Application note

Real-time quantification and quality assessment of active pharmaceutical ingredients in hot-melt extrusion using process Raman spectroscopy

Authors

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Industry/Application:

Pharma PAT / Hot-melt extrusion

Products used:

Thermo Scientific™ MarqMetrix™ All-In-One Process Raman Analyzer, Thermo Scientific™ MarqMetrix™ Threaded BallProbe™ Sampling Optic, Thermo Scientific™ Pharma 11 Parallel Twin-Screw Extruder

Goals:

Demonstrate the real-time capability of process Raman spectroscopy to accurately quantify the concentration of active pharmaceutical ingredients (APIs) in a holt-melt extrusion process, and provide insight into quality assessment including the technique's interaction with polymers, polymorphism, and uniformity in hot-melt extrudate.

Key Analytes:

Acetaminophen and Soluplus®

Key Benefits:

- Real-time measurements of API concentration, distribution, degradation, interactions, and polymorphism are acquired with cost and time benefits achieved by eliminating laboratory analytics.
- Raman spectroscopy provides users with actionable feedback control capabilities for decision-making using real-time data.
- This analytical technique offers a reliable and nondestructive PAT platform for workflow automation.

Introduction

Hot-melt extrusion (HME) is an established pharmaceutical manufacturing technology used for improving drug solubility and bioavailability, controlled release, as well as taste masking and abuse deterrence. As part of Quality by Design (QbD), process analytical technology (PAT) is employed to ensure consistent product quality and process control. Raman spectroscopy was used in this study to monitor in real time not only the drug concentration but also critical quality attributes (CQA) such as solid-state forms (crystalline/amorphous) and drug-polymer interactions during HME. The data provided by in-line analysis enables immediate adjustments to the process by the feedback loop, ensuring optimal product quality. Consequently, this approach enhances the efficiency and reliability of the HME process, leading to improved pharmaceutical products. In this study, we demonstrate the integration of the Thermo Scientific™ MarqMetrix™ All-In-One Process Raman Analyzer with the Thermo Scientific™ Pharma 11 Parallel Twin-Screw Extruder (Figure 1). This integration enabled real-time quantification of acetaminophen concentration in Soluplus® matrix and provided insight into the dispersion uniformity and interactions of acetaminophen with Soluplus®, as well as the polymorphic state.

Methods

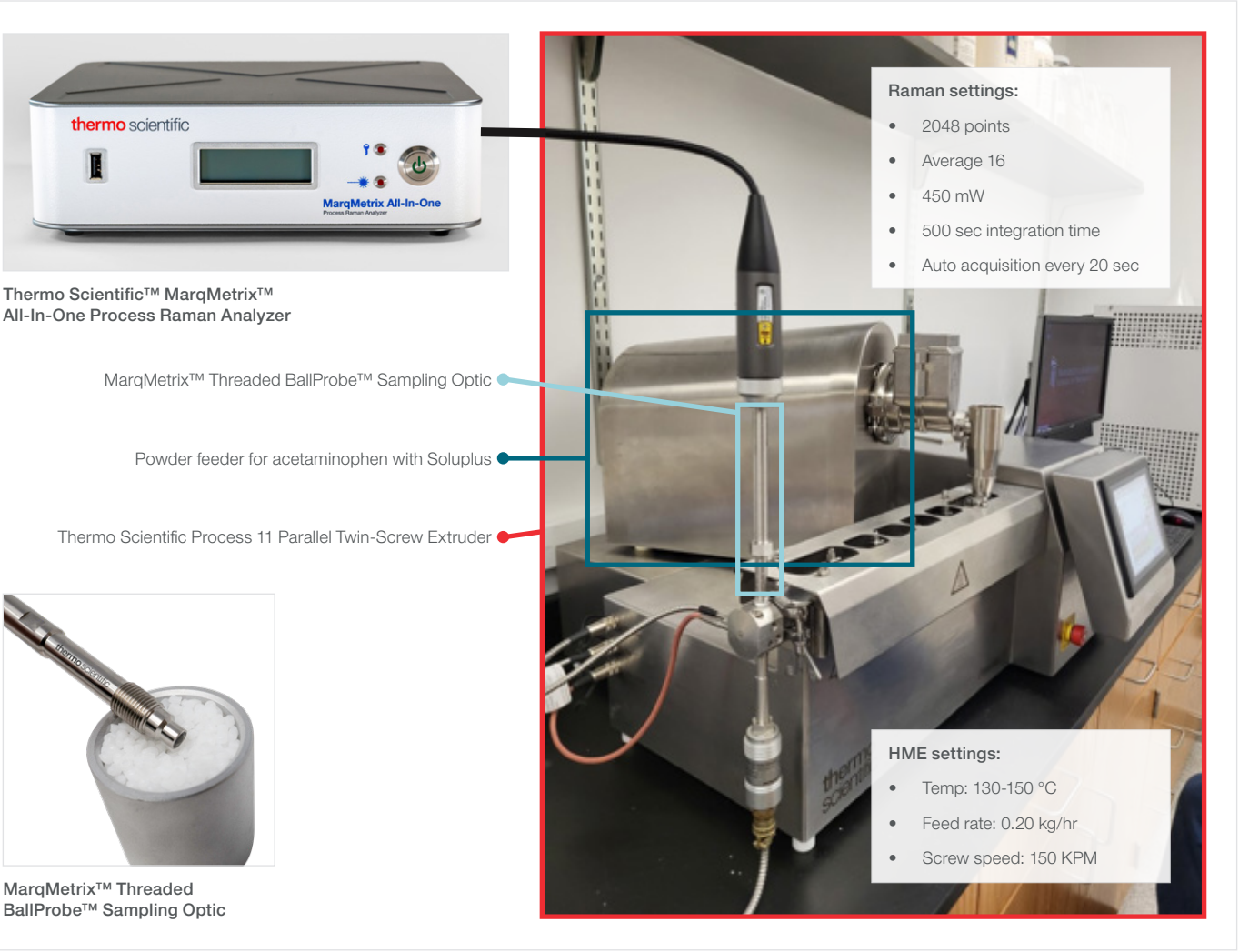

Figure 1. The Thermo Scientific MarqMetrix All-In-One Process Raman Analyzer and MarqMetrix Threaded BallProbe Sampling Optic, with the Thermo Scientific Pharma 11 Parallel Twin-Screw Extruder.

For this study, Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (PCL-PVAc-PEG)) was obtained from BASF and acetaminophen USP was used as supplied. Blends of acetaminophen in Soluplus®, prepared at concentrations of 0%, 10%, 20%, 25%, 40%, or 50% (w/w), were fed into the Pharma 11 twin-screw extruder under constant temperature, feed rate, and screw speed settings. Blends of 0%, 10%, 25%, and 50% were used for regression calibration while the 20% and 40% blends were used for validation. For consistency of experimental design, the HME conditions were held constant, which may not have been optimal for all formulations studied. All HME runs used a powder feed rate of 0.20 kg/hr, a screw speed of 150 RPM, and temperature held between 130-150 °C. The process Raman analyzer was coupled with the Thermo Scientific™ MarqMetrix™ Threaded BallProbe™ Sampling Optic, installed at the die recorded measurements at 24 second intervals. This sampling optic enabled in-line measurement during the extrusion process. The setup is shown in Figure 1. Spectra were acquired using a 450 mW laser power, 500 second integration time, and an average of 16 measurements per spectra, resulting in one spectrum every 16 seconds. Extrudate samples were collected every few minutes for offline assay by HPLC or UV-Vis spectroscopy. The Raman spectra were pre-processed and correlated to the reference values through a Partial Least Squares (PLS) regression model. The acetaminophen form and interactions were determined by spectral subtraction of the Soluplus® features and comparison of the resulting spectra with reference spectra of the various forms of acetaminophen. The Raman spectra of the amorphous and three crystalline forms of acetaminophen differ, allowing for the estimation of the amounts of amorphous form present.[1]

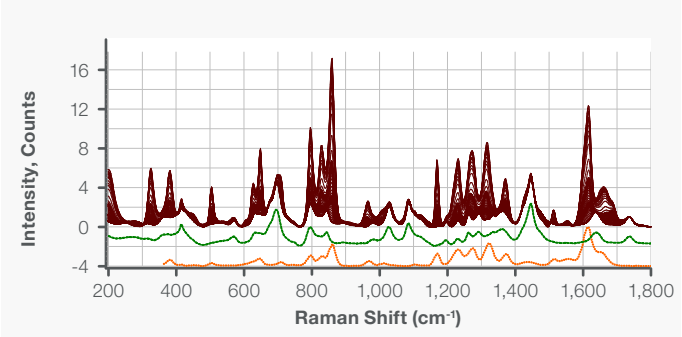

Figure 2. Fingerprint region of Raman spectra collected during a HME run where the acetaminophen concentration was varied from 0%, 10%, 25%, and 50% (w/w). Reference spectra (dotted) for amorphous acetaminophen1(red) and Soluplus® (green) are shown for comparison.

To gain insight into the electronic interaction of amide I region of acetaminophen in the dispersed phase within the Soluplus® matrix, Raman spectra of 0 %, 20%, and 44 % (w/w) blends of acetaminophen in Soluplus® were baseline-removed using an Automatic Whittaker filter (lambda = 1000, asymmetry =0.001). The spectral region of approximately 1500 to 1850 cm^{-1} was selected. The selected region was deconvoluted into individual peaks by fitting it with Gaussian functions with an initial guess of full width at half maximum (FWHM) of 8 cm^{-1}, noise defined by the standard deviation in the region 1780 to 1830 cm^{-1}, and peak positions as negative peak observed in the Savitzky-Golay filter (order = 2, window width = 9, derivative = 2nd) transformation. Global optimization was performed to optimize peak position, width, and height to minimize the residual between observed and fitted data that was used as loss function for defining the convergence. The data management and preprocessing calculations were done using Python and SOLO 9.3.1 software package (2024, Eigenvector Research, Inc., Manson, WA, USA 98831). The peak deconvolution work was performed using Python programming and replicated with the Thermo Scientific™ OMNIC™ Software Suite.

Results

A PLS regression model was developed for the quantification of acetaminophen concentration. Raman spectra were collected in-line with the addition of blends of 0%, 10%, 25%, and 50% (w/w) acetaminophen in Soluplus®. The Raman spectra displayed clear changes in peak intensities corresponding to different acetaminophen concentrations (see Figure 2).

Samples were collected for high-performance liquid chromatography (HPLC) analysis every two to three minutes during the HME run. HPLC confirmed there was no degradation of the acetaminophen. It also provided calibration data for the Partial Least Squares (PLS) regression model. The PLS model showed good agreement between Raman predictions and HPLC results using two latent variables (RMSEC=0.5%, RMSECV=0.7%, R^2_{Cal}=0.998) as shown in supplementary information (Figure S1).

The model was then used to predict the concentration of acetaminophen during a second HME run after adding 20% and 40% acetaminophen blends. UV-Vis results of the collected samples were used to validate the model. The measured values were in good agreement with the Raman predictions with a standard root mean square error of prediction (RMSEP) of 1.4% as shown in Figure 3. In addition, the frequent data and accurate model predictions from in-line Raman analysis effectively tracked the progress of mixing, from the addition of acetaminophen to reaching the equilibrium state.

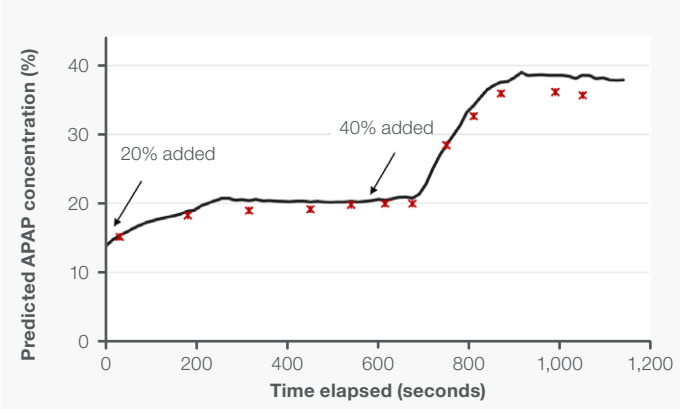

Figure 3. Acetaminophen concentration prediction by Raman spectroscopy during validation run of hot-melt extrusion of 20% and 40% acetaminophen in Soluplus®. Offline determinations by UV-Vis are indicated by *. The RMSEP was approximately 1.4%.

Spectral subtraction confirmed that acetaminophen remained in the amorphous state in the die throughout the process. The Raman features of Soluplus® were subtracted from selected spectra of the calibration run by scaled subtraction. A comparison of the subtracted spectra to the spectra of pure amorphous and crystalline forms of acetaminophen shows very good agreement with the amorphous form for all three concentrations (see Figure 4).

The positions and shape of the amide I band (symmetric C=O stretch) of acetaminophen near 1650 cm^{-1} show significant differences when comparing the 10%, 25%, and 50% blends and pure amorphous forms (see Figure 4). In the presence of Soluplus®, the amide I band of acetaminophen shifts to higher Raman shifts (lower energy). This suggests that the carbonyl (C=O) functional group of acetaminophens is involved in hydrogen bonding or dipole-dipole interactions with itself or Soluplus®. To better understand these interactions, the Raman spectra collected during the HME process for approximately 0%, 20%, and 44% w/w blends of acetaminophen in Soluplus® were deconvoluted using a Gaussian function over the spectral range of 1500 to 1850 cm^{-1}. The results are shown in Figure 5 and summarized in Table 1.

The 0% acetaminophen sample serves as the negative control, showing only the Gaussian fits for the Raman signature of Soluplus®. Four noticeable peaks for Soluplus® were resolved at approximately 1551 cm^{-1}, 1606 cm^{-1}, 1637 cm^{-1}, and 1736 cm^{-1} (red arrows in Figure 5). In the presence of 20% or 44% acetaminophen, three distinct peaks appeared at approximately 1618 cm^{-1}, 1668 cm^{-1}, and 1687 cm^{-1} (green arrows in Figure 5). The 1618 cm^{-1} peak is attributed to the aromatic ring (symmetric C=C stretch) and showed no appreciable shift in position compared to pure amorphous acetaminophen. The 1668 cm^{-1} and 1687 cm^{-1} peaks are attributed to the symmetric stretching of the carbonyl in the amide I bond. As mentioned above, the amide I peak of pure acetaminophen appears at 1650 cm^{-1}. The red shift of the amide I peak to higher Raman shift regions (lower energy) indicates the presence of interactions between acetaminophen and Soluplus® or other acetaminophen molecules. The presence of two amide I peaks in the acetaminophen-Soluplus® melts suggests that acetaminophen exists in two discrete environments.

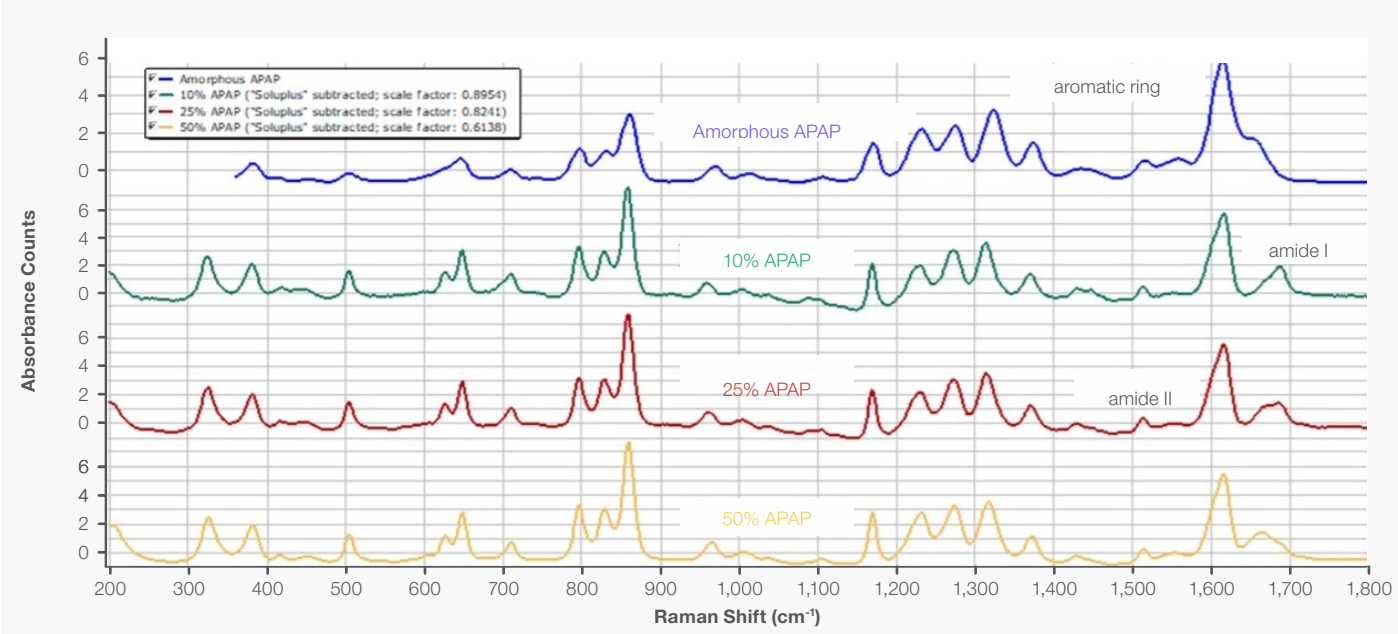

Figure 4. In-line HME Raman spectra of 10% (b), 25% (c), and 50% (d) melts of acetaminophen in Soluplus® with Soluplus® peaks removed by scaled subtraction of the Raman spectrum of Soluplus®. Spectra are compared with the Raman spectrum of the pure amorphous form of acetaminophen (blue trace).[1]

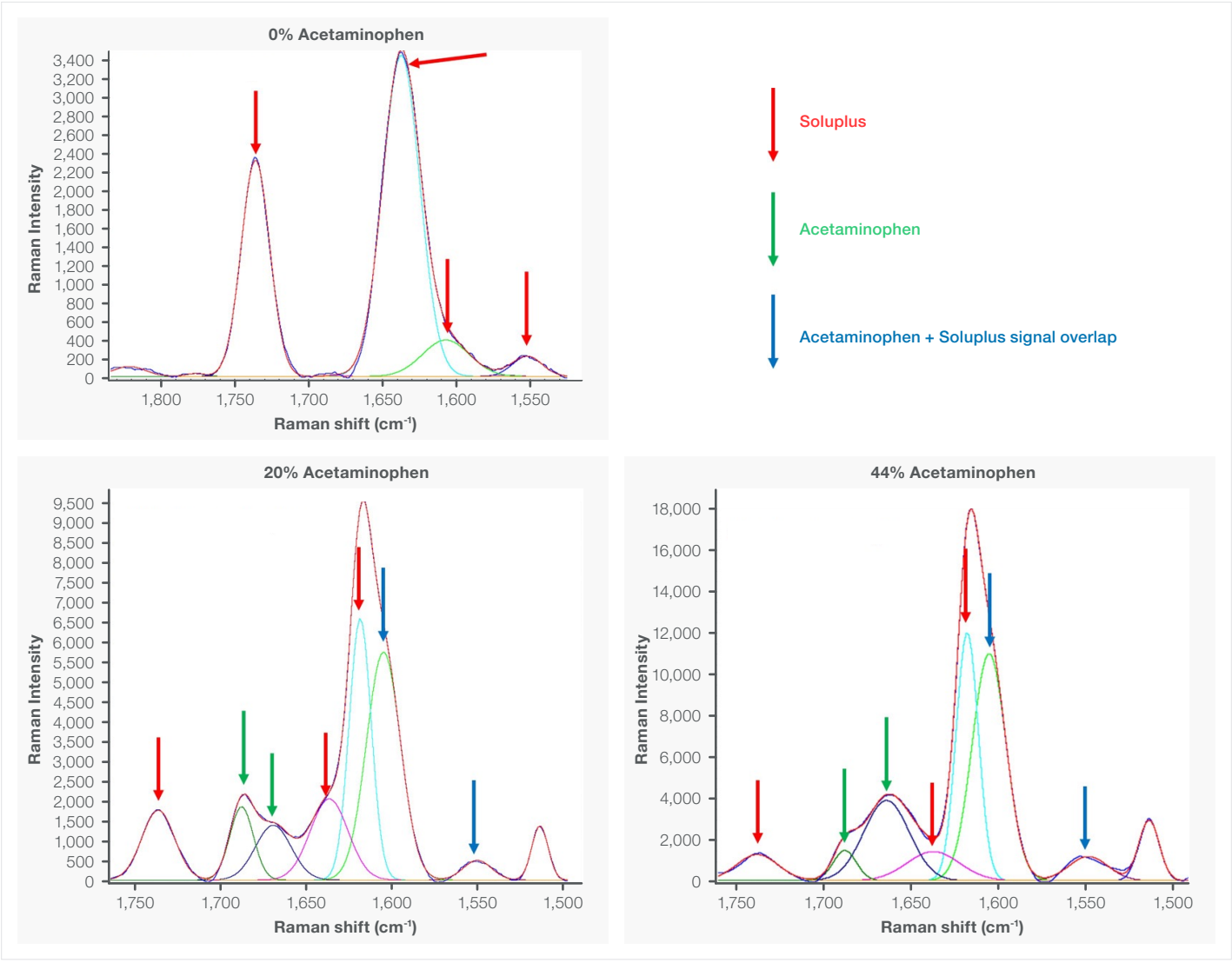

Figure 5. The peak deconvolution of Raman spectra for 0%, 20%, and 44% acetaminophen samples. Red arrows indicate peaks for Soluplus®, green for acetaminophen, and blue for overlapping peaks. The increase in the 1668 cm^{-1} peak area with higher acetaminophen concentration is associated with acetaminophen-acetaminophen interactions. The decrease in the 1687 cm^{-1} peak area with lower Soluplus® concentration is linked to acetaminophen-Soluplus® interactions. Detailed interaction analysis is beyond the scope of this work.

These interactions can be decoupled using the peak area data shown in Table 1. In these experiments, the mixture consists solely of Soluplus® and acetaminophen, summing up to 100%. When acetaminophen concentration increases, Soluplus® concentration decreases. An increase in acetaminophen concentration from 20% to 44%, or a decrease in Soluplus® concentration from 80% to 56%, results in an increase in the peak area of the 1668 cm^{-1} peak while the peak area of the 1687 cm^{-1} peak decreases. The results indicate that the 1668 cm^{-1} peak is proportional to the acetaminophen concentration and can be assigned to the population of acetaminophen molecules engaged in acetaminophen-acetaminophen interactions. The peak full width at half maximum (FWHM) also increased with acetaminophen suggesting a heterogenous interactions. Similarly, the 1687 cm^{-1} peak is proportional to Soluplus® concentration, and can be assigned to the population of acetaminophen molecules engaged in acetaminophen-Soluplus® interactions.

0% Acetaminophen					
Peak	**Peak Type**	**Center X**	**Height**	**FWHM**	**Area**
1	Gaussian	1551.775	215.9189	23.5615	5415.331
2	Gaussian	1606.999	390.3034	37.3379	15512.6
3	Gaussian	1637.312	3441.944	29.6903	108780.5
4	Gaussian	1736.161	2318.571	22.7029	56031.78
20% Acetaminophen					
1	Gaussian	1549.612	496.6129	19.4898	10302.86
2	Gaussian	1604.476	5741.272	23.4581	143361.6
3	Gaussian	1618.092	6586.736	15.1464	106197.1
4	Gaussian	1636.271	2043.859	25.9974	56560.53
5	Gaussian	1668.977	1379.627	24.5931	36116.58
6	Gaussian	1687.497	1845.965	16.1911	31814.99
7	Gaussian	1736.282	1759.316	22.4673	42075.24
44% Acetaminophen					
1	Gaussian	1548.268	1165.003	26.3746	32707.4
2	Gaussian	1605.238	10997.85	22.8078	267007.3
3	Gaussian	1617.815	12025.42	14.904	190780.5
4	Gaussian	1637.302	1404.451	35.4067	52970.45
5	Gaussian	1664.195	3877.147	30.7406	126869.2
6	Gaussian	1688.137	1462.164	15.5566	24212.74
7	Gaussian	1738.409	1261.208	28.0617	37673.23

Table 1. Results of peak deconvolution using Gaussian function.

Further details of the interactions, such as the details of molecular interactions, order of reaction, linear or nonlinear response, kinetic, and thermodynamic parameters, can be measured with more kinetic data using Raman spectroscopy, which is beyond the scope of this work.

Conclusions

The process Raman analyzer, combined with a chemometric regression model, accurately predicted acetaminophen concentration, enabling real-time process monitoring during production. The results confirmed that acetaminophen remained in an amorphous state throughout the HME process, with no observable transition to crystalline forms, ensuring consistent product quality. Additionally, insights into API-polymer interactions were derived from the Raman spectra. This underscores process Raman as a powerful PAT tool for the pharmaceutical industry.

References

1. J.F. Kauffmana, L.M. Batykeferb, D.D. Tuschelb, J. Pharm. Biomed. Anal. 48 (2008) 1310-1315.

Supplementary Information

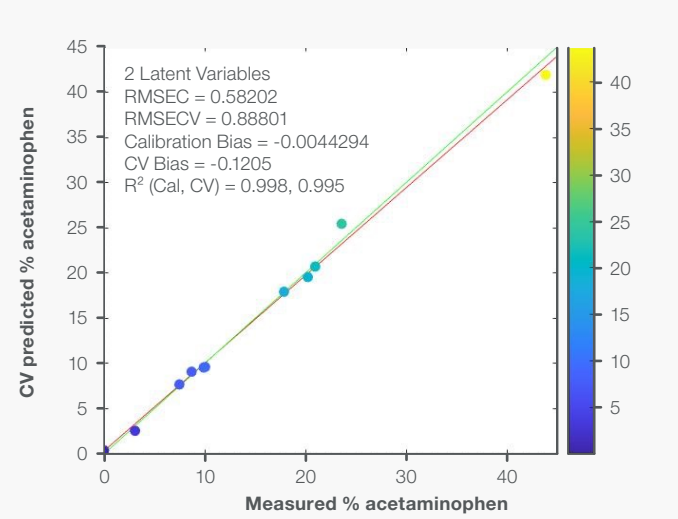

Figure S1. Correlation plot between measured acetaminophen using HPLC and predicted concentration during cross-validation of the PLS calibration model. The model statistics are shown in the figure inset.

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