Application note

Product quality control

API quantification using TruScan RM Handheld Raman Analyzer with TruTools for finished product quality control

Authors

Lin Chen, Ph.D, Michael Gallagher, O. Dean Stuart, Thermo Scientific, Tewksbury, MA

Introduction

Inspection of the quality of final product and raw materials before manufacturing a drug product is a critical step to ensure the product is suitable for its intended use with established identity, purity and quality under Good Manufacturing Processes (GMPs). Finished product quality control is to ensure the correct APIs are present and correct API strength in the final products before release and shipping out to other chains, for example other global sites. The traditional registered methods such as high-performance chromatography (HPLC) for the quality management of pharmaceutical products are expensive, time consuming and destructive. The pharmaceutical industries are looking for faster, more efficient and reliable tools to conduct finished product quality inspection. Optical spectroscopic techniques like Raman spectroscopy allow rapid analysis in a fast and non-destructive manner.

Raman spectra obtained from finished products exhibit unique features including API and excipient characteristics, which are used to identify each individual product. Not like traditional raw material identification, final or finished drug products usually have a more complex formulation matrix. Truscan RM, with the embedded TruTools chemometric functionality enabled, has the capability for identification in minutes by extracting and analyzing the relevant information from spectra. The results may also be displayed on the device screen and may be evaluated on site while testing, which largely improves inspection efficiencies from 2-3 days to just 2-3 minutes.

thermo scientific

Here, handheld Raman spectroscopy using TruScan RM and TruTools is used to quantify end-user cough syrup APIs. Two API concentrations have been well predicted by using Partial least square (PLS) quantification models. The results were compared to those obtained from HPLC using the methodology described in the European Pharmacopoeia and found be to be in excellent agreement. The methods have been also validated by precision, linearity, accuracy and robustness tests. TruScan RM with TruTools is proven to be a powerful tool for inspecting finished product quality in an efficient and timely manner.

Sample preparation and method development

Samples were presented for analysis by transferring 4ml of syrup liquid from the packaging bottles into standard sample vials. In some cases, the samples can be measured through the packaging directly.

The chemometric training set of samples was prepared by a 3 level, 2 factor full factorial design. 11 samples in total for tests, the sample matrix is list in the table. HPLC results were used to be reference values for comparison.

All the raw Raman spectra were collected using Truscan RM with TruTools at 785 nm excitation. Customised acquisition parameters for collecting the spectra are used (laser power at 250 mW, exposure time 500 ms and 20 coadds) to get the detector fill percentage in the linear detector response region. These parameter settings may vary in a different sample matrix.

	API_ I (wt%)	API_II (wt%)	Excipient (wt%)
1	20.0	1.0	79.0
2	15.0	0.5	84.5
3	15.0	1.0	84.0
4	10.0	1.0	89.0
5	15.0	0.5	84.5
6	15.0	0.5	84.5
7	15.0	0.0	85.0
8	20.0	0.5	79.5
9	10.0	0.0	90.0
10	10.0	0.5	89.5
11	20.0	0.0	80.0

Table 1: Training sample samples for quantification PLS method development

Full spectral range (2850 cm^{-1} to 250 cm^{-1}) was collected from Truscan RM, as shown in Figure 1. The characteristic bands of API_I and API_II can be clearly identified with the change in concentration. After pre-processing the raw training set data by Standard Normalised Variate (SNV), followed by first derivate, and mean centre, two individual PLS models for each API were created using 3 latent variables, as seen in Figure 2. Both models show good prediction through cross-validation by correlating the reference values and the values calculated by the models prediction set, with R^2 being 0.995 for API_I and 0.978 for API_II.

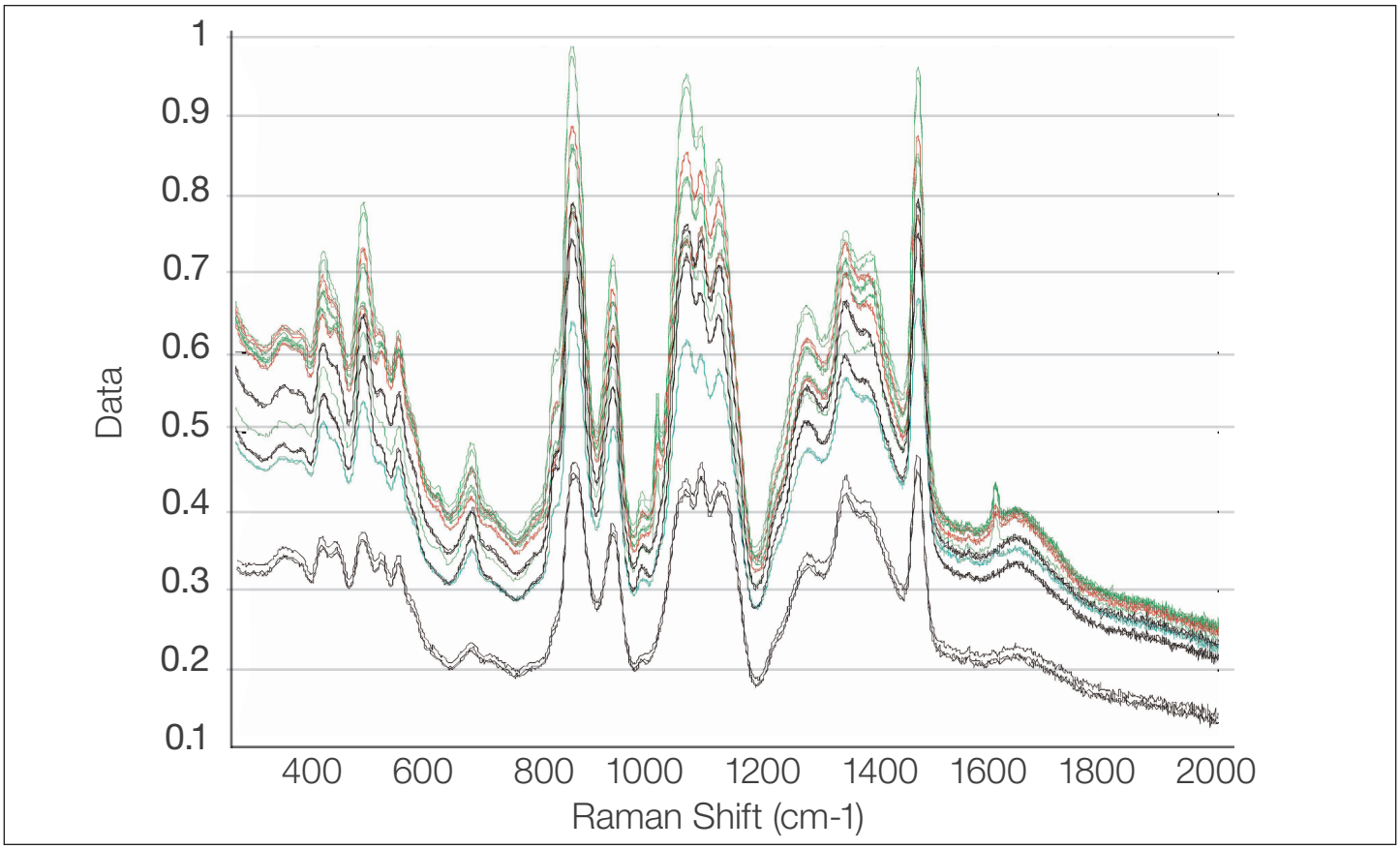
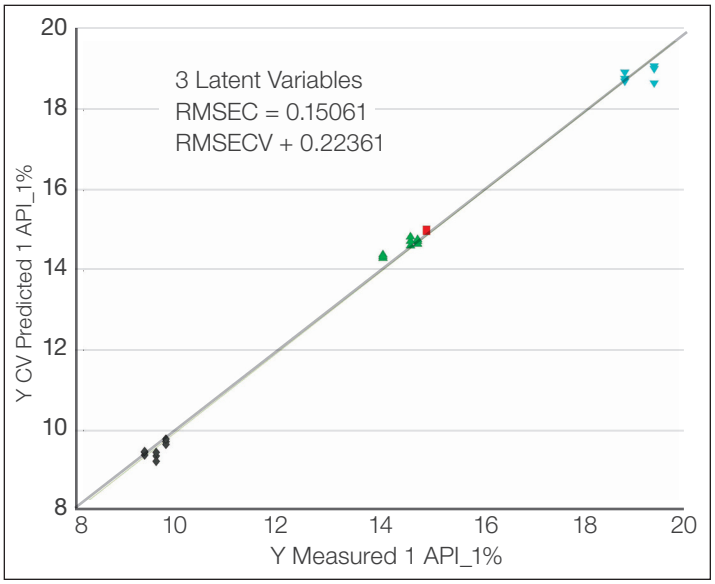


Fig 1. Raw Raman spectra of training set samples collected from TruScan RM with TruTools by using setting parameters (250 mW, 500 msec, 10 coadds). The spectra shown here is in the range between 250 cm^{-1} and 2500 cm^{-1}



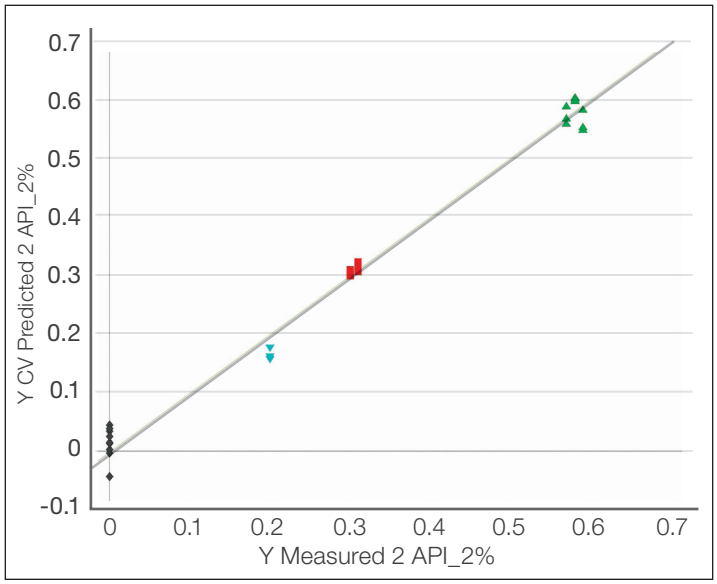


Fig 2 Individual PLS model for API_I and API_II was built. R2 for API_I is 0.995; and for API_II is 0.978

Method validation and comparison to HPLC

The method was also validated by the external validation set, which are different batches and different concentration samples from the training set samples. Predictions based on the PLS model were compared to individual assay value by HPLC, as listed in Table 2.

Validation sample	TruScan with TruTools API_I%	HPLC API_I%	TruScan with TruTools API_II%	HPLC API_II%
1	15.77	16.18	0.35	0.37
2	13.82	13.72	0.25	0.24
3	13.89	13.72	0.25	0.24
4	13.74	13.73	0.25	0.24
5	15.30	15.27	0.12	0.12
6	15.11	15.27	0.14	0.12
7	11.48	11.59	0.25	0.24
8	11.60	11.59	0.23	0.24
9	15.23	15.4	0.25	0.24
10	15.16	15.4	0.24	0.24
11	13.45	13.64	0.35	0.36
12	13.47	13.64	0.34	0.36
13	11.57	11.56	0.11	0.12
14	11.71	11.56	0.12	0.12
15	13.79	13.52	0.13	0.12
16	13.97	13.52	0.14	0.12
17	11.59	11.71	0.34	0.36
18	11.58	11.71	0.33	0.36

Table 2. Comparisons between TruScan with TruTools quantification results and HPLC assays.

HPLC assay and Truscan RM prediction results have shown good correlation with R^2 of 0.9836, indicating the remarkable capability of portable handheld Raman in the quantification of final products with comparable results to standard HPLC assay results. By using TruScan RM with TruTools, one is able to quantify API_II concentration as low as 0.2 wt% in final product.

The outlier detection function embedded in TruTools can provide instant response for at-line testing, and can filter out unacceptable samples, such as poor quality or incorrect samples for further investigation.

Sample	TruScan with TruTools API_I wt%	HPLC API_I wt%	TruScan with TruTools API_II wt%	HPLC API_II wt%
1	15.13	14.92	0.24	0.2
2	14.82	14.92	0.22	0.2
3	15.27	14.92	0.25	0.2
4	15.09	14.92	0.23	0.2
5	15.09	14.92	0.24	0.2
6	14.77	14.92	0.24	0.2
7	14.96	14.92	0.24	0.2
8	15.15	14.92	0.24	0.2
9	15.12	14.92	0.23	0.2
10	14.65	14.92	0.21	0.2
RSD (Repeatability, %)	1.25		3.97	

Table 3: TruScan with TruTools Repeatability tests for the API_I of 14.92% and API_II of 0.2%

The repeatability tests for two APIs in final product have been also performed on TruScan RM. The results are shown in Table 2. It is verified that the repeatability of RSD for two APIs are both less than 5%, indicating good performance and reliable predication results for the validation samples.

According to the validation criteria from ICH Q2, the two APIs quantification methods have been further validated by precision, linearity, accuracy, robustness and collinearity tests. The models created by the end-user are also deployed for real batches sample tests, with validation having achieved satisfactory results.

Summary

This feasibility study has demonstrated TruScan RM with TruTools is an efficient, cost-saving and non-destructive tool to quantify final product APIs, providing a fast, reliable solution to final product release testing for quality control with results comparable to traditional HPLC assays. This handheld Raman quantification methods of two APIs in finished products has been approved in 2021 by MHRA (Medicines and Healthcare Products Regulatory Agency, UK) to replace the HPLC methods for final product release.

Learn more at **thermofisher.com/trutools**