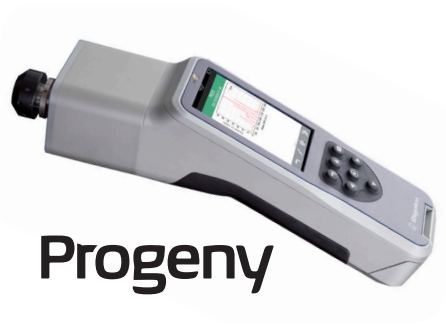
Handheld Confidence.

APPLICATION NOTE

DRUG PRODUCT IDENTIFICATION USING HANDHELD RAMAN



- IDENTIFY DRUG PRODUCTS AND DRUG SUBSTANCES
- VERIFY API DOSE AND PLACEBOS
- REDUCE MATERIAL TRANSFER

Handheld Raman spectroscopy is well accepted as a technique for raw material and excipient identification within the pharmaceutical industry. Using the correct Raman excitation wavelength can extend its capabilities into the areas of drug substance and drug product identification.

MINIMIZE SAMPLE INTERFERENCE WHILE MAXIMIZING EFFICIENCY

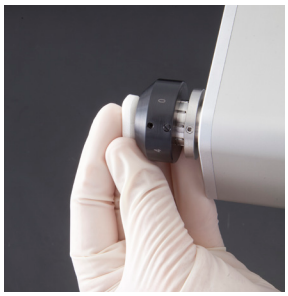
Handheld Raman is an attractive ID method because it provides a portable measurement that can distinguish different concentrations of active pharmaceutical ingredients (API) in drug product (DP) doses and placebos with little or no sample preparation. Progeny, a handheld Raman analyzer with 1064nm excitation, is less prone to fluorescence interference typically experienced by handheld analyzers with 785nm excitation. The advantages of using Progeny for identification can be applied to initial DP and API release testing as a secondary identification method since potency is typically determined by a primary technique such as HPLC. Handheld Raman can also be applied to in-process control testing during post packaging operations, final release testing and receipt ID testing of finished goods. This eliminates the need to send samples to an analytical laboratory and provides significant savings. As well as portability, 1064nm handheld Raman has advantages compared to traditional ATR-FTIR and compendial wet chemical techniques. This includes reduced sample preparation, minimal instrument clean up and the removal of exposure risks of high potency APIs, because of Raman's ability to measure through containers – such as plastic bags, thin plastic, clear glass and amber glass bottles.

COMPOUND	DOSAGE FORM MATERIAL ID (DMID)	POTENCY	API LOADING
Drug Product – Gelatin Capsule	D1200160	125 mg	28%
Drug Product – Gelatin Capsule	D1200158	75 mg	28%
Drug Product – Gelatin Capsule	D0401369	25 mg	9%
Drug Product – Gelatin Capsule PBO capsule fill	D1200155	0 mg	0%
Non-Film Coated Drug Product Tablet	D1306646	12.2 mg	4%
Non-Film Coated Drug Product PBO	D0904600	0 mg	0%
Film Coated Drug Product Tablet	D1005304	10 mg	10%
Film Coated Drug Product Tablet	D1306478	2.5 mg	5%
Film Coated Drug Product Tablet	D0904975	5 mg	5%
Film Coated Drug Product Tablet	D1005706	10 mg	5%
Film Coated Drug Product Tablet PBO	D0904596	0 mg	0%

Table 1. Details on the contents of each of the three sets of samples investigated.

FEASIBILITY STUDY

A collaborative study was performed in conjunction with Pfizer Inc., Global Analytical Research and Development, by analyzing several different DP formulations of API at different loading levels using Progeny. These experiments were intended to verify whether a qualitative analysis approach, such as correlation, would suffice in the discrimination between similar products with different API concentration. Three sets of DP tablet and capsules with API/excipient blends with API loading – in the range of 4 - 28% – and corresponding matching placebos were analyzed (see Table 1). Placebos were investigated in this study because these particular DP samples were made for clinical trials.



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Drug Product in Gelatin Capsules

Different API loading in the capsule contents and the placebo are easily distinguished for these active compound formulations. This was demonstrated by measuring the contents of each capsule through plastic bags and adding each spectrum to Progeny's library. Figure 1 shows the spectra from these four samples.

The samples were then measured six more times and each new measurement compared to the library spectra. This comparison is done using a correlation algorithm and the hit quality index (HQI) is a measurement of how closely the measured spectrum matched the library spectra. Table 2 shows the average HQI values from the different capsule contents. The average HQI values differ by more than the standard deviation for all samples with different percent API loading. This indicates that the different API loadings can be distinguished using Progeny.

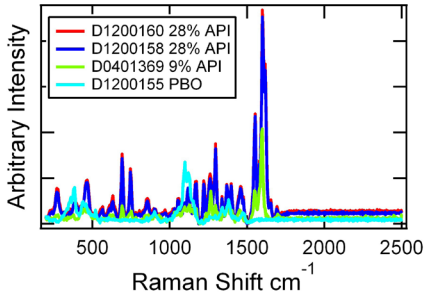

Figure 1. Representative 1064nm Raman spectra of capsule contents and placebo.

Material	D1200160 28% API	D1200158 28% API	D0401369 9% API	D0904600 PBO
D1200160 28% API	0.95	0.95	0.70	0.00*
D1200158 28% API	0.95	0.95	0.70	0.00*
D0401369 9% API	0.48	0.49	0.88	0.07
D0904600 PBO	0.00*	0.00*	0.01	0.93

Table 2. Average HQI for six repeat measurements of capsule contents, standard deviation is < 0.15.
*The same percent API loading cannot be distinguished by Raman, however potency of these two capsules can be determined by size and weight.

Non-Film Coated Drug Product Tablets

For this DP, a single potency currently exists. Clear differences are seen in the Raman spectra of the placebo and the active tablet containing 4% w/w API. The materials were measured as-is, and as was done with the capsule contents, each spectrum was added to the library and then six subsequent measurements were compared to the library. The differences between the HQI values for the 4% API tablet and the PBO are large enough that the two can be easily distinguished using a 1064nm Raman analyzer. Figure 2 shows a measurement taken by Progeny of the 4% API tablet, demonstrating correct identification and a clear Raman spectrum.

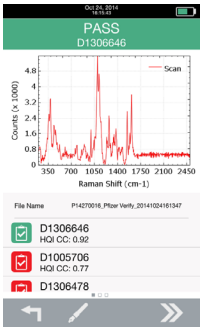

Figure 2. Progeny screen shot of correct ID results from measuring a 4% w/w API tablet (D1306646).

Film-Coated Drug Product Tablets

Tablets from this set of samples were not distinguishable by Raman. Strong TIO2 bands dominated the spectra. Figure 3 shows a Raman spectrum example of a film-coated tablet. Even after filing off the Opadry White (TIO2) coating, the Raman spectra were dominated by peaks from the excipients. However, the potency can be distinguished by tablet size/shape/weight.

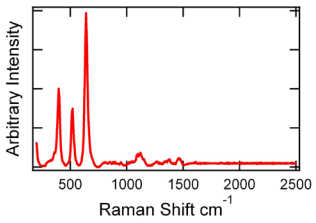

Figure 3. 1064nm Raman spectrum of Opadry White coated tablet showing strong TIO2 bands.

CONCLUSION

Progeny could easily distinguish different API loadings and placebos for two of the three drug products from clinical trials investigated. For appropriate DP formulations, the use of this portable and rapid technique could be applied to in-process control checks of packaging lines and subsequent post package verification testing of DP without transferring the DPs to an analytical laboratory. Handheld Raman technology not only offers efficiency and fast data collection for final release of post-packaged DP, but also allows for an extra layer of quality to be incorporated into the post-packaging and post-package release testing, all while reducing material transfer steps and analyst exposure to high potency APIs and DPs.

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