

Applications of Raman Microscopy: Fast Scanning Chemical Mapping of Drug Delivery Systems

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Raman spectroscopy is a versatile and information rich spectroscopic technique. As a tool for pharmaceutical analysis it has many applications, ranging from the polymorphic characterisation of drug and excipients to process control. Coupling a Raman spectrometer to a microscope produces a technique capable of giving detailed chemical and physicochemical information with spatial resolution at the micrometer scale. However, the technique is not without problems. The Raman signal can be small relative to intrinsic fluorescence. In some cases Raman scattered light is not observable at all in the presence of strong fluorescence, a problem often encountered with natural carbohydrates and their derivatives, a set encompassing many pharmaceutical excipients. Additionally, Raman microscopy is often regarded as a slow technique, and indeed acquisition of Raman maps can, in some cases, extend to several days. Here we report on the performance of a high sensitivity Raman microscope (Witec Confocal Raman Microscope CRM 200) giving rapid scanning and high spatial resolution. Use of a cooled Charge Coupled Device (CCD) with efficient coupling of excitation laser (high flux point source) and collection optics allow the acquisition of Raman spectra from $<1 \mu\text{m}^3$ voxel (true confocal conditions) with a dwell time in the millisecond range. This in turn allows the acquisition of Raman maps with micrometer spatial resolution, where spectra are acquired for each individual pixel, in hours rather than days.

Here two examples where Raman microscopy complements other high-resolution spatial imaging techniques are shown. In the first example Raman maps of the distribution of a micronised drug within a tablet formulation give the drug particle size distribution. This data is subsequently correlated with Time of Flight Secondary Ion Mass Spectrometry (ToF-SIMS) images. In the second example Raman mapping was performed on a formulation comprised of a drug substance compounded with Hydroxypropylmethyl Cellulose (HPMC). Data were acquired using a 785 nm excitation source, which reduces the fluorescence problem frequently encountered with HPMC. The maps show that the drug can exist as a molecularly dispersed state or as a phase separated state. In the latter, detailed examination of the spectra from regions of interest show that the drug is detected in a crystalline state. This is reflected in the compromised bioavailability. These results were verified using Scanning Thermal Microscopy (SThM) and Localised Thermal Analysis (LTA).

In summary one of the major disadvantages of Raman microscopy, namely slow acquisition rates, has been addressed by a new generation of Raman microscope design. High sensitivity allows collection of true confocal spectra in millisecond time periods, and consequently detailed chemical maps with a resolution approaching the diffraction limit.