Solid State Analysis of Multicomponent Pharmaceutical Powders by Red-Excitation, Dispersive Raman Spectroscopy

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The application of a high-sensitivity, dispersive Raman spectroscopy system to the solid-state analysis of pharmaceutical powders is described.

The Raman system consists of a diode-laser for excitation, a sample chamber with environmental control of the sample powders, a single stage spectrograph with an additional non-dispersive stage, and a cryogenically cooled CCD sensor. The data processing method for stability testing used in this study is applicable to diode-laser based Raman spectroscopy in general. The wavelength axis of each spectrum is only calibrated coarsely with an accuracy of 2 pixels of the sensor (2 - 3 cm^{-1}). Spectra with slightly different wavelength calibration are then aligned relative to each other with an accuracy of a fraction of a pixel using the line-shapes of reference peaks in the spectra. This procedure significantly improves the signal to noise level in the difference spectra of Raman spectra excited by diode lasers. The method does not require knowledge or calibration of the exact line position of the laser.

Examples for typical applications such as stability testing, protein conformational analysis, and polymorph determination are presented. The high sensitivity of the system allows semi-quantitative measurement of amorphous content and polymorph differentiation in multi-component systems. All three polymorphs and the amorphous fraction of mannitol in a spray-dried salmon calcitonin – mannitol formulation of varying composition were successfully analyzed.

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