PROCESS ANALYTICAL TECHNOLOGY FOR IMPROVED PROCESS UNDERSTANDING AND CONTROL OF A HOT MELT EXTRUSION PROCESS

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Abstract
The development and application of an in-line near infrared spectroscopic measurement system is discussed. Key results included a rapid, in-line method to measure the composition of a multi-component process stream at the exit of the extruder, and identification of a process model that is used to understand the disturbance rejection capabilities of the process. The composition monitoring yielded further process understanding; specifically system residence time distribution mapping and process disturbance identification. Lastly, the potential for prediction of process disturbance rejection capabilities is discussed.

Introduction
Quality control for a pharmaceutical intermediate manufactured in continuous process involves unique challenges compared to batch processing. For example in a batch process, product quality is typically verified at the end of the batch via analytical testing. While in a continuous process, the product quality needs to be verified continuously during the manufacture. To facilitate continuous verification of product quality, process analytical technology (PAT) methods can be employed. PAT can be described as the utilization of analytical measurements in combination with modeling to enable process control. PAT systems typically provide a direct or indirect measurement of product quality. Spectroscopic techniques are extensively used in PAT implementations because these methods usually do not require any sample preparation, are non destructive, and are reasonably rapid (on the order of milliseconds to minutes), and can be implemented in-line, on-line, and at-line. For the reasons mentioned above, near infrared (NIR) spectroscopy has been utilized by the pharmaceutical industry for chemical and physical analysis of solids. For example, NIR has been applied to real time powder blend monitoring [5], content uniformity of tablets [6,9], film coating thickness, particle size distribution [8], moisture end point determination in fluidized bed drying [13], and polymer concentration in single screw melt extrusion[14].

In this work we describe the development and implementation of an in-line transmission NIR measurement system that can measure the composition of a multi-component melt stream at the exit of a twin screw extruder. We demonstrate the use of this method for characterizing the system dynamics, and accessing the ability of the process to dampen mass flow rate disturbances, and for real time process monitoring and quality control. The process knowledge gained from the PAT system is shown to be useful for both process development and routine manufacturing.

Materials
The formulation of the extrudate used in this work is proprietary. The extrudate, a pharmaceutical intermediate, consists of three components, a surfactant, a polymer, and the active pharmaceutical ingredient (API). The API has 0.90mmol of aromatic hydrogen per gram of formulation. The surfactant has long aliphatic chains and zero aromatic hydrogen. The polymer also has zero aromatic Hydrogen. The polymer used does contain an aliphatic backbone, but does not have long saturated aliphatic chains like the surfactant. These molecular differences in the API, surfactant, and polymer exhibit sufficient spectroscopic selectivity in the near infrared region to permit quantitative calibration.

Process Equipment
Processing was conducted on a 27mm twin screw extruder (Leistritz, model # ZSE27HP). Solids were introduced into the extruder using two loss in weight mass feeders, one for feeding a polymer (K-Tron, model # K2ML-KT20-D5) and a second (K-Tron, model # KCL24-KT20) for API. The API was gravity fed and the polymer was added via a side stuffer. Data from the mass feeders were logged using a portable data acquisition system. A liquid surfactant was fed into the process using a gear pump and the mass flow rate was controlled with a Coriolis type mass flow meter. Data from the liquid addition system was logged on the mass flow rate controller.

Process Instrumentation
The PAT system utilized was a Brimrose Luminar 2060 AOTF NIR Process Spectrometer operated in transmission mode, using 600 micron fiber optic cables, and 600 micron core size transmission probes. Source intensity was attenuated with a tunable neutral density filter. Data was acquired every 1.31 seconds as the average of 30 scans. Spectra were recorded over the range of 1100nm to 2100nm. Spectra were logged on a
computer dedicated to controlling the PAT analyzer. Real time predictions during processing were made using the Brimrose On-Line Predictor software package. A custom built three port die adapter was used to allow simultaneous NIR transmission and Raman scattering measurements. This adapter utilizes two plate heaters to maintain temperature, and is controlled as additional zone by the extruder via an onboard thermocouple. The optical path-length of the measurement cell is 5mm. In this manuscript, only transmission NIR data will be discussed. Reflectance spectra of the pure components at room temperature were also recorded on the Brimrose NIR, using a micro bundle reflectance probe for solids analysis.

**PAT Method Development**

**Generation of calibration samples**

Data from two engineering development campaigns were used to develop a NIR calibration for monitoring the composition of the three component extrudate in real time. Variation in extrudate composition was achieved by executing a series of simultaneous mass flow rate set point changes in the three independent feed streams to the extruder. Approximately 50 gm samples were collected once steady state was achieved after each step change for high performance liquid chromatography (HPLC) analysis. NIR spectra were collected continuously. Table 1 summarizes the compositional changes and processing conditions used to calibrate the NIR method. The compositions of surfactant and API were varied orthogonally, with the polymer concentration co-varying to make up the difference. Additionally, two sets of processing conditions that have different total mass flow rates and screw speeds were used to generate the calibration samples.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Surfactant Conc</th>
<th>API Conc</th>
<th>Polymer Conc</th>
<th>kg/hr</th>
<th>Screw RPM</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>0.98</td>
<td>0.735</td>
<td>1.08</td>
<td>10</td>
<td>200</td>
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<tr>
<td>2</td>
<td>0.99</td>
<td>1.24</td>
<td>0.93</td>
<td>10</td>
<td>200</td>
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<td>3</td>
<td>1.5</td>
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<td>0.94</td>
<td>10</td>
<td>200</td>
</tr>
<tr>
<td>4</td>
<td>0.47</td>
<td>0.985</td>
<td>1.08</td>
<td>10</td>
<td>200</td>
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<tr>
<td>5</td>
<td>0.97</td>
<td>0.985</td>
<td>1.01</td>
<td>10</td>
<td>200</td>
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<tr>
<td>6</td>
<td>0.95</td>
<td>0.795</td>
<td>1.07</td>
<td>20</td>
<td>300</td>
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<tr>
<td>7</td>
<td>0.96</td>
<td>1.2</td>
<td>0.95</td>
<td>20</td>
<td>300</td>
</tr>
<tr>
<td>8</td>
<td>1.34</td>
<td>1.035</td>
<td>0.94</td>
<td>20</td>
<td>300</td>
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<tr>
<td>9</td>
<td>0.64</td>
<td>1.005</td>
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<td>1.0</td>
<td>20</td>
<td>200</td>
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</table>

**Table 1** Summary of processing conditions used to generate calibration samples and HPLC assay results for the calibration samples.

**Partial Least Squares Modeling of Near Infrared Spectra**

Partial least squares calibration [10] methods that simultaneously predict the composition of all three components in the extrudate were developed using Unscrambler (version 9.7) based on both the laboratory reference values and the target values. Calibrations using the target values were employed to enable real time process monitoring of subsequent runs, after calibration on the day of processing. Models based on HPLC assay values were developed for future processing runs were conducted pending the completion of laboratory analysis. The NIR prediction results in this work were conducted off-line after the actual processing using the HPLC reference values, although the target value models were found suitable for process monitoring on the day of processing. Reduced averages of fifteen consecutive spectra were used to account for the sampling time and sample size. The spectral pre-processing used for the PLS models were standard normal variate (SNV) [10] and a 21 point Savitsky-Golay first derivative treatment [11] over the entire spectral range (1100-2100nm) then multivariate regression was conducted on the pretreated spectra using the 1600nm-1800nm region. Full cross validation [10] was used to assess model performance.

**System Identification**

The dynamic response of the process measured by the PAT system to the step change inputs were fit to first order plus dead time process (FOPDT) models [12]. The FOPDT model is shown in Equation 1, where \( I(t) \) is the component concentration as a function of time, \( K \) is the process gain (K=1, mass flow changes are fully realized), \( \Delta x \) is the magnitude and the direction of the step change, \( u(t-t_0) \) is the unit step change with dead time, \( t \) is time, \( t_0 \) is dead time, \( \tau \) is the process time constant, and \( I(0) \) is the concentration of the component before the step change. A set of global FOPDT parameters \( (t_0, K, \tau) \) for each component were estimated by minimizing the sum of the squared errors over all of the measured step changes using non-linear least squares.

\[
I(t) = K \cdot \Delta x \cdot u(t-t_0) \cdot (1 - \exp(-((t-t_0)/\tau))) + I(0) \quad (1)
\]

**Time Series Analysis**

To quantify the input disturbance rejection capability of the extruder the periodogram (spectra power density) of the differential form of the identified process model was calculated using the Time Series Tool in Matlab version 7.3.0 R2006b. The periodogram [2] is defined as the absolute value of the square of the finite Fourier transform (FFT) versus a frequency vector as described by equation 2, where \( U \) is the FFT of the time series \( u(t) \), \( N \) is the number of elements in the time series, and \( \omega \) is the frequency in inverse time.

\[
|U_N(\omega)|^2 = \frac{1}{\sqrt{N}} \sum_{t=1}^{N} |u(t)e^{-i\omega t}|^2 \quad (2)
\]

**Results and Discussion**
Near Infrared Multivariate Calibration

SNV treated NIR reflectance spectra over the modeling range 1600-1800nm of the pure components at room temperature are shown in figure 1. From figure 1, it can be seen that the API has a distinct non-overlapping peak in the 1600-1660nm region of the spectra that corresponds to the aromatic C-H bands in the first overtone region. A Partial Least Squares modeling technique was utilized (PLS2) where all three components are predicted from the same model. The spectral region of 1600-1800nm was used for modeling because the extrudate components have chemical groups that have strong absorbance in this region. Additionally, this range is robust to moisture variability. While it is possible to predict the API and surfactant concentrations and then obtain the polymer concentration by mass balance, we found that predicting the polymer concentration was essentially equivalent to calculating it, and that it is was found to be more convenient to display the data in real time. The multivariate regression metrics are listed in table 2. The $R^2$ values for the calibrations are 0.993, 0.998, and 0.995 for the API, surfactant, and the polymer respectively. Additionally, the root mean square error of calibration (RMSEC) of the regression is 0.417, 0.155, and 0.427 for the API, surfactant, and the polymer respectively.

![Figure 1 SNV pretreated NIR reflectance spectra of the pure components of the extrudate formulation.](image)

Table 2 PLS2 Calibration Parameters

<table>
<thead>
<tr>
<th>Comp</th>
<th>SLOPE</th>
<th>OFFSET</th>
<th>R-SQUARE</th>
<th>RMSEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>0.986</td>
<td>0.285</td>
<td>0.986</td>
<td>0.349</td>
</tr>
<tr>
<td>SURF</td>
<td>0.99</td>
<td>0.0954</td>
<td>0.99</td>
<td>0.275</td>
</tr>
<tr>
<td>POLY</td>
<td>0.992</td>
<td>0.532</td>
<td>0.996</td>
<td>0.354</td>
</tr>
</tbody>
</table>

Real Time Process Monitoring and Detection of Process Disturbances

The NIR calibrations were used to predict the extrudate composition during processing. Figure 2 shows example of NIR model predictions for API, surfactant, and polymer during an engineering batch of a hot melt extrusion process. From figure 2, it is clear that the target compositions were achieved. The variability over the run time shown for each component is 5.0%, 3.1%, and 1.5% RSD for the API, surfactant, and polymer respectively. Figure 3 shows an example of a process perturbation that was detected by the PAT system in real time. The root cause of this perturbation was attributed to raw material lot change, where the bulk density of the material lot varied from the material that the mass feeder was calibrated on. When the more dense API lot reached the screws of the mass feeder, it started over feeding the API. The loss on weight controller on the mass feeder detected the overfeeding and compensated for the increased powder density.

![Figure 2 Process Monitoring by PAT, API (upper panel), Polymer (middle panel), Surfactant (lower panel).](image)
Figure 3 Process Disturbance Detected by PAT. API lot change caused process perturbations related to API lot density, 0.22g/ml to 0.50g/ml.

**Process Model Identification and System Dynamics**

The processes response measured by the NIR (predicted extrudate composition) to the step changes used to generate the calibration samples were fit to a first order plus dead time model, (see equation 1). The best fit global FOPDT model parameters are shown in Table 3. The process time constants are similar for all three components in the formulation. This is consistent with expectations, because in this case the extruder acts as a CSTR-PFR model in the sense that all mass elements will experience the same environment as they pass through the extruder. The processing environment is fixed by the extruder process parameters (screw profile, barrel temperature profile, mass flow rate, screw speed) and the formulation rheology. The process dead times are also similar, but their variation is consistent with the location in which they are introduced into the process. Although the mass feeder dynamics are included in the measured responses, a simple FOPDT adequately describes the data. More sophisticated models were considered, but rejected because the FOPDT model adequately described the data. It should be noted that the identified model only contains information about the longitudinal mixing in the extruder and temporal variation. It does not contain any information concerning radial mixing.

<table>
<thead>
<tr>
<th>Model Parameter</th>
<th>API</th>
<th>Surfactant</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau$ (time constant sec$^{-1}$)</td>
<td>11.1</td>
<td>10.5</td>
<td>10.3</td>
</tr>
<tr>
<td>$t_0$ (dead time sec)</td>
<td>59.4</td>
<td>66.2</td>
<td>62.2</td>
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</table>

**Process Disturbance Rejection Capability**

With a model of the process identified from the step testing, the disturbance rejection capability of the process can be assessed by calculating the periodogram of the time derivative of the identified process model. Figure 4 shows the periodogram of the process model. This plot is informative of the extruder's ability to dampen mass feeder input disturbances and suggests that the extrusion process acts as a low pass filter. Specifically, input signals that contain energy content at frequencies above 0.05 cycles/second will almost be entirely damped. Conversely, input signals that contain energy content at frequencies below 0.05 cycles/second will pass through the extruder virtually un-damped and will affect product uniformity. Additionally, the amplitude of the instantaneous variability in mass flow rate is practically irrelevant as long as frequency of the variability is above the critical frequency (above 0.05cycles/second in this work) as long as the mean flow rate is on target. This knowledge can be used to either set mass feeder performance specifications or could be used to redesign the extrusion process (screw profile, or screw speed, total mass flow rate) to be compatible with known mass feeder performance.

The mass feeder performance is highly dependent on the feed material properties, such as particle size, Carr index, and compatibility. In addition to providing insight on the process dynamics and the disturbance rejection capability the identified process model can be used for real time predictive process monitoring. This could be achieved by numerical convolution of the differential form the process model with the time discretized mass flow rate data coming from the mass feeders.

**Conclusions**

The NIR transmission method described in this work was demonstrated to provide value over the entire development life cycle of an extrusion process. The method was shown to be useful in process development to characterize the system dynamics and to identify a process model. In routine manufacturing the NIR system was demonstrated to be able to detect process upsets and to continuously ensure product uniformity over the entire manufacturing run.

**References**


Key Words: Process Analytical Technology, Near Infrared, Process Monitoring.