Key Issues
- **Polymorphic form ID**
- **Rapid screening of drug candidates**
- **Automated instrumentation for unattended data collection**

**Introduction**
As the rate-determining step in early pharmaceutical development has moved from synthesis to analysis, new methods have been sought for rapidly screening drug candidates and for processing the data produced. The need to process an increased numbers of candidates has led to the development of the field of high-throughput screening (HTS).

One of the most important properties of solid-state drug candidates is their polymorphic form. Many molecular solids, such as organic drug candidates, can crystallize in several different polymorphic forms, differing only in the space group of the extended solid or the conformation of the constituent molecules. Usually considered along with polymorphs are pseudopolymorphic versions of a compound such as solvates and hydrates. Differences in polymorphic form and in solvation or hydration may greatly affect the dissolution, stability, and bioavailability properties of the drug, so characterizing these forms early in a candidate’s lifetime and selectively producing only the desired polymorphic form or version is of the utmost importance in drug manufacture.

**Analysis Methods**
Traditionally, the method most commonly used for characterizing polymorphs is x-ray diffraction (XRD) supplemented by infrared (IR) spectroscopy, but the sample preparation required by IR and the data collection cannot be easily automated—an essential feature in a screening tool.

Improvements in technology have made Raman spectroscopy, another form of vibrational spectroscopy, amenable to automated rapid data analysis, bringing its advantages of non-contact analysis with no sample preparation into the pharmaceutical discovery laboratory. The **RamanRxn1™ High Throughput Screener (HTS)** from Kaiser Optical Systems, Inc., (Kaiser) enables automated data collection and analysis on small quantities of solid in a wellplate (Figure 1). The large volumes of data that are generated in automated experiments can be analyzed automatically using chemometric methods. Data analysis can be targeted within a well to ensure that material is sampled effectively even when the material covers only part of the well.

Raman spectroscopy has the analytical and instrumental capability to follow a candidate form from discovery to manufacture. This ability maximizes available knowledge for transfer at each step of scale-up as a candidate API transitions to a drug product.

**Polymorph Identification**
Three products from an evaporation experiment in which a single drug candidate was crystallized by slow evaporation from different solvents are found in Figure 2. The white-light images of the crystals, shown at the left of the figure, suggest that three different crystalline forms were produced, which is confirmed in situ and without sample preparation by the three unique Raman spectra shown at the right of the figure. After Raman analysis, these three polymorphs can be evaluated separately for their suitability in the desired dosage form. The use of Raman HTS...
in the discovery lab is an example of PAT viable techniques in R&D.

**Solvates**

Except for hydrates, solvates are not usually suitable for use in drug formulations. However, they are often intermediates in the formation of the final drug product, so it is important to characterize them in order to understand the formation of the final product. Although the solvents used in these experiments were similar, the Raman spectra of the various solvates (Figure 3) are sufficiently different to easily distinguish them.

**Figure 2.** Raman spectra of three unique polymorphs formed by crystallizing a drug candidate by evaporation from three different solvents.

**Channel Solvates**

Unlike in other solvates, in which the solvent molecules form part of the crystal lattice, in channel solvates the solvent molecules are found in channel-like interstices between molecules of the drug.

**Figure 3.** Raman spectra of solvates.

**Conclusion**

Raman spectroscopy is ideal for high-throughput screening of polymorphs in the initial stage of pharmaceutical product development. As shown for channel solvates, Raman spectroscopy is equally effective for analysis of solids and of slurries—unlike XRD, for which slurry analysis is extremely difficult—providing the versatility needed to handle a variety of drug candidates.

With the RamanRxn1 HTS, each well in these experiments could be analyzed in approximately 30 seconds. Each well can be autofocused to provide high-quality data despite varying well fills. Unlike with a conventional Raman microscope, the entire wellplate can be analyzed unattended, freeing personnel to accomplish other tasks while data collection is completed automatically.

*Current model is Raman WorkStation™*

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**Reference:**