Application Note 410000046-A

QTRam® for Content Uniformity Analysis of Low-Dose Pharmaceutical Tablets

Compressed tablet is the most common form of orally administered drug. The United States Pharmacopeia (USP) chapter <905> requires that dosage uniformity of such products containing less than 25 mg or less than 25% active pharmaceutical ingredients (API) by weight must be analyzed for content uniformity, which is based on the assay of each API in a number of individual dosage units. Traditional wet chemistry methods such as titration or HPLC require complete dissolution of the tablets in suitable solvents, which destroy the samples, create waste, and can be labor intensive and time consuming. Vibrational spectroscopic techniques, notably NIR absorption and Raman scattering, are nondestructive, fast, and require no consumables. Transmission Raman Spectroscopy (TRS) is particularly promising due to its ability to sample a large portion of the sample's volume.

QTRam is a compact transmission Raman analyzer designed specifically for content uniformity analysis of pharmaceuticals in solid dosage forms. In this note, we use a model drug, acetaminophen, to demonstrate the capability of QTRam to quantify low concentrations of API in compressed tablets.

EXPERIMENTAL AND RESULTS

Acetaminophen, also known as paracetamol and APAP, is chosen as a model API in this study due to its availability and low toxicity. We target a hypothetical formulation of 1.5 mg API in a 300 mg tablet, i.e. 0.5% APAP w/w. Nine blends were prepared, and their concentration profiles in % w/w are listed in Table 1. Blends consisted of APAP, mannitol, silicified microcrystalline cellulose (MCC), croscarmellose (CMC), and magnesium stearate (MgSt).

The blended powders are compressed into round tablets of 10 mm diameter and 3.0 mm thickness, each weighing roughly 300 mg.

Table 1. Tablet blend concentrations in w/w/%

Blend ID	APAP	Mannitol	Silicified MCC	CMC	MgSt	Total
Blend 1	0.0	15.37	77.07	6.56	1.00	100.00
Blend 2	0.1	17.43	79.47	2.00	1.00	100.00
Blend 3	0.3	12.91	79.58	6.20	1.00	100.00
Blend 4	0.5	11.21	81.31	5.98	1.00	100.00
Blend 5	1.0	14.09	81.91	2.00	1.00	100.00
Blend 6	1.5	15.32	76.36	5.82	1.00	100.00
Blend 7	2.0	11.70	75.43	9.87	1.00	100.00
Blend 8	2.5	10.98	83.52	2.00	1.00	100.00
Blend 9	3.0	18.39	75.61	2.00	1.00	100.00

DATA COLLECTION

QTRam is used to measure transmission Raman spectra of the uncoated tablets. The interrogated sample area is 4 mm in diameter as set by the excitation and collection apertures. BWAnalyst, the 21 CFR pt 11 compliant software for QTRam, is used to collect all spectra. Each spectrum is an average of 10 scans, and each scan takes 3 seconds. Two or three spectra were acquired from each tablet sample. The unprocessed spectra are overlaid in Figure 1.

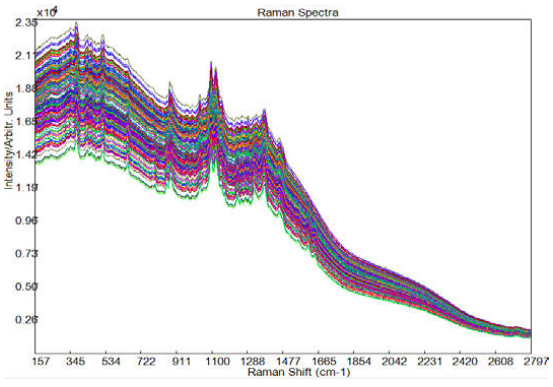


Figure 1. Unprocessed TRS spectra of the nine tablet blends collected by QTRam.

Figure 2 shows the spectra of a 3% API tablet, with the arrows colored in green, red, and blue, indicating isolated Raman peaks due to the APAP, MCC, and mannitol, respectively. Raman features from croscarmellose and magnesium stearate are too broad or weak to distinguish visually.

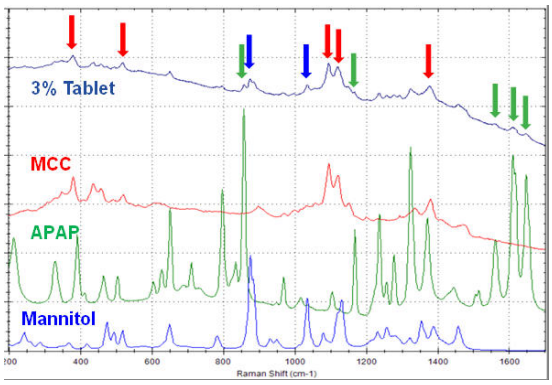


Figure 2. TRS spectrum of a 3% APAP tablet showing Raman peaks attributable to major ingredients.

CHEMOMETRICS

For quantification, partial least squares (PLS1) regression models are built using B&W Tek's chemometric software BWIQ. Assuming the API is distributed uniformly in the scale of the interrogated volume, we use the blend concentration as the reference for the individual tablets. Eight tablets are used from each blend, which should reduce the calibration error caused by unideal uniformity by way of averaging.

The preprocessing steps are:

- Savitzky-Golay first derivative;
- Manual region selection: 200 to 1700 cm^{-1};
- Standard Normal Variate normalization; and
- Mean centering.

We first built a survey calibration model using all 9 blends. This resulted in a root mean squared error of calibration (RMSEC) of 0.046% APAP w/w using 4 latent variables (LV). This gave us an indication that we can accurately quantify the API in a hypothetical formulation with a target concentration of 0.5% APAP w/w. To improve the model's performance, we narrow down the range to include only the blends up to 1.5%.

Figure 3a shows the calibration model using 4 LVs. The 4 LVs explain 94% of the X variance and nearly 100% of the Y variance, with a RMSEC and root mean squared error of cross-validation (RMSECV) of 0.022% and 0.027%, respectively. To test the model, the API of a number of tablets of the 0.5% and 0.0% concentrations are predicted and compared with the blend concentration, shown in Figure 3b. The root mean squared error of prediction (RMSEP) is 0.023%, with a very low bias of 0.008%. This gives a limit of detection (LOD) of 0.074%, and a limit of quantification (LOQ) of 0.23%, estimated as 3.3 and 10 times the RMSEP, respectively. The precision, calculated as the standard deviation of at least 6 runs of the same tablet, is 0.016% APAP w/w.

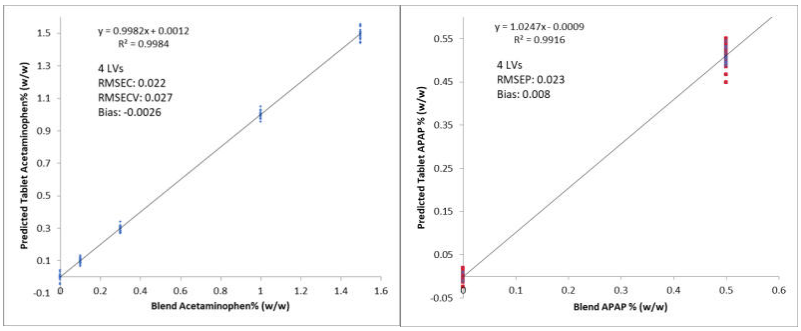


Figure 3. (a) Calibration model, and (b) results of validation.

CONCLUSION

The QTRam is capable of fast and accurate analysis for content uniformity of low-dose pharmaceutical tablets.

CONTACT

Metrohm Polska
ul. Centralna 27
05-816 Opacz-Kolonia
info@metrohm.pl