Inline Monitoring of a Hot Melt Extrusion Process by Near Infrared Spectroscopy

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Overview

Purpose: Introduction to FT-NIR method development for utilization as an in-line monitoring technique for quality attributes in an extrudate such as drug load homogeneity. Discussion of important pre-requisites for method development for process monitoring.

Methods: Theophylline was used as model drug and was compounded in 5 different concentrations from 0% - 20% into a polymeric matrix of polyethylene oxide. Lactose was added as reflective material for improvement of the NIR-signal. Spectra were collected in-line on the extruder for each concentration and a calibration model was built to predict the drugload in unknown extrudates. The quality of the FT-NIR model is investigated with statistical tools.

Results: The data presented in this poster show relevant pre-requisites to develop successful quantitative FT-NIR models which allow prediction of drug loads as in-line measurement in a hot melt extrusion process.

Introduction

Melt extrusion technology is becoming a more widely accepted technology for development and production for pharmaceutical dosages forms for many different reasons. By the specific characteristics such as a precise shear rate application and a precise temperature control the process allows the formulation of a wide range of drug molecules. One prominent application is the bioavailability enhancement, where inside the extruder the drug is converted into its amorphous form and molecular level dispersion into a glassy solution is achieved. Precise control of temperature and shear stress allows for precise conversion of drug molecules from one crystalline modification into another crystalline modification. Due to the hot melt extruders design, the residence time distribution of the material processed is also well controlled. The process is operated normally in a continuous mode allowing high flexibility in targeted product size. By implementation of process analytical tools (PAT) such as FT-NIR or Raman spectroscopy, product quality attributes can be monitored in real-time ensuring a constant desired product quality.

With the advent of PAT and quality-by-design (QBD) there is a paradigm shift to designing in quality and real time monitoring of critical quality control parameters to ensure quality product. By developing an in-depth understanding of the hot melt extrusion process and the interaction of process parameters and their influence on product quality optimization. To guarantee product quality, the QBD concept of operating the process in a pre-determined parameter window can be applied and replace the traditional process operation in a fixed parameter set that leads to cost of poor quality. This poster is going to discuss briefly the basic implementation and method development of FT-NIR to monitor drug load in real-time.

Methods

For the extrudate polyethylene oxide was used as polymeric matrix. Sentry® WSR N10 was kindly donated by Dow Wolff Cellulosics, Midland, MI, USA. Theophylline anhydrous was used as model drug in 0%, 5%, 10%, 15% and 20% concentration. Theophylline was kindly donated by BASF SE, Ludwigshafen, Germany. Lactose was used in some experiments as reflective material for the NIR light. Lactose was purchased from Meggle, Germany.

For the extrusion process the materials were blended in PE-bags by shaking by hand for 3 minutes. The blends were fed with a single screw feeder (FW 18, Brabender Technologies, Germany) with a feeding rate of 500g/h into a Pharma 16 HME extruder (Thermo Fisher Scientific, Karlsruhe, Germany). The mass was extruded at a screw speed of 100rpm with temperatures up to 120°C. The screw profile contained two kneading sections for melting and mixing of the pre-blends used.

At the end of the extruder close to the nozzle, a fiber optic probe is installed in a standard ½"-20 UNF Dynisco extruder port. The probe allows the FT-NIR to collect reflection spectra in a matter of seconds. For this study spectra were collected for every drug concentration for approx 30 minutes each.

FIGURE 1. Pharma 16 HME Twin-screw extruder with coupled Antaris MX FT-NIR spectrometer

Results

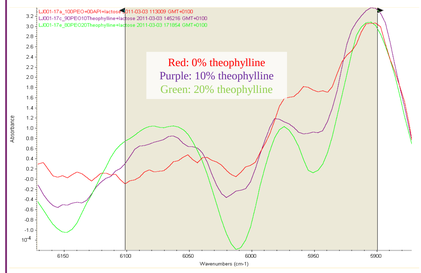
For this study a goal was to investigate some important pre-requisites to predict a drug load by FT-NIR measurements. In a first instance depending on the opacity of the melt one has to decide whether to develop a measurement based on transmission of NIR-light through the extrudate or to develop a method basing on reflection of the NIR-light back from the extrudate (for opaque extrudate).

TABLE 1. Investigated formulations

Formulation	PEO	Theophylline	Lactose	PEO/Theo.--ratio
U001/17a	89.6	0.0	10.4	100/0
U001/17b	85.1	4.5	10.4	95/5
U001/17c	80.6	9.0	10.4	90/10
U001/17d	76.1	13.4	10.4	85/15
U001/17e	71.6	17.9	10.4	80/20

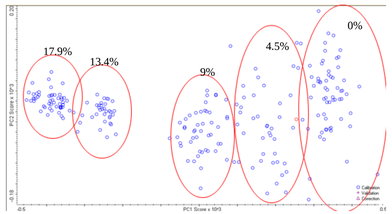
The set-up chosen for this study was measuring in reflection mode only. A first set of experiments contained PEO as polymer and theophylline as drug only. As no amorphous glassy solution was formed, the extrudate became more and more opaque depending on the theophylline content. For 0% and 5% theophylline the extrudate appeared translucent. In a second set of experiments lactose at a fixed content was added to all blends to improve reflectivity from the extrudate for the NIR-light and to improve the signal quality.

FIGURE 2. 2 shows the differences in second derivatives from the spectra . The drug loads can be clearly separated and identified.



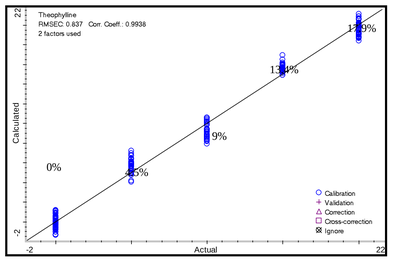
The spectra shown in figure 2 are for visual discrimination of the plotted data only. For a precise evaluation of useful information contained within the spectra – such as discriminating effects like drug loading within the several batches investigated - a principal component analysis (PCA) can be performed. The data shown in figure 3 show the principal component 2 plotted versus principal component 1. In case of the batches containing lactose the principal component 1 contains the information for the different drug concentrations as shown in figure 3. Principal component 2 shows that as the drug load increases the cluster size for each drug concentration decreases due to the improved quality and consistency of the reflection spectra as drug content increases. As can be seen clusters can make the identification of the different drug loadings very clear.

FIGURE 3. Principal Component Plots of PC2 vs. PC1



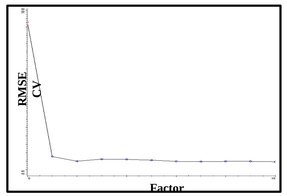
A suitable quantitative calibration which allows to predict the theophylline content should be appropriate and will be evaluated in the next section.
Figure 4 shows the resulting quantitative calibration model for theophylline % in the extrudate. As expected from the principal component analysis the addition of lactose leads to a suitable calibration model with a correlation coefficient of 0.9938 and a RMSEC of 0.837. This model can clearly discriminate between the tested different drug loadings. For this study pre-blends were manually blended and the resulting data collected on the extruder produced a robust and accurate model.

FIGURE 4. Calibration plot for the extrudates



A good indicator of PLS model performance for an application is the PRESS (Predicted Residual Sum of Squares) plot. The PRESS plot shows the relationship between the error of the calibrations and the number of factors needed for the calibration model. Achieving a calibration model with low error and few factors indicates that model is well suited for the application. For a PLS model, the 1st factor explains the most spectral variation and each additional factor explains the remaining variation. The ideal trend is for the majority of spectral variation that correlates with the component of interest to be explained with just a few factors. For quantifying theophylline in the extrudate, only 2 factors were required for the PLS model which is a good indicator of a robust model for trending the hot melt extrusion process.

FIGURE 5. PRESS Plot for the extrudates

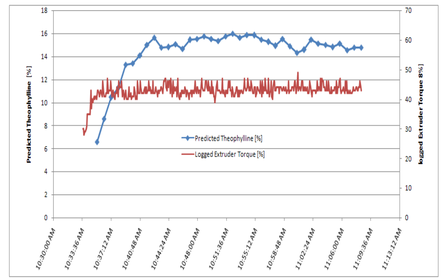


Finally the model obtained from the batches containing lactose was used in a workflow developed in Thermo Scientific RESULT software for automated in-line analysis using the Antaris MX. The workflow with associated calibration model was used to monitor a extruder production run containing 15% theophylline. Spectra were collected directly after the extrusion run was started to see the start-up phase of the extrusion process .

Figure 6 shows the predicted theophylline content as blue curve in % and the measured extruder torque in % as red curve. The feeder was running with 500g per hour. The torque readings are recorded since they are important parameters to judge if the extrusion process has reached a steady state for production of product of consistent quality . But as can be seen, the theophylline predictions from FT-NIR show a homogeneous product is obtained much later than is indicated by the recorded torque.

The Antaris MX FT-NIR with reflection probe is shown to predict the15% theophylline within the error of the calibration model.

FIGURE 6. Predicted theophylline content in a test formulation and logged Extruder torque show when the process reaches steady state



Conclusion

The study showed important pre-requisites to allow an accurate prediction of drug loading with an in-line FT-NIR measurement. By FT-NIR the extrusion process can be monitored for several quality attributes. It is important to consider the possible influences of different process parameters on the FT-NIR spectrum to allow a sophisticated in-line process and quality monitoring in the melt extrusion process. The study also showed that in utilizing FT-NIR the real constant process conditions can be better determined than with the extruder parameters such as torque itself. The advantage of using FT-NIR is that quality attributes of the extrudate are monitored directly in-line in real-time.

Future studies will investigate more in depth the influence of different process conditions on the FT-NIR signal to allow developing reliable FT-NIR prediction models where all possible circumstances are considered.

References

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