Non-invasive monitoring of powder mixing with near infrared spectrometry and acoustics

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Introduction

Unit operations such as granulation, blending and tableting are integral steps in the production of many pharmaceutical products. Maintaining control of these operations is essential to ensure product quality, meet the requirements of the regulatory authorities and minimise wasted batches.

The objective of powder mixing is to agitate two or more materials to a homogeneous state. Three main affects may contribute to this process: convective mixing, diffusive mixing and shear mixing, depending on the type of mixer and the properties of the particles. Segregation occurs in competition with mixing and prevents a perfect homogeneous powder blend being obtained. Hence the quality of a powder mixture depends upon the dynamic equilibrium between mixing and segregation, which in turn, depend on the physical and chemical properties of the particles.

The duration of powder mixing in a pharmaceutical process is frequently determined by experimental trials or operator experience. The quality of a blended powder product can be expressed in terms of composition variance, which will decrease over time as a mixing takes place (Figure 1) The most commonly used method to determine blend homogeneity is analysis of "grab" samples by, for example, high performance liquid chromatography. The analysis is often carried out by skilled staff, in a laboratory located away from the process (off-line analysis). Apart from the increased time associated with off-line analysis (often longer than the mixing process itself), representative sampling of a bulk powder can be difficult to achieve. Depending on the method of removal, segregation can be artificially introduced and poor sampling, rather than poor mixing, may be the cause of an off-specification assay. There are therefore many benefits associated with moving from off-line analysis to placing analytical equipment close to the process (at-line) or actually on/in the process (on-line).

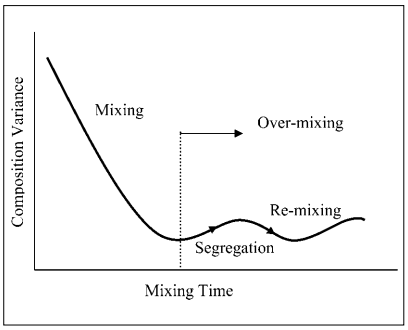

Figure 1. Ideal mixing profile for a powder blending process.[3]

Near infrared spectrometry

Near infrared (NIR) reflectance measurements can be made non-invasively through a window, are rapid and non-destructive. The mixing of powders in a small scale (0.5 L) high-shear blender serves to illustrate the usefulness of non-invasive NIR measurements for identification of homogeneity and the investigation of factors that affect the mixing process

The procedure followed was to mix cellulose in the vessel for 5 min and then add the second component, with mixing continued for a further 10 min. NIR spectra were acquired every 0.5 s. The reference measurement, made before the start of the experiment, was obtained from reflective paper placed inside the glass vessel. The spectra were converted to log $1/R'$ (Figure 2), where R' is the ratio of the reflectance of the sample to the reflectance of the reference. First derivative spectra were calculated to remove baseline offsets and make regions of the spectra undergoing change more obvious. A plot of the first derivative absorbance against time for any of the peaks caused by the added compound, provides a NIR mixing profile. This is illustrated in Figure 3 for the absorption of aspirin at 8956 cm^{-1}. Cellulose absorbs weakly at this wavenumber. The peak in the mixing profile is due to the first pass of the aspirin through the observation region, before dilution to the homogeneous state is achieved by further mixing. Analysis of the mixing pattern (300–600 s) and the homogeneous region (700–900 s) provide information about the nature of the mixing process

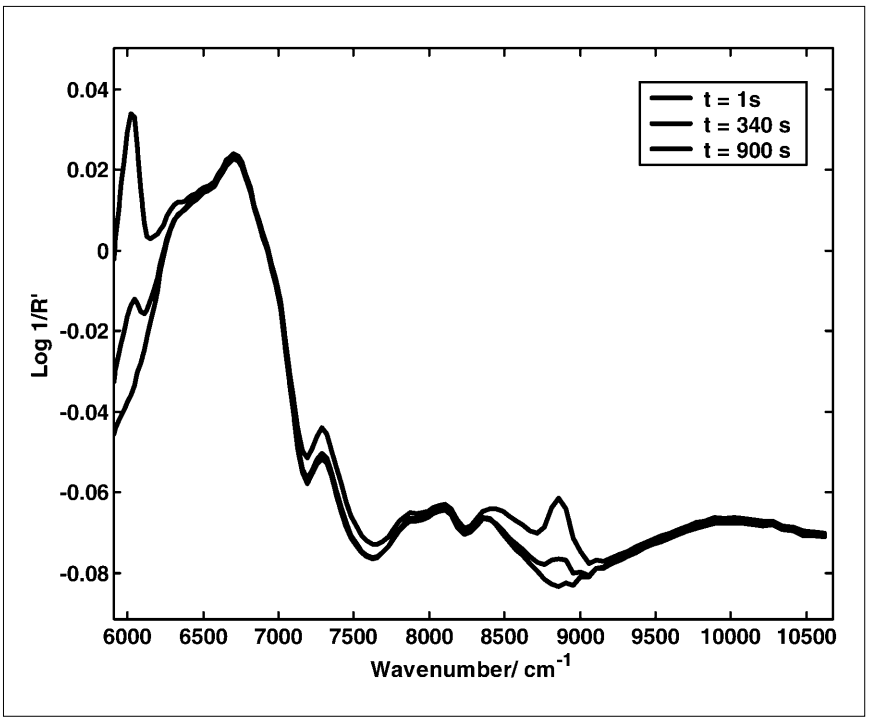

Figure 2. Log 1/ *R'* NIR spectra: 10% w/w addition of aspirin to 75 g cellulose mixing at 50 rpm. Spectra obtained before (1 s), just after (340 s) and well after (900 s) addition of aspirin.

and how this is affected by particle related parameters.

Acoustic emission

Acoustic emission (AE) monitoring is also a non-invasive technique and detects sounds emanating from inside the process by use of a sensor or transducer. The transducer contains piezoelectric materials that convert pressure waves into electrical impulses, which can be detected, amplified and displayed. Transducers may be attached anywhere on a vessel that is physically coupled to the process, although extremes of temperature and pressure should be avoided by use of a waveguide. Although there are many sound sources in a powder mixing process, those at high frequencies outside the audible region are the most useful, as they are less susceptible to extraneous interferences because they travel over relatively short distances.

The use of broadband transducers was favoured for the monitoring of powder mixing in the 0.5 L high-shear blender because of the additional information that may be available in the acoustic emission spectrum. The transducer was coupled to the wall of the vessel with silicon-based grease and held in place with insulation tape. Acoustic signals were acquired every 1 s, converted to power spectra and summed in groups of five to improve the signal-to-noise ratio. Figure 4 shows three acoustic frequency spectra obtained before (1 s), straight after (340 s) and well after (900 s) addition of aspirin to cellulose. Mixing profiles were obtained by calculating the signal area over a range of frequencies in the power spectrum, and then plotting the area against time (Figure 5).

Information obtained

The mixing profiles obtained with NIR and AE can be used to determine a qualitative end-point of mixing once the signals become constant. The NIR profiles generally indicate a constant level more clearly than do the AE profiles, which with current methods are more variable (noisy). There is also the potential to quantify the amount of secondary material in the mixture by relating the final signal magnitude in the NIR and AE mixing profiles to calibrated responses obtained for known concentrations of compounds mixed with cellulose. The signal level changes linearly with concentration for NIR spectrometry, whereas it has been observed that a non-linear change occurs with the acoustic measurements.

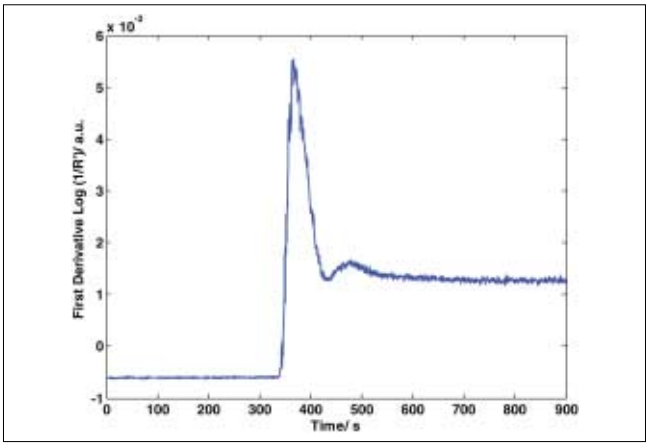

Figure 3. NIR mixing profile of aspirin at 8956 cm^{-1}: 10% w/w addition of aspirin to 75 g cellulose mixing at 50 rpm.

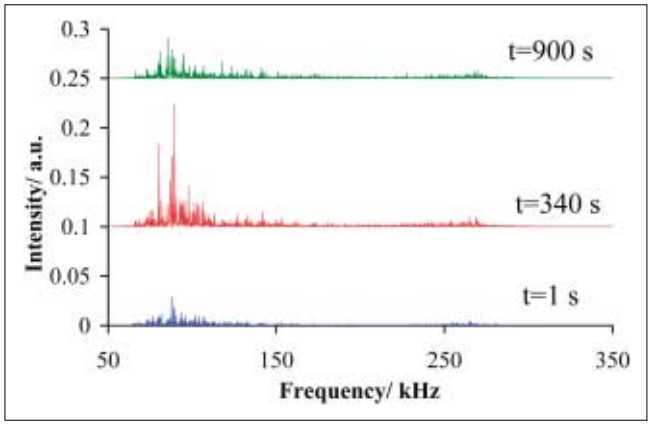

Figure 4. Acoustic power spectra: 10% w/w addition of aspirin to 75 g cellulose mixing at 50 rpm. Spectra obtained before (1 s), just after (340 s) and well after (900 s) addition of aspirin.

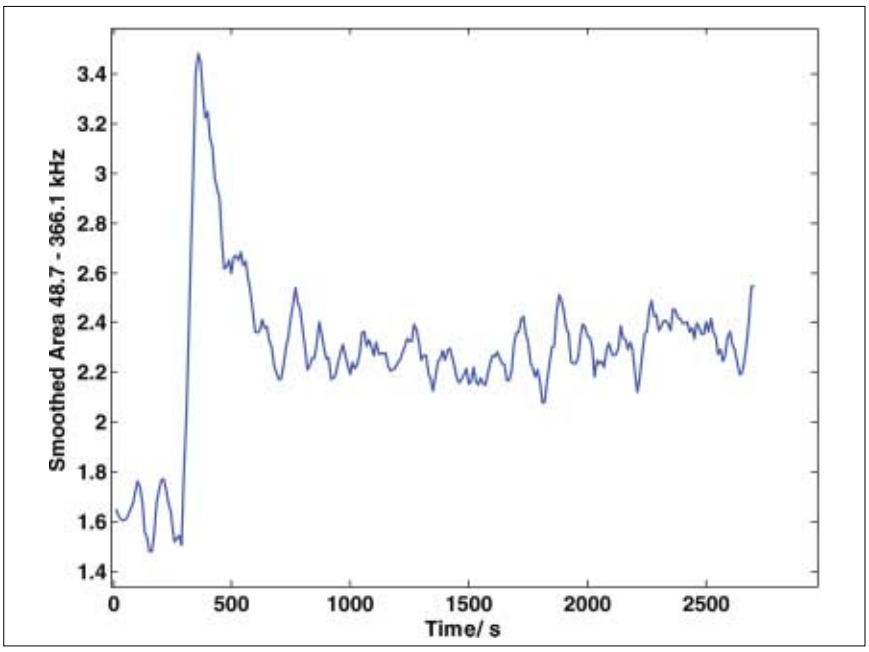

Figure 5. Acoustic mixing profile: area calculated between 48.7 and 366.1 kHz for a 10% w/w addition of aspirin to 75 g cellulose, mixing at 50 rpm.

The NIR mixing profiles are slightly different depending on whether the added particles are spherical, cubic or needle shaped. Both the NIR and AE procedures are sensitive to the median particle size of the added compounds. Features in the NIR spectra and the derived mixing profiles have been observed to change systematically as the median particle size is altered. In certain regions of the acoustic frequency spectrum, the magnitude of the peaks is affected by both the median particle size and concentration of the added compound, where as the magnitude of other peaks only change with concentration.

Conclusions

NIR reflectance and acoustic emission measurements can be used non-invasively to monitor powder mixing. NIR spectrometry is the more established technique and is increasingly being used to monitor manufacturing operations in the pharmaceutical industry. The application of broadband transducers to generate acoustic frequency spectra is less common and requires further development of signal processing and interpretation procedures to realise the full potential of the technique. However, research conducted so far is encouraging and further advances are expected. Although NIR spectrometry and AE have individual advantages and limitations, the simultaneous deployment of both techniques is relatively straightforward. It is anticipated, therefore, that synergistic combination of measurements from both procedures will provide better understanding and control of mixing processes and other similar unit operations.

Further reading

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