon Buls cube was used to mix the pharmaceutical ingredients. The mixing speed was 16 revolutions per minute. The blend was compressed into tablets using a Manesty™ Betapress, modified with a stainless steel tube, to accept an NIR probe between the hopper and the feedframe. This machine compressed tablets at a rate of 325 tablets per minute.

A Turbula Type T2C Mixer, operated at about 40 rpm, was used to mix caffeine/Avicel® blends (batch sizes of 175–200 g) containing 2, 5, 10 or 15% caffeine for evaluating sensitivity to concentration changes as powder blend flowed from the hopper to the press. This blender was also used to mix several (150 g) Avicel®/magnesium stearate (1%) blends, which were used as spacer blends, placed between each of the caffeine/Avicel® blends on the Manesty™ Betapress. Each blend was lubricated using approximately 1% magnesium stearate.

Manual sampler

Blend samples of approximately 200 mg were obtained using a Sampco grain sample thief fitted with a 0.75 cm^{-3} sampling chamber.

Instrumentation

NIR spectra of the flowing powder were measured with a Buhler Model NIRVIS Fourier transform (FT)-NIR spectrophotometer equipped with a 1 m fibre optic cable coupled to a reflectance probe. The fibre optic probe end is approximately 11 cm long with a 1.2 cm diameter angled quartz window and a 0.5 cm diameter fibre bundle. A block diagram of the Manesty™ Betapress/FT-NIR configuration used to measure the NIR spectra of the flowing powder is presented in Figure 1. The probe end was in-

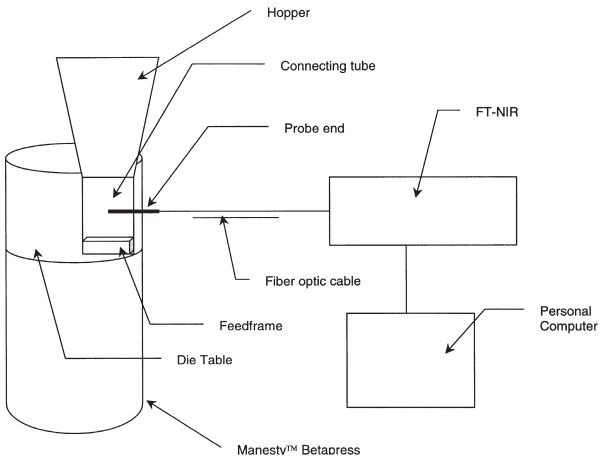

Figure 1. Block diagram of the FT-NIR fibre optic probe system attached to the Manesty™ Betapress.

serted to the centre of the connecting tube (6 cm tube diameter) with the angle of the probe end facing up to ensure contact of the probe with the flowing powder. Spectral acquisitions were started manually and three scans were acquired per NIR spectrum.

NIR spectra of the thieved samples were measured using the same FT-NIR spectrophotometer equipped with a sample desk module instead of the fibre optic probe. Data were collected using three scans per spectrum.

Measurements of solutions from the thieved samples were performed with a Hewlett-Packard Model 8453 UV-vis photodiode array with a 0.5 cm quartz cuvette. Absorbance data were acquired at 275 nm, the absorbance maximum wavelength for caffeine.

Data treatments

Multiplicative scatter correction (MSC Full) and second derivative spectral calculations[11] were evaluated as pre-treatments to normalise the baseline offset for the NIR probe spectra collected from the Buls cube. Since little difference was found with spectra corrected with either of these pre-treatments, MSC Full pre-treated spectra were chosen for the evaluation of the spectra obtained with the fibre optic probe inserted into the Buls cube and the spectra of the thief samples obtained from the NIR sample desk module.

The standard deviation of the ten locations in the Buls cube per timepoint was calculated using the absorbance maximum for caffeine in the NIR probe spectra. The standard deviation was calculated in a similar manner for the thieved samples collected at each specified timepoint for both the NIR spectra acquired by the sample desk and UV-vis absorbance data at 275 nm.

During the blend-flow experiments on the press, NIR spectra were acquired approximately every ten seconds during the tableting process. These NIR spectra were pre-treated by second derivative spectral calculations as a means to normalise the spectra because this pre-treatment provided a better means than the MSC Full corrected spectra to visualise differences in the caffeine levels.

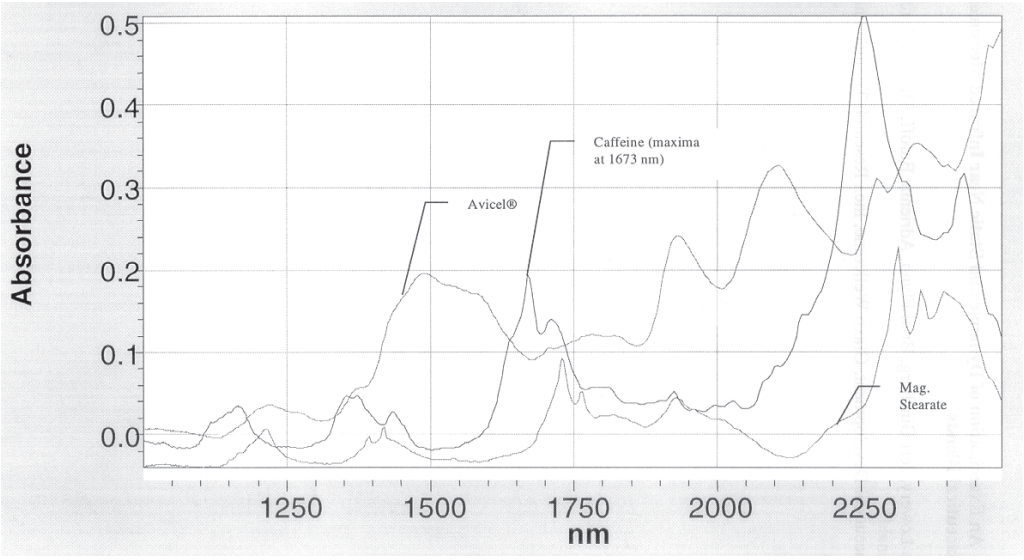

Figure 2. NIR spectra of Caffeine, USP, Avicel® PH102 and magnesium stearate measured with the fibre optic probe set-up.

Three-dimensional plots were obtained using MATLAB Version 5.3 software (The Mathworks).

Procedure

A Buls cube was charged with the ingredients for a 2.6 kg batch containing 15% caffeine. At each sampling timepoint, the mixer was stopped and the cover removed to allow NIR spectra to be measured manually with the fibre optic probe or to thieve samples. The blend was probed or thieved at ten different locations in the Buls cube. The probe timepoints included every 15 s for up to 2 min, every 30 s from 2 to 5 min, every 60 s from 5 to 10 min and every 3 min from 10 to 31 min. The blend was thieved near the probe sites in the Buls cube at the 2, 5, 10, 16, 22 and 31 min timepoints. Thieved samples were transferred into 8 mL KIMAX® sample vials. NIR spectra of these samples were measured with a sample desk attachment through the bottom of the vial. The individual powder-blend samples were then prepared as a solution, filtered and analysed by UV spectroscopy. After mixing for 31 min, magnesium stearate, the lubricant, was added at approximately the 1% level to the blend and the contents of the Buls cube were mixed for an additional four minutes to ensure adequate lubrication for tableting.

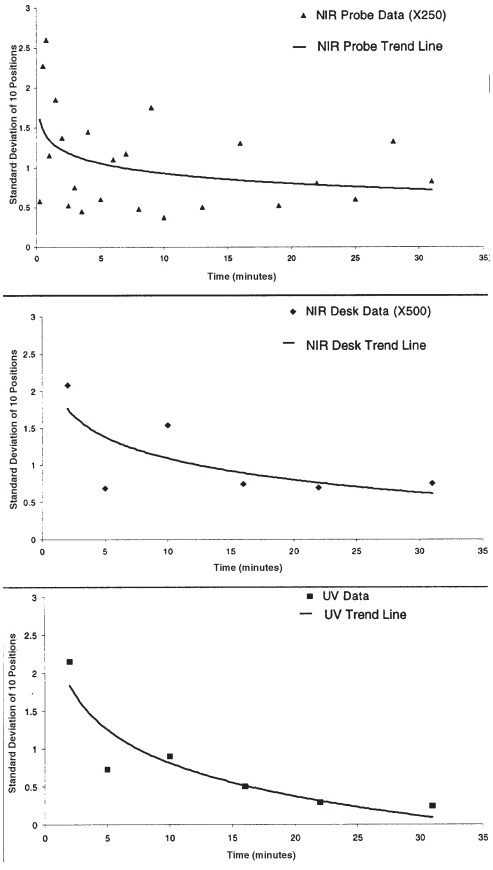

Figure 3. Plot of spectral standard deviation versus mixing time for NIR fibre optic probe measurements of the blend in the Buls cube and the NIR sample desk and UV measurements of the thieved samples.

Results and discussion

NIR spectra of the pharmaceutical ingredients

To select an appropriate wavelength to monitor caffeine, the "active" ingredient in the model formulation, NIR spectra of caffeine, Avicel® PH102 and magnesium stearate as bulk powders were obtained with the fibre optic probe attachment. NIR spectra for these ingredients are presented in Figure 2. A caffeine peak at 1673 nm, presumed to be the first overtone of a C–H stretch[12] from the guanine backbone of caffeine, was selected for monitoring because absorbances from the Avicel® and magnesium stearate in this spectral region are flat.

Static measurements: NIR spectra from the Buls cube blend.

Standard deviations of the absorbance data obtained by NIR fibre optic probe, NIR sample desk attachment and UV-vis measurements across the ten positions in the Buls cube were calculated. In Figure 3, these values are plotted against mixing time. Note that the magnitudes of these values are scaled for data trend comparison. Minimisation trends were found for all of these measurement techniques. However, the greatest

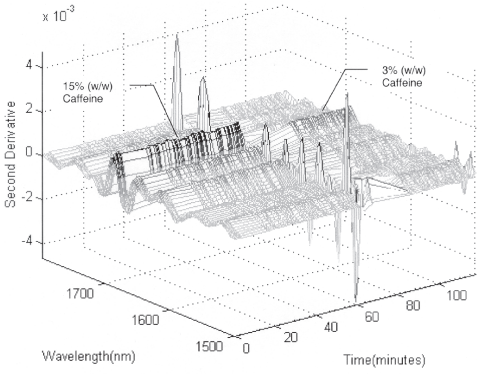

Figure 4. Three-dimensional plot of the second derivative NIR fibre optic probe spectra for the 15 and 3 % w / w caffeine blends in Avicel® v. flowtime through the Manesty™ Betapress NIR setup.

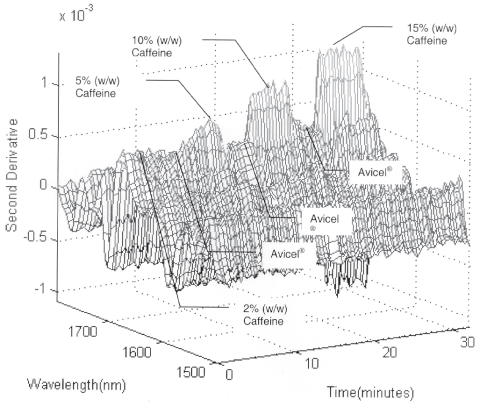

Figure 5. Three-dimensional plot of the second derivative NIR fibre optic probe spectra for the 2, 5, 10 and 15 % w / w caffeine blends in Avicel® and Avicel®/magnesium stearate spacer blends v. flowtime through the Manesty™ Betapress NIR setup.

variability in this trend was found with the NIR fibre optic probe measurement. Sources of variability for this method may be attributed to inserting the probe manually into the powder blend; these sources include perturbing the blend with the probe, maintaining a steady hand with the probe in the Buls cube during spectral acquisition and compacting the blend as the probe is inserted into the powder.

Blend–flow measurements: NIR spectra from the Manesty™ press

After the 15% caffeine blend in Avicel® was mixed in the Buls cube, it was transferred to a plastic Mauser drum and then to the hopper on the Manesty™ Betapress fitted with an NIR fibre optic probe. NIR spectra were measured using a fibre optic probe as the blend passed from the hopper to the feedframe for approximately 60 min. The tablet press was then stopped and a 3% caffeine blend in Avicel® was added to the hopper and passed through the press. NIR spectra were again collected as this blend flowed from the hopper to the feedframe.

A three-dimensional plot of the second derivative spectra for both these caffeine blends (15 and 3%) against runtime is presented in Figure 4. In this plot, differences in the caffeine levels can be seen. This plot demonstrates the feasibility of monitoring the level of an active as a blend feeds into a tablet press from the hopper.

To further determine sensitivity of the measurement, NIR measurements were also obtained for 200 g batches of blend containing 2, 5, 10 and 15% caffeine in Avicel® as they flowed through the modified Manesty™ Betapress. Due to the small quantities of blends used and poor flow characteristics of the material, the hopper was removed from the feed system. A small tube was used as a mini-hopper to contain blend and control powder flow by the NIR probe. Each active-containing blend was added to the mini-hopper in sequential order, separated by Avicel® to minimise contamination from the different caffeine blend layers.

A three-dimensional plot of the second derivative spectra for the different blends v. runtime is presented in Figure 5. The second derivative spectra of this plot show that the dynamic measurements performed with the probe are sensitive to these differences in the active levels down to 5% caffeine.

However, small differences between the second derivative spectra for the 2% caffeine blend and the Avicel®/magnesium stearate blend were found.

Conclusion

The data obtained from the NIR probe placed on-line between the hopper and the press demonstrates that the post-mixing blend can, potentially, be monitored for an active and used to evaluate the quality of the blend. This probe configuration was able to differentiate 5, 10 and 15% caffeine blends from an Avicel® blend containing 1 %magnesium stearate. Because this approach provides a dynamic system, monitors the blend after additional manipulation, immediately prior to the actual tableting process, it may provide a more representative picture of the actual blend entering the tablet press feedframe and, ultimately, the final tableted product.

The NIR data , including transfer from the blending vessel (ie, Bols cube) obtained by manual insertion of the fibre optic probel, exhibited a similar profile to that of the thieved samples but contained greater variability from timepoint to timepoint. Sources of variability for this method may be attributed to inserting the probe manually into the powder blend; these sources include perturbing the blend with the probe, maintaining a steady hand with the probe in the Buls cube during spectral acquisition and blend compaction as the probe is inserted into the powder. In addition, an inadequate number of data points may have been collected by both the probe and sample thief to build an accurate picture of the mixing dynamics. Because more frequent probing and/or thieving of a blend is impractical, on-line dynamic NIR measurements are recommended during blending to improve understanding of the blending process.

Future considerations

The use of an on-line, fixed NIR probe for an evaluation of blend uniformity in the blender should be performed. These on-line measurements would presumably reduce the variability observed with the probed and thieved sampling schemes.

As far as the Manesty™ Betapress work, an investigation into correlating spectra of the blend obtained on-line to the caffeine values in the tablets should be performed to determine the feasibility of quantifying the active level based on the spectral results.

In addition, the effect of probe depth through the side of the connecting tube needs to be examined, along with the possibility of using several probes simultaneously at different probe depths. These studies may provide information of any mixing dynamic of the blend as it empties from the hopper into the feedframe of a press.

Although spectra of the flowing powder were acquired using a scanning instrument in this investigation, the sensitivity to changes in the active content of the blend is compromised because the spectra are averaged from several scans of a moving sample, which may be changing in composition. An acousto-optical tunable filter or diode array NIR instrument, which is more amenable to measuring a dynamic sample because of faster data acquisition capabilities, would be better suited to perform these measurements.

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