Application Note

Biopharma/Pharma

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Quantification and Identity Testing of Soft Gel Capsules using Transmission Raman Spectroscopy

Efficient and cost saving analytical technique requiring no sample preparation

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Introduction

Transmission Raman Spectroscopy (TRS) is a widely accepted technique that is used for content uniformity (CU), assay, and drug product identity (ID) testing of pharmaceutical oral solid dose (OSD) products (*1,2*). The Agilent TRS100 Raman pharmaceutical analysis system enables fast, non-destructive analysis of tablets and capsules, without the need for chemical preparation or skilled analytical chemists, improving the operational efficiency of quality control (QC) laboratories.

The TRS100 uses transmission Raman to provide bulk volumetric analysis of OSD pharmaceutical products. The instrument can analyze active pharmaceutical ingredients (API) and excipients in a range of different sample types including tablets, powders, hard and soft gel capsules.

This application note discusses how the TRS100 can be used to generate both a qualitative (ID) and quantitative analysis of soft gel capsules. The processes of calibration, model development, and method validation are also discussed.

Experimental

Instrumentation

The TRS100 Raman pharmaceutical analysis system was used for the analysis of the soft gel capsules. The system is controlled using Agilent ContentQC software and is supplied as standard with an integrated third-party chemometric software package, Solo by Eigenvector (*3*). The first part of the analysis focused on the quantification of the soft gel capsules for CU and assay analysis. The second part of the study demonstrated how the TRS100 can be used to verify the identity of soft gel capsules with differing dose strengths.

Content uniformity and assay

A Partial Least Squares (PLS) calibration model was used for the quantification of the soft gel capsules. The product formulation details of the capsules are given in Table 1.

Table 1. Product formulation of the soft gel capsules.

Component	Percent (%)
API	42.0

For the calibration, a set of calibration samples with 90, 95, 98, 100, 102, 105, and 110% Label Claim (LC) of API concentration were prepared. Owing to the practical difficulties of generating an intact calibration set of soft gel capsules, an alternative method was devised. Empty capsule shells (Figure 1) were flattened and placed in the TRS100 sample tray. The calibration standard liquid gel was then dispensed on top of the capsule shells. Clear adhesive film was used to seal the base of the tray (Figure 2), resulting in the final set of calibration standards, as shown in Figure 3.

Figure 1. Empty soft gel capsules used to prepare the calibration standards.

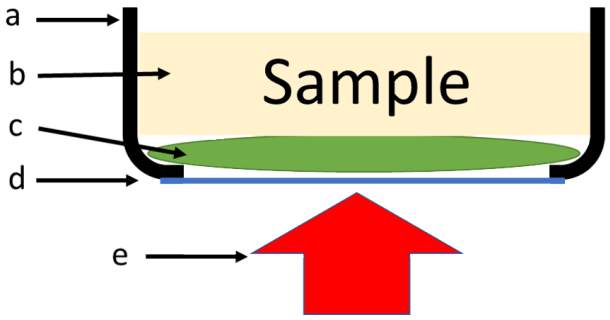

Figure 2. Schematic of sample setup. a) Agilent TRS100 tray, b) liquid sample, c) empty capsule, d) clear tape, e) laser of the Agilent TRS100.

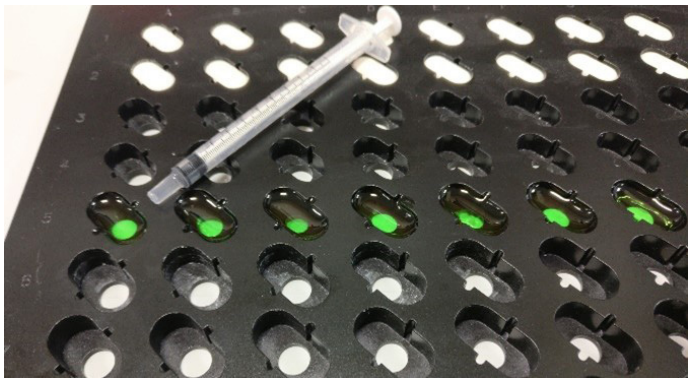

Figure 3. Calibration samples in the Agilent TRS100 tray.

This experimental design provided an excellent approximation of a real capsule, as demonstrated in the results section of the note.

The seven calibration standards were analyzed using the TRS100 with a laser power setting of 0.65 W for 10 seconds per sample (exposure 2 seconds x 5 accumulations). The calibration data is shown in Figure 4, bottom. The data was preprocessed via first derivative and normalized (Standard Normal Variate, SNV). When compared to the pure API and Excipient A derivatized spectra, spectral variation was observed in correspondence with concentration of API and the Excipient A around 850, 1200, 1450, and 1620 cm^{-1} (Figure 4).

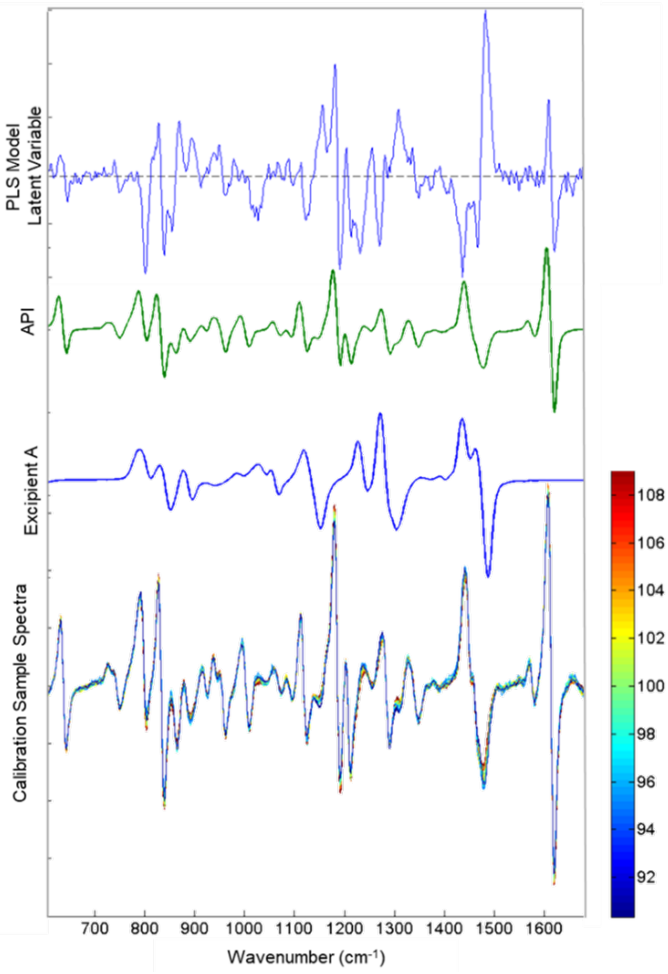

Figure 4. From bottom to top: calibration spectra colored according to API concentration 1st derivative SNV, excipient A, API 1st derivative SNV, and PLS model latent variable 1.

Identity testing

Gel capsules with three different dose strengths were analyzed using the TRS100 under the same acquisition settings used for calibration. These samples were used to investigate whether an identification model could be obtained using the TRS100.

Results and discussion

Content uniformity and assay

The calibration samples were used to build a PLS predictive model in the Solo chemometric software. The chosen model used two latent variables over the spectral range 650 to 1700 cm^{-1} using 1st derivative, normalized (SNV), and mean center preprocessing. Excellent model values were obtained, as shown by the linearity (R^2 of 0.995) of the calibration. Also, low and similar values for Root Mean Square Error of Calibration (RMSEC) and Root Mean Square Error of Cross Validation (RMSECV) of 0.36 and 0.45%, respectively, indicate good accuracy (Figure 5).

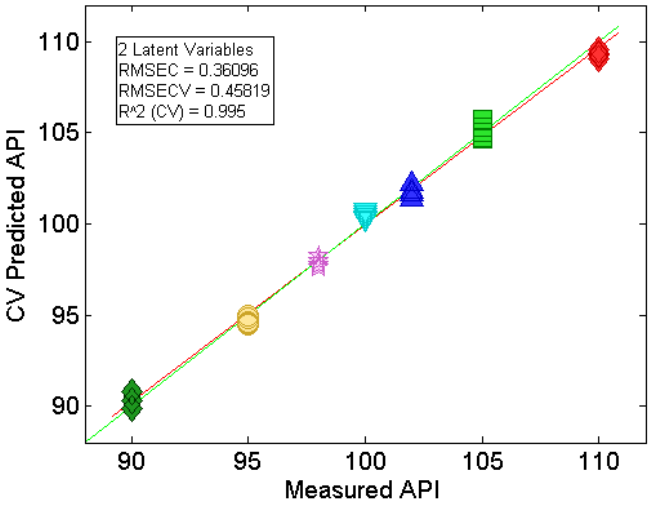

Figure 5. PLS quantitative model generated in the chemometrics software.

For this proof-of-concept study, the model was evaluated by testing whole intact finished dose forms. The results shown in Figure 6 and Table 2 indicate excellent prediction accuracy for the API concentration in the soft gel capsules. The predicted concentration of API compared well with the expected 100% LC with an average result of 100.2%LC and a standard deviation of 0.2% and RMSEP of 0.27%.

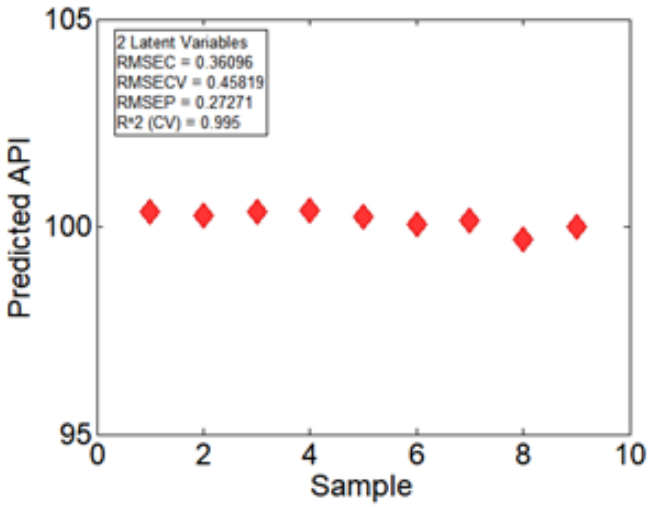

Figure 6. PLS model predictions of validation samples.

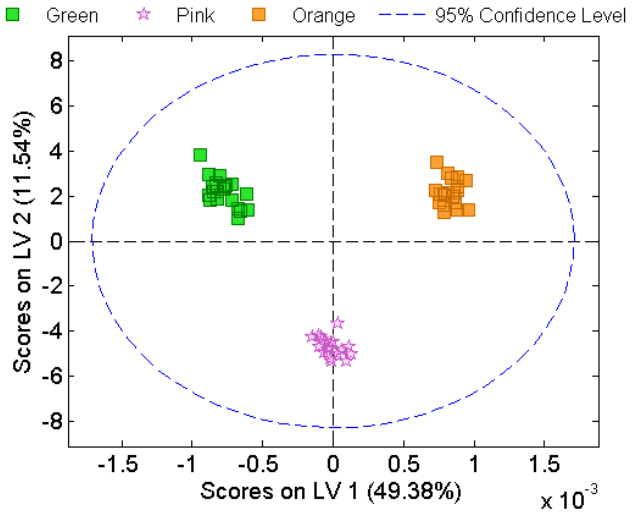

Figure 7. Successful identification of capsules by concentration of API. Different colors correspond to different dose strengths of soft gel products.

Table 2. Quantitative PLS model results as percentage of label claim (%LC).

Sample	TRS100 Result %LC	
1	100.4	
2	100.3	
3	100.4	
4	100.4	
5	100.2	
6	100.1	Average
7	100.2	100.2
8	99.7	St.Dev
9	100.0	0.2

Identity testing

Gel capsules with three different dose strengths were analyzed using the TRS100. Spectral data, which was acquired using the ContentQC software, was exported to the Solo chemometric software package for analysis. A PLS-DA classification model was built, as shown in Figure 7. The results indicate clear separation between gel capsules of different dose strengths, allowing them to be easily identified. Distinct clustering of the samples by dose strength demonstrates the suitability of the TRS100 for identification testing of soft gel capsules.

Implementation in pharmaceutical QC labs

This proof-of-concept study has shown that the TRS100 is a suitable candidate for CU, assay, and ID testing of soft gel capsules. Before being implemented in a QC lab environment, further testing would be needed. More samples would be required to ensure accuracy, precision, repeatability, and robustness per the lab's analytical method development guidelines. Also, a comparison study of the Raman method to the primary analytical method (usually HPLC) would be needed.

The TRS100 with ContentQC software and Solo chemometric software presents a complete solution that enables compliance. The software features include; secure logon, configurable user management and user permissions, plus a secure database and configurable backup functions.

Other functions of the Agilent ContentQC software are suited for the use in pharma QC environments. The reporting function allows CU, assay, and ID test results to be outputted into a single PDF report at the end of the measurement session. Data is saved in the secure database or can be configured to be sent to network locations or Laboratory Information Management System (LIMS).

Conclusion

Transmission Raman spectroscopy (TRS) can provide analysis of a range of pharmaceutical oral solid dose forms, including soft gel capsules.

The study has shown that the Agilent TRS100 Raman quantitative pharmaceutical analysis system is suitable for content uniformity, assay, and identity testing of soft gel capsules.

The method was fast, requiring only 10 seconds of measurement time, and no sample preparation, solvents, chemicals, or consumables were needed. Given the simplicity and speed of the method, the TRS100 provides an efficient, cost effective, and sustainable workflow for QC testing of soft gel capsules.

References

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