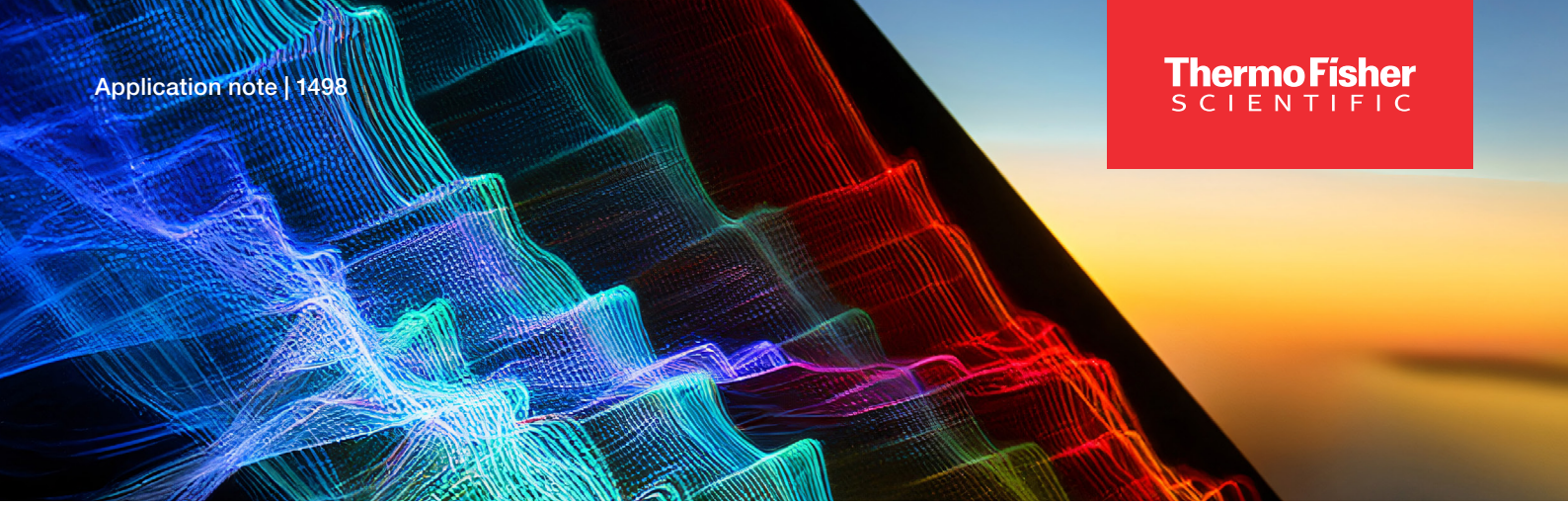

Using the Thermo Scientific MarqMetrix All-In-One Process Raman Analyzer for real-time monitoring of a hot-melt extrusion process

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Summary

The use of class IV active ingredients in the pharmaceutical industry requires different processing methods due to the poor solubility of molecules in this class. Hot-melt extrusion (HME) is used here, which helps to bring these active ingredients into solution in a polymer matrix and thus significantly increase their release in the subsequent dosage form.

Raman spectroscopy can be a helpful tool in this process to obtain important data from the extrusion. The technique enables online process monitoring by providing real-time data relating to chemical composition, crystallinity and homogeneity of the material during extrusion. Analysis by a system like the Thermo Scientific™ MarqMetrix™ All-In-One Process Raman Analyzer can improve control by monitoring of critical quality characteristics such as distribution and polymorphism of the active ingredient. Raman spectroscopy also supports compliance with GMP guidelines and other regulatory requirements by providing detailed and reproducible data.

Here is a non-exhaustive list of reasons in favor of using Raman spectroscopy as a PAT (Process Analytical Technology) in extrusion:

- Raman analysis provides fast information in real time.
- Multiple analyses can be performed per scan (API content, moisture, crystallinity, etc.).
- No sample preparation is required, so no waste is generated.
- The technique is non-invasive; neither sample nor process are affected by the measurement.
- The instrument is easy to operate and robust, showing resistance to chemical and physical degradation.
- The point of analysis and the base device can be separated by a fiber optic cable, which creates flexibility.

Background

In the pharmaceutical industry, it is important to monitor and document all process steps. As a rule, product inspections are conducted after the individual production steps, i.e., when the material has already been manufactured. Raman spectroscopy makes it possible to observe the process online in the course of production and correct it, if necessary, before a faulty batch occurs.

Experiments and results

Experimental setup

A model API was incorporated into a polymer matrix at different concentrations using a Thermo Scientific™ Pharma 11 Twin-Screw Extruder. (Figure 1). Two gravimetric feeders were used to feed API and polymer separately into the twin-screw extruder and maintain a consistent total feed rate. The spectra of the extrudate were measured and recorded in the die at the end of the process using a Thermo Scientific MarqMetrix All-In-One Process Raman Analyzer equipped with a ball probe sampling optic extruder probe (Figure 2). The probe was connected to the outlet of the extruder die. The data obtained were used to calculate a model to determine the concentration of API in the melt online during the process.

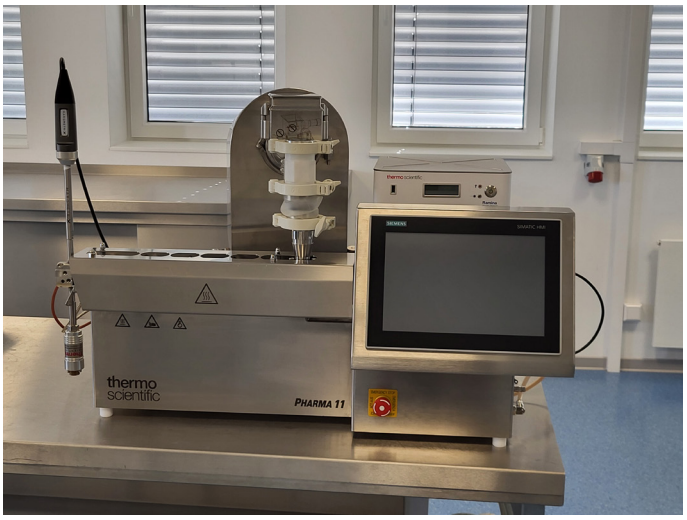

Figure 1. Setup of Thermo Scientific Pharma 11 twin-screw extruder with gravimetric feeder and Dynisco extruder probe (Figure 2) in the die body to connect to the MarqMetrix All-In-One Process Raman Analyzer

Figure 2. Ball probe sampling optic extruder probe, used to connect the extruder with MarqMetrix All-In-One Process Raman Analyzer

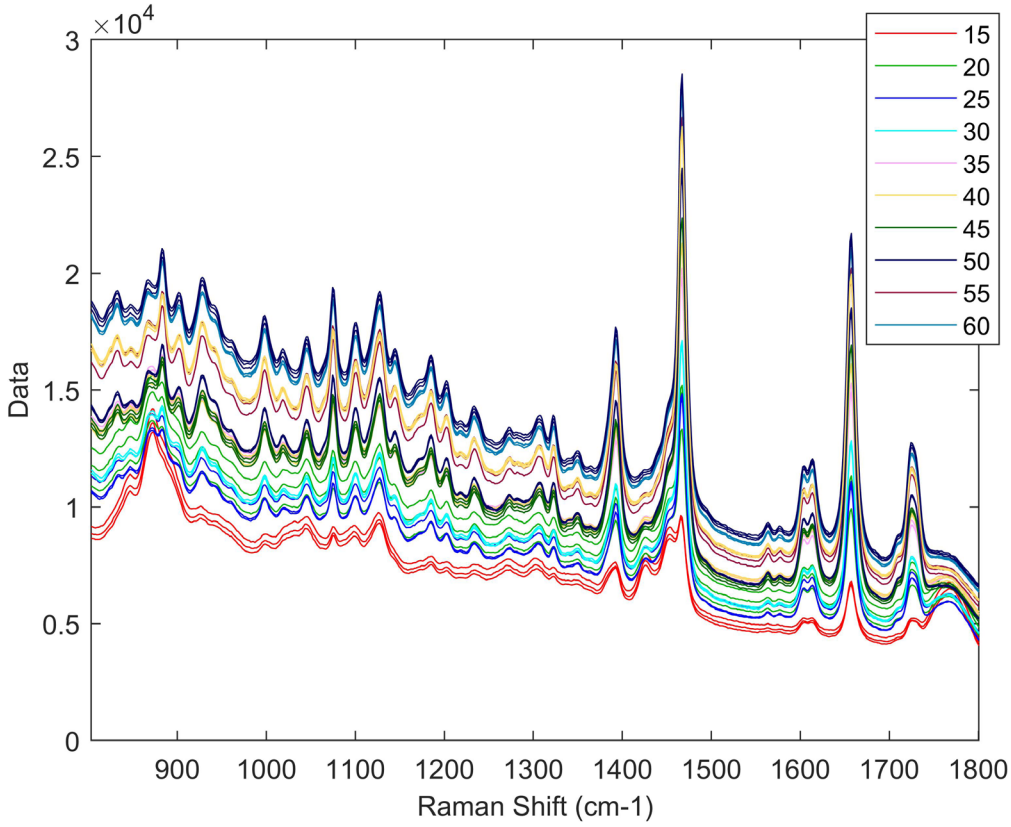

Figure 3. The Raman spectroscopic data were collected using the MarqMetrix All-In-One Process Raman Analyzer.
The data were recorded at one-minute intervals throughout the entire crystallization process. The plotted spectra in the analysis focus on the region between 800 and 1800 cm-1, as this range contains predominant features from both the polymer and the API. This specific spectral region provides valuable information about the API concentration during the hot-melt extrusion process.

The feed rates of polymer and API were adjusted to achieve an API concentration of 15 to 60% during extrusion at a constant throughput. After each adjustment, measurements were paused for four minutes, until a new equilibrium was reached in the extruder. Once equilibrium was achieved, new measurements were resumed with the Raman analyzer.

A continuous monitoring mode with an integration time of 800 ms, 10 mean values and a laser power of 300 mW was used. Each scan lasted 16 seconds per analysis.

Samples of the extruded material for a HPLC analyses were collected in parallel to the measurements with the Raman analyzer. Each pellet had a size of 1 mm x 1 mm. The time of sampling was recorded and correlated with the Raman spectra.

HPLC measurement and results

In order to verify the actual API content in the extrudate and to correlate the results with the Raman spectra, the test samples were analyzed using HPLC. Two analyses were carried out per measuring point, one with 2 mg and one with 30 mg of extrudate. The results were similar, indicating a homogeneous composition of the samples. A discrepancy was found between the dosed amount of API and the actual content, particularly for the lowest and highest concentrations of active ingredient. The deviations between the dosed quantity and the actual quantity determined using HPLC can be explained by the extremely low dosing rate of 24 g/h for the low concentration and by the limited quantity of active ingredient for the high dosing. However, since the focus here was on the measurement of extruded product with a Raman spectrometer and the application with HME, this aspect was not evaluated further.

Table 1. API concentrations in the feeding and the results from the HPLC measurements

Sample #	Polymer (g/h)	Polymer (%)	API (%)	API (g/h)	Time stamp (h:min:sec)	Double check (g/h)	1st round HPLC result (api%)	2nd round HPLC result (api%)
1	136	85	15	24	13:34:03	160	12	13
2	128	80	20	32	13:39:25	160	22	22
3	120	75	25	40	13:44:21	160	28	30
4	112	70	30	48	13:48:50	160	32	33
5	104	65	35	56	13:53:29	160	38	39
6	96	60	40	64	13:57:41	160	38	38
7	88	55	45	72	14:02:02	160	44	45
8	80	50	50	80	14:06:49	160	49	51
9	72	45	55	88	14:10:27	160	52	54
10	64	40	60	96	14:14:14	160	50	51
Test 1	80	50	50	80	14:18:26		50	51
Test 2	96	60	40	64	14:22:13		44	45
	Start: 13:28:58							
	End: 14:23:37						n = 5	n = 3
							Sample weight ~ 2 mg/sample	Sample weight ~ 30 mg/sample

Spectral data analysis and model development

Using the spectra recorded during the extrusion process, two initial quantification models were developed based on the two HPLC data sets (see Figures 4 and 5).

The selected spectral range was from 800 to 1800 cm-1 and the pre-processing methods included 1st derivative (order: 2, window: 15 pt, tails: polyinterp), SNV and mean centering.

The calibration set for the model calculations included the ten samples with different API concentrations and was compared with the two test approaches (50% and 40% API).

The partial least squares (PLS) method was used to develop the calibration models. The two initial models performed well, with the model from the first HPLC round slightly outperforming the model from the second HPLC round in terms of lower root mean square error (RMSE) values for calibration (C), cross-validation (CV) and prediction (P). These models need to be validated with new, unknown data sets before they can be used.

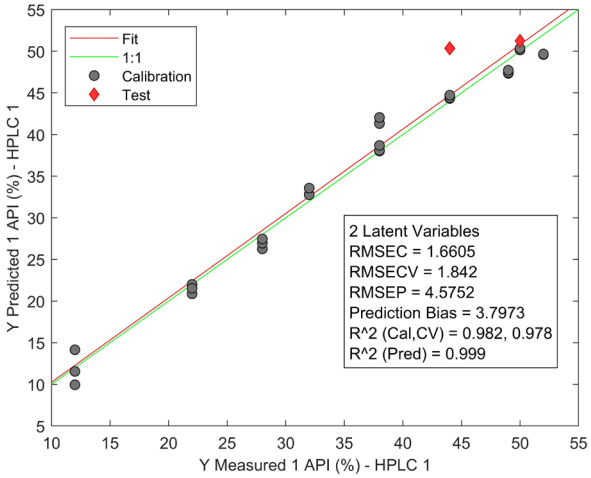

Figure 4. Model development calculated from first round of HPLC results.

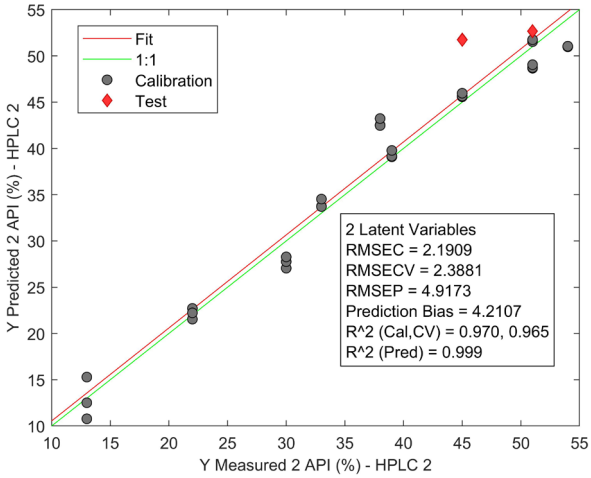

Figure 5. Model development calculated from second round of HPLC results.

Conclusion and impact

This study demonstrates the feasibility of real-time monitoring during the hot-melt extrusion process for pharmaceutical products. The measurement is non-contact and non-destructive, and if necessary it can be performed at a certain distance from the product for safety reasons by using a probe.

Online measurement was demonstrated to offer key advantages, including complete documentation of the concentration of active ingredients in the product. With the MarqMetrix All-In-One Process Raman Analyzer, this information is automatically compiled and saved, thereby fulfilling regulatory requirements. Perhaps even more importantly, the rapid analysis provided by process Raman spectroscopy makes it possible to intervene in the production process if deviations are detected, which could ultimately prevent losses caused by faulty batches.

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