Application Note: 51836

Monitoring the Output of Pharmaceutical Hot Melt Extruders with Near-infrared Spectroscopy

Thomas Chirkot, Thermo Fisher Scientific, Somerset, NJ, USA
Sheelagh Halsey, Thermo Fisher Scientific, Hemel Hempstead, UK
Alan Swanborough, Thermo Fisher Scientific, Stone, UK

Key Words

- Antaris
- API
- Extruder
- Formulation
- Hot Melt Extrusion
- Near-infrared

Introduction

Recent drug discovery has been characterized by high throughput screening technologies that make a wide variety of candidates available. Although the number of new drugs available is great news in a therapeutic sense, it has drawbacks in that many of the new chemical entities have solubility issues. This can lead to problems with formulation with regard to the bioavailability of the active pharmaceutical ingredient (API).

Overcoming these issues is of prime importance to maintaining a healthy pipeline of new drug substances. One solution is through novel formulation techniques such as hot melt extrusion (HME). Using the HME technique, the drugs are combined with thermoplastic polymers at temperatures in the general range of 50 to 180 °C. The extruder can be set to different temperatures and has several sections that may be configured for different functions of melting, mixing, sequential addition of formulation constituents and vacuum venting.

Currently the use of HME is increasing due to a number of advantages:

- Formulation of products with improved solubility and bioavailability, thus reducing dosing intervals for the patient.
- Formulations allow taste masking of APIs
- The continuous technology is reproducible avoiding batch-to-batch variability.
- As a continuous process, it allows lower cost manufacturing due to reduced operation steps and smaller volumes of materials in use.
- Creates thermodynamically stable solid solutions which can deliver improved temperature and mechanical stability of the product.
- Amenable to in-line monitoring

Understanding the interactions between formulation characteristics and the extruder mechanisms is important to process efficiency. This note shows some basic research on the influence of screw speed and the throughput rate on the blend uniformity of an extrudate.

The use of near-infrared (NIR) spectroscopy for the analysis of active ingredients in pharmaceutical formulations is well known. Increasingly, with the advent of process analytical technology (PAT) and quality by design (QbD), NIR is being used to monitor processes on-line or in-line due to its unique advantages. The technique is non-destructive, has excellent signal-to-noise ratios and can use fiber optics to take sampling to the process. NIR spectroscopy is an ideal choice to monitor the output of a hot melt extruder.

Experimental

This work was carried out using a Thermo Scientific PRISM Pharmalab 16 HME twin screw extruder (Figure 1). These pictures show the equipment and how all the product contact parts of the extruder can be dismantled, allowing thorough cleaning away from the extruder. Because the barrel is split, every part can be thoroughly inspected for cleanliness (Figure 2).

Figure1: Pharmalab extruder

Figure 2: Extruder with all process contact parts removed

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NIR spectra were collected with a Thermo Scientific Antaris FT-NIR instrument equipped with an extruder probe (Figures 3-5). This probe is designed to take reflectance measurements of the extrudate and can be used in processes up to 300 °C. Transmission probes are also available for measuring clear extrudates.

The probe was fitted directly into the output die of the extruder, so that product could be monitored in real time (Figure 6). The analysis conditions used were: scan range 4000-10000 cm^{-1} using 8 cm^{-1} resolution with 32 scans averaged giving an analysis time of approximately 15 seconds. The analyzer was run with continuous spectral acquisition, so that repeatability data could be collected for each experiment.

The analyzer was calibrated with a range of ibuprofen between 2.5 and 10% using a fixed flow rate of 1 kg/h and screw speed of 200 rpm. Thermo Scientific TQ Analyst software was used to develop a partial least squares (PLS) calibration. To develop the calibration, spectra were collected for the individual ingredients. (Figure 7).

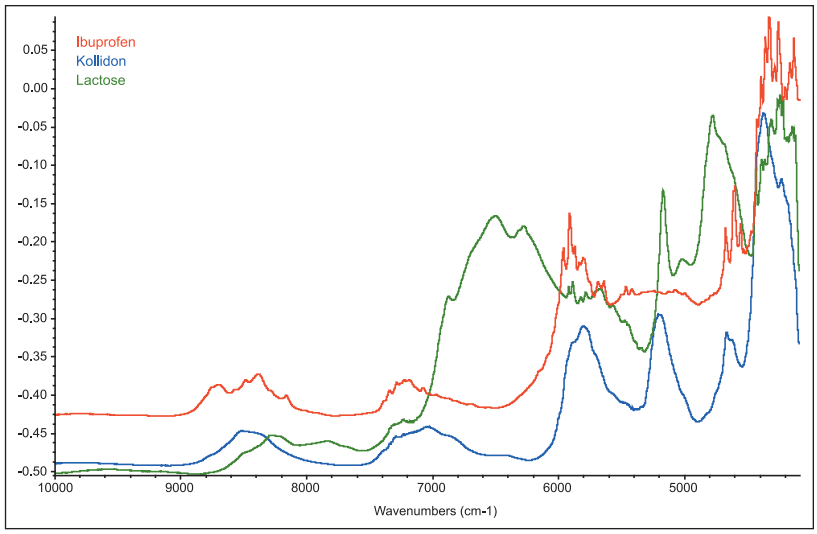


Figure 7: Individual spectra of ingredients

The spectra were converted to second derivative, prior to calibration development, to enhance the peak shape and separation (Figure 8). No specific unique peak was found for the ibuprofen, but three regions were identified that showed useful information.

The calibration obtained for ibuprofen showed a good correlation 0.992 and an acceptable error of 0.4%. (Figure 9).

The principal component (PC) score plots for spectra with the same process conditions with only the ibuprofen concentration changing is shown in Figure 10. The plot shows that the first PC describes the change in ibuprofen content very well.

The size of the ellipses for each concentration are very similar which shows that there is no extra variation not attributed by the concentration differences. This demonstrates that the first factor in the calibration is mainly describing the change of concentration of the ibuprofen.

Figure 3:
Antaris MX FT-NIR
process analyzer

Figure 4: Extruder probe

Figure 5: Extruder probe detail

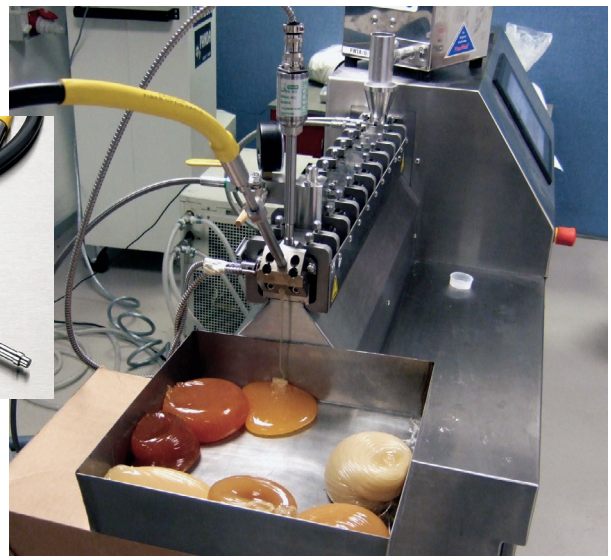


Figure 6: Probe fitted to output die of Pharmalab 16 HME

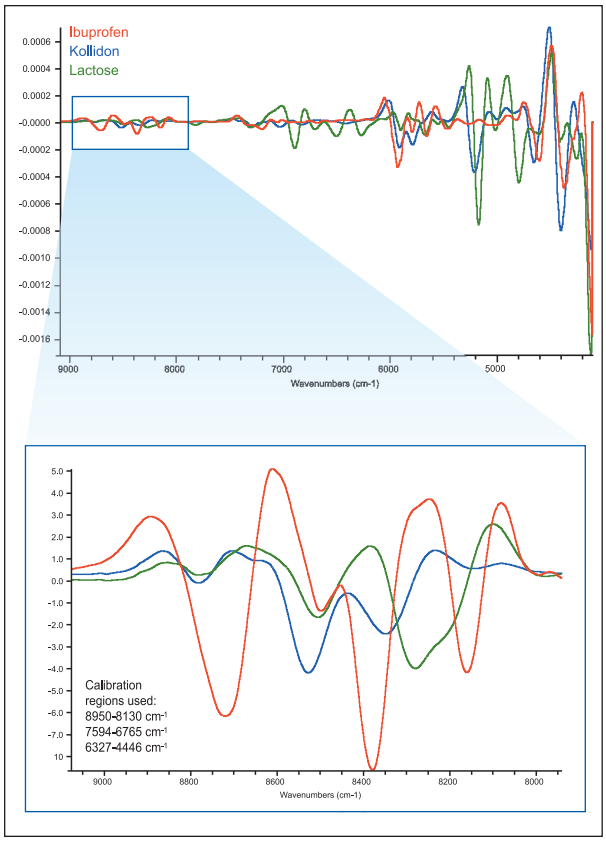


Figure 8: Second derivative spectra of ingredients

A 3^2 factorial design was constructed to evaluate the influence of changing the screw speed and the feed rate on the blend uniformity of the extrudate. The screw speed rates were 200, 400 and 600 rpm. The feed rates used were 1, 1.5 and 2 kg/h. The extruder was run at 160 °C at the output die. The formulation consisted of 5% ibuprofen and 95% Kollidon®/lactose (95/5 g ratio). Individual runs were processed for approximately 15 minutes, and the first 10 spectral readings were discarded to account for start-up instability. The remaining data (about 30 for each run) were compiled and an RSD value was calculated for each condition. Analysis of variance techniques ($\alpha = 0.05$) were utilized to test for the significance of the factors of influence on the response variable.

Results

Each experiment was monitored with the calibration developed; a typical output is shown in Figure 11. The readings vary for a few minutes until the new process conditions stabilize, then the predictions settle to a stable value.

Figure 12 shows the PC score plots for spectra with the 5% ibuprofen with the process conditions changing. The major variable is the change of rpm along the first PC score. The sample ellipses are smaller at low rpm than at high rpm, which means the higher rpm introduces more variability into the spectra. There is also a smaller variation in the spectra due to feed rate along the second PC score.

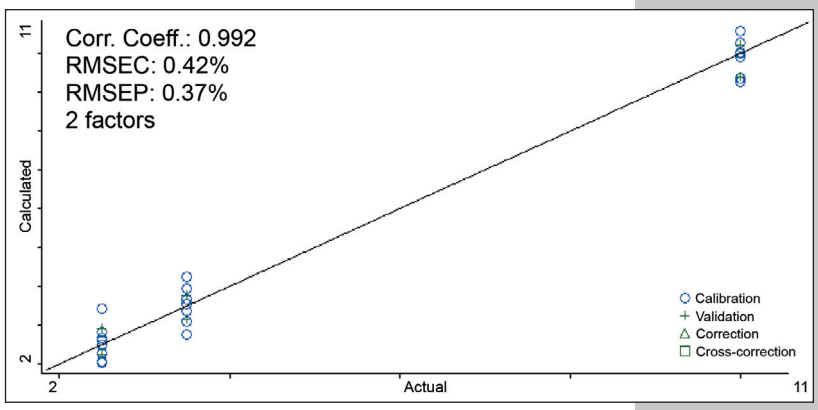


Figure 9: Ibuprofen calibration at 1 kg/h flow rate and 200 rpm screw speed

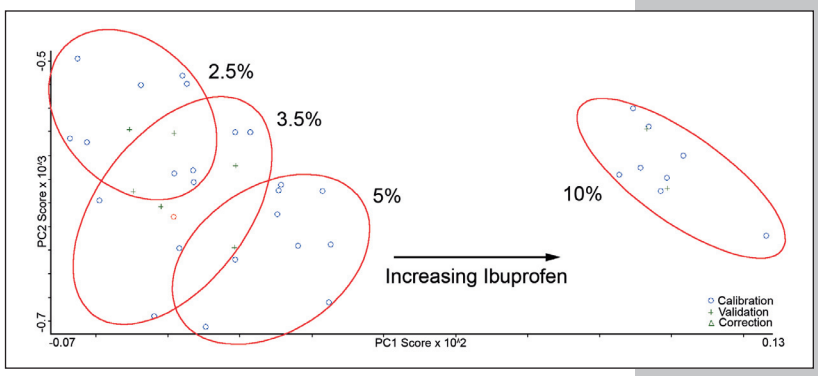


Figure 10: PC score plots for ibuprofen calibration

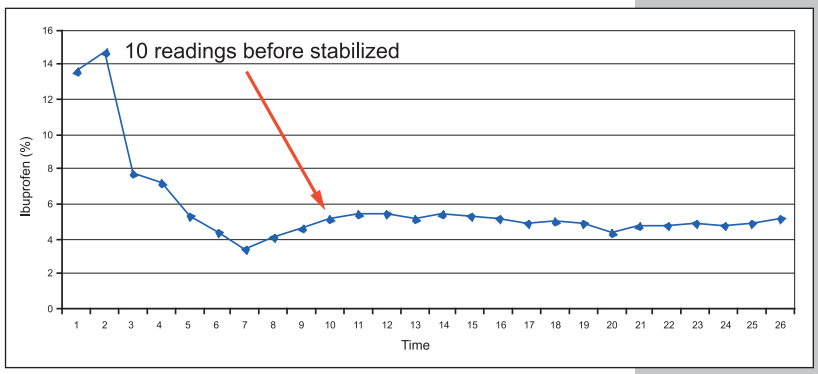


Figure 11: Ibuprofen predictions of extruder run

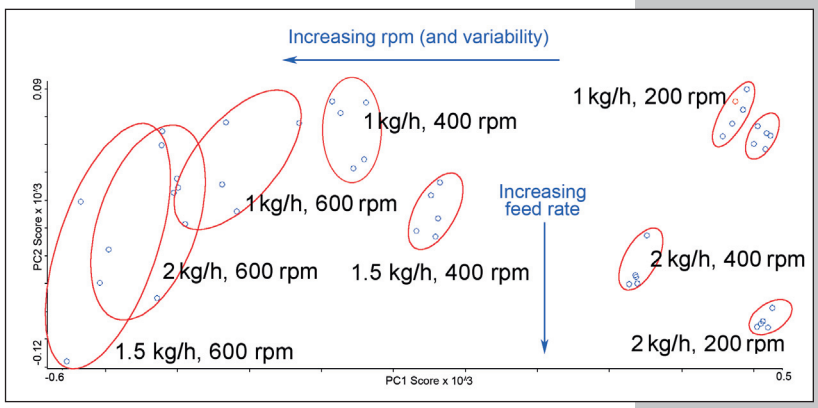
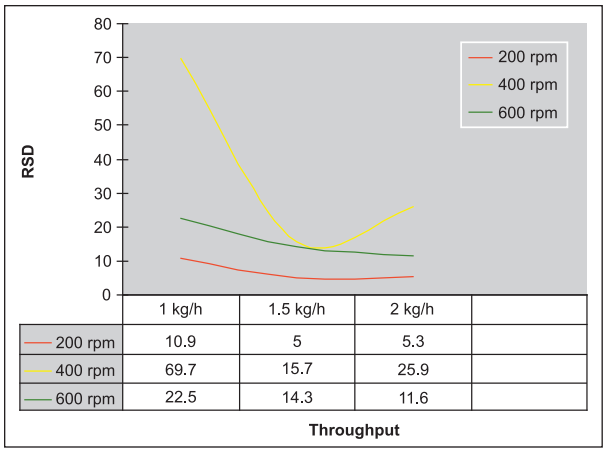
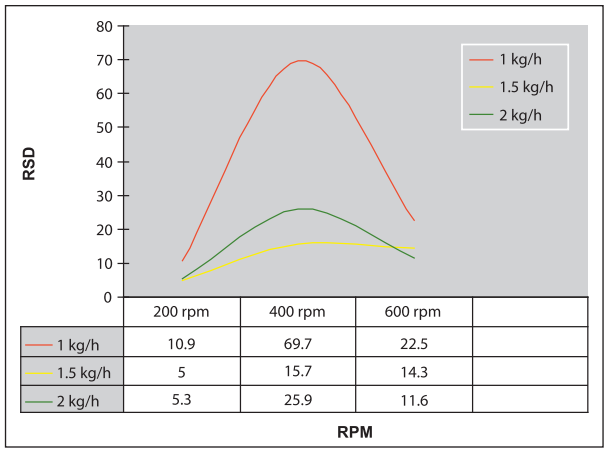


Figure 12: PC score plots for ibuprofen concentration with different process conditions



	1 kg/h	1.5 kg/h	2 kg/h
200 rpm	10.9	5	5.3
400 rpm	69.7	15.7	25.9
600 rpm	22.5	14.3	11.6

Figure 13: RSD plots with changes in screw speed



	200 rpm	400 rpm	600 rpm
1 kg/h	10.9	69.7	22.5
1.5 kg/h	5	15.7	14.3
2 kg/h	5.3	25.9	11.6

Figure 14: RSD plots with changes in feed rate

These data show that the NIR system is sensitive to processing conditions of the extrudate. Process conditions would normally be standardized for a particular product, so the change in spectral response at different screw speeds should not be an issue. However, these data also show the potential for the NIR technique to optimize process conditions without referring to reference methods. For example, processing conditions could be chosen with regard to the least sample-to-sample spectral variability.

The relative standard deviation (RSD) was calculated on the stabilized predicted values for each process condition. A plot of these values with changes in screw speed and feed rate is shown in Figures 13 and 14. In general, the 200 rpm and 1.5 kg/h experiments showed the least variability of predicted ibuprofen.

A statistically significant relationship was established for the influence of screw speed and feed rate on the blend uniformity of the extrudate. The calculated RSD values showed that 2 of the 9 conditions met the generally accepted pharmaceutical criterion for RSD of 6% or less. The RSDs ranged from 5.0 to 69.7%. A purely quadratic relationship was noted for the influence of screw speed on the blend uniformity. The influence of feed rate on uniformity had both linear and quadratic character.

A significant interaction term between the two factors was also noted. In general, the 200 rpm and 1.5 kg/h series showed the best repeatability thus demonstrating the best conditions for this particular process. These results are in general agreement with the data obtained from the PC scores plots.

Conclusions

The Antaris™ FT-NIR analyzer was successfully applied for measuring ibuprofen in extrudate. A calibration was developed that could be used to monitor the output from the Pharmalab extruder in real time. A general process algorithm was established for the content uniformity of the extrudate as changes were being made to factors in the extruder. PC scores plots in conjunction with analysis of variance algorithms could be used to optimize the process conditions under test. These relationships may be exploited within feed forward or feedback loops for immediate process control. Thus NIR analysis has the potential for use as a process analytical technology (PAT) tool with extruders for both process development of new processes and control of existing ones.