Raman Spectroscopy: An emerging analyzer tool for the pharmaceutical industry

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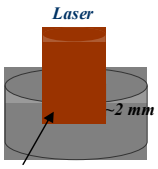
Raman spectroscopy is currently of interest as a process monitoring tool for pharmaceutical unit operations. In this study, the performance characteristics of Raman spectrometers with different sampling optics have been investigated in the context of process monitoring, with emphasis being placed on assessing homogeneity in powder blends and following changes in solid state form during wet granulation. A novel large spot non-contact Raman sampling device provides significant advantages over the standard systems both as a result of the enhanced sampling volume and because of the greater robustness of the system to fluctuations in the sampling distance during process.



Analyzed volume of solid sample

As analytical instrumentation advances in sophistication, there is growing interest in interfacing such instruments to pharmaceutical unit operations with the aim of enhancing process understanding, and ultimately monitoring and controlling the process. Optical spectroscopic techniques are especially suitable for in-line process monitoring since remote sampling can be achieved by transmitting radiation to and from the sample via fiber optic cables. For example, near infrared spectroscopy (NIR) is now widely used as an in-line technique for pharmaceutical processes, in particular to extract information about moisture content.

Raman spectroscopy is complementary to infrared spectroscopy and can provide certain advantages due to the fact that water is a poor Raman scatterer, while active pharmaceutical ingredients (APIs) are generally good Raman scatters making it possible to study changes in water rich environments such as wet granulation.

However, due to the limited intensity of the Raman scattering, the exciting radiation is generally focused into a high intensity cone of light in order to facilitate the collection and detection of sufficient inelastically scattered photons. Consequently, for static samples, only the small portion of the sample that interacts with the focused beam is sampled. For many commercial systems, the incident radiation is typically focused to a spot size of less than 500 µm in diameter. This can be a significant disadvantage for real time applications, since such focusing can lead to two significant problems, i.e. sub-sampling and loss of signal intensity if the sample moves out of the focus of the incident radiation. For example, if blend homogeneity is of interest, a 100 µm spot needs to travel over a considerable area before a representative sample volume can be measured in a binary mixture composed of 200 µm particles and any movement of the sample relative to the sampling device must be such that a reasonable interaction of the material with the incident radiation is maintained. In addition, since the Raman effect is weak, an integration time of at least at least 5 seconds is typically required in order to obtain a Raman spectrum of

sufficient quality. Consequently, although Raman spectroscopy has been used to monitor pharmaceutical processes where it is possible to maintain a good contact with the sample, such as chemical reaction and crystallization monitoring, there are limited reports of the use of this technique for measuring processes which are spatially more dynamic and heterogeneous.

Recently Wikström *et al*. demonstrated that Raman spectroscopy could be used for in-line monitoring of solid state phase transformations during high-shear wet granulation using an immersion probe coupled to fiber optics to interface the radiation with the sample. For the immersion optics utilized in this study, the irradiating radiation is focused close to the window sealing the probe. The probe was placed into the granulation bed and material that was swept past the probe was analyzed. However, the authors noted that there were a number of problems associated with this approach including the potential for the material to stick to the probe window and it was concluded that invasive probes could not be considered optimum for monitoring these types of pharmaceutical processes.

Having previously established the utility of Raman spectroscopy for obtaining information about phase transformations during wet granulation, the objective of the current study was to evaluate different sampling devices for in-line monitoring.

The immersion optics used previously was compared with non-contact optics. In addition, the importance of sampling volume and depth of focus was investigated by comparing a sampling device with a standard spot size and focusing optics with a large spot size, unfocussed system.