Product Quality Control of a HME Co-Extrudate Using a Raman Imaging Microscope

Dirk Leister[1], Katharina Paulsen[1], Ines Ruff[2], Karl C Schwan[2], Simon Nunn[3], Martin Long[3]
Thermo Scientific, Karlsruhe[1] / Dreieich[2], Germany / Madison[3], WI United States

Overview

Purpose: Introduction to hot melt co-extrusion for utilization as a drug delivery method. Influence of process parameters on final drug product quality. Application of Raman imaging microscopy as a analytical tool for quality control of the co-extrudate.

Methods: Co-extrusion with a newly designed co-extrusion die and a pharmaceutical relevant polymer/active formulation. Chemical mapping with Raman microscopy to provide evidence on extrudate integrity and absence of drug migration.

Results: The results presented in this poster show the successful utilization of Raman imaging microscopy as a tool for quality control of co-extrudates.

Introduction

During recent years hot melt extrusion (HME) has found its way into contemporary drug design as it is a technology that proofed to be potent to overcome some of the major hurdles formulation scientists facing today. The most widespread application of HME is the formulation of poorly soluble drugs so that high and reliable drug absorption can be guaranteed when being administered to patients. In order to achieve this goal a solid dispersion of an active pharmaceutical ingredient (API) into a thermoplastic polymeric carrier is being formed during the HME process. Often times the cooled down extrudate is grinded to a powder and together with other excipients used for a traditional tabletting process.

More recently the direct shaping of extrudates as the final dosage form has come to the researcher's attention and drug delivery systems like implants, transdermal patches and co-extrudates gain more pharmaceutical relevance. A co-extrusion is a simultaneous HME of two materials through a single die. The different polymer melts form a multi-layer extrudate that can come in different shapes. Depending on their formulation (e.g., pH dependency of the polymer chosen for each layer) these co-extrudates can be used for development of oral solid dosage forms with different release properties or combination therapy, if multiple APIs are used.

When producing a co-extrudate different quality attributes have to be monitored and analyzed carefully to ensure the desired drug quality. Beside the pharmaceutical relevant parameter like the drug release profile, physical parameters like

- the integrity of the different layers within the co-extrudate
- the constant layer thickness
- and the possible migration of API from one layer into another

are of high importance to the final drug quality.

Utilizing a Raman imaging microscope for the analysis of the final co-extrudate comprise different advantages. The video image of the microscope gives a good overview of the obtained sample and helps to focus on regions of interested to be analyzed by Raman spectroscopy. The great amount of spectroscopic data generated by Raman imaging allows the determination of the spatial distribution of components and their physical properties throughout the sample. When these data are fed into a powerful imaging software to generate Raman images, this can help for a quick visual analysis of the co-extrudate.

Within this poster we present different co-extrudates generated using a novel co-extrusion die design analyzed with Raman imaging spectroscopy for the above mentioned physical properties.

Materials and Methods

Sample Preparation

For this study a double layered strand co-extrudate was produced, consisting of a round shaped inner core covered by a concentric thin membrane layer.

For the inner core the formulation is comprised of:

- 80% Kollidon® VA 64 as the polymeric matrix
- 10% Itraconazol as the model API
- and 10% GranuLac® lactose

This formulation was manually mixed for three minutes in a PE- bag and dosed into the feed port of the extruder using a FlexWall® gravimetric single screw solids feeder.

The outer membrane layer consists of 100% Eudragit® E PO.

For the HME of the core a Thermo Scientific™ Pharma 16 co-rotating twin-screw extruder was used. All processing parameters can be seen in **table 1**. The extrusion of the membrane layer was conducted using a Thermo Scientific™ Process 11 co-rotating Twin-Screw Extruder. The Eudragit® was dosed into the feed port of this extruder using a MiniTwin® gravimetric twin-screw solids feeder. Processing parameters of the Process 11 extruder are also listed in **table 1**.

Table 1. Processing Parameters of HME

Pharma 16 Twin Screw Extruder

	Barrel Temperature [°C]	Screw Speed [rpm]	Throughput [g/h]
SAMPLE A	145	250	500
SAMPLE B	145	250	1000

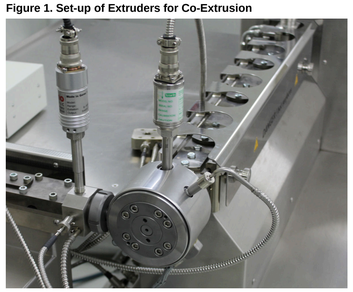
Process 11 Twin Screw Extruder

	Barrel Temperature [°C]	Screw Speed [rpm]	Throughput [g/h]
SAMPLE A	150	200	280
SAMPLE B	150	200	280

Temperature of Co-Extrusion Die 145°C

The two extruders were placed in a 90° angle with their barrel outlets and each was mounted to the co-extrusion die, as shown in **figure 1**.

Figure 1. Set-up of Extruders for Co-Extrusion



Sample Analysis

In the R&D state of drug formulation the set-up of a co-extrusion has to be flexible for a variety of different core to membrane ratios as well as for different absolute diameters of the final co-extrudate. At the same time the concentricity of the core and membrane has to be assured. Die designs were adjustments are regulated manually by using screws for the relative positioning of core to membrane, can be problematic when small absolute diameters should be achieved, as the manual adjustment can lead to none centric extrudates. The die design used in this study can change the absolute diameter of the co-extrudate by an exchangeable strand insert from 2 – 12mm absolute diameter. This insert is always positioned centric by its mechanical design and is not adjusted manually. The ratio of core diameter to membrane thickness is achieved by altering the relation of the melt throughput of the two extruders used.

To evaluate the influence of the above described process parameters onto the membrane thickness two samples were produced. With sample A having a throughput of the core extruder of 500 g/h and the membrane extruder of 280 g/h. And sample B having a increased throughput of the core extruder to 1000 g/h whereas the membrane extruder throughput stays constant. The co-extrusion die insert provided a total diameter of 4mm.

Samples were produced by cutting the completely cooled down strand into slices of approx. 1mm thickness. The samples were mounted on a glass slide and put into the Raman microscope. A Thermo Scientific™ DXR™xi Raman imaging microscope and Thermo Scientific™ OMNIC™xi software were used for acquiring and processing the Raman imaging data presented in this poster.

Figure 2. DXRxi Raman imaging microscope

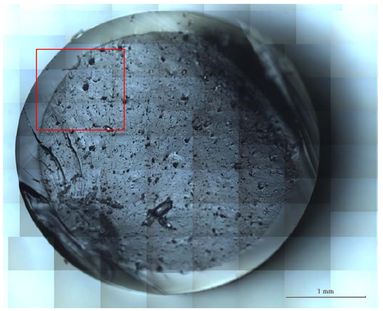
All video images were made using a 10x magnification. The Raman spectra were collected using a 532nm laser with a 10µm step size. The image is the result of an MCR (multivariate curve resolution) analysis of the spectroscopic data. MCR differentiates the Raman spectra into components; the constituents are assigned different colors to produce a chemical image and identified using automatic library searching routines. From all single components of the two layers, as well as from the dissolved Itraconazol in Kollidon® VA64, reference spectra were taken.

Results

One goal of this study was to develop an understanding of the influence of the HME process parameters on the final co-extrudate.

The visible appearance of the different layers can be seen in figure 3, showing a video image of the product obtained for the parameter setting SAMPLE A. The picture was taken with a 10x magnification and appropriate lightning. As no plasticizer was used throughout the experiment the whole extrudate was quite brittle and thus hard to cut. Both polymers for the core and the membrane layer showed similar hardness and the adherence between the two layers was good. The membrane layer shows a uniform thickness and a good integrity with no defects to be detected.

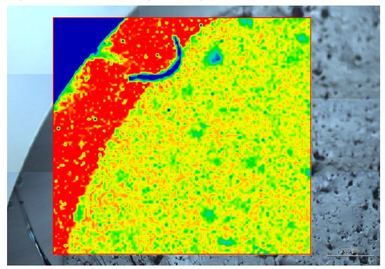
Figure 3. Video Image Sample A



The complete diameter of the co-extrudate is 3,6mm with the layer thickness varying between 280-300 µm. As described in the materials and methods part, the strand insert used in the Co-Ex die was of 4mm diameter in total. The chosen throughputs of the two extruders were set to achieve a 400µm membrane layer. The measured values are thus in good accordance if one takes into account, that the take-off of the co-extrudate happened with a fixed speed conveyor belt, that did not compensate for any pulsation occurring in the extruder. Also the round shape of the extrudate and the concentricity looks good.

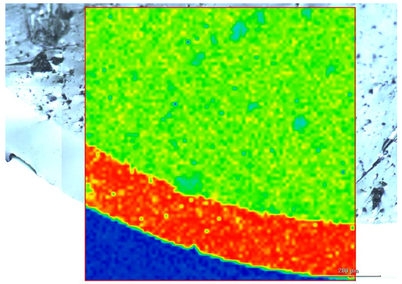
The red rectangle drawn in the top left corner of figure 3 was analyzed by Raman imaging to get a chemical mapping and be able to determine the distribution of the API, as well as to judge possible API migration from the core into the membrane. Figure 4 shows the analytical result with the Eudragit® membrane in red and the solid dispersion of Itraconazol in Kollidon® VA64 being yellow/green. The blue color represents measuring artifacts caused by air bubbles created from water vapor during extrusion or an inclusion of a solid particle (curved line in the top middle section of the analysis window. What can be seen from the chemical mapping is the fact, that no significant migration from API into the membrane has happened and also no crystalline API is present anymore.

Figure 4. Raman MCR Image of Sample A



In **figure 5** a sample of the co-extrudate of Sample B is shown. A similar quality of shape and API distribution compared to Sample A could be observed. As the throughput of the core extruder has been doubled a reduction of the membrane layer thickness was expected. This could be found when measuring the two layers of the co-extrudate. With a total diameter of 4,1mm and a membrane thickness varying between 160-180 µm also these values are in good correspondence with the calculated values.

Figure 5. Raman MCR Image of Sample B



Conclusion

Hot Melt Extrusion is an innovative technology to establish new and novel drug delivery systems such as mulit layered co-extrudates. HME is offering a variety of advantages over traditional methods including more control over dosages and forms of the products. With a carefully chosen die design a relatively easy-to-use and versatile R&D set-up for co-extrusion can be realized. Different co-extrudates with varying ratios of core to membrane thicknesses can be achieved by simply adjusting the respective extruder throughputs.

With new formulation tools also new challenges arise for the analytical requirements. It is necessary to understand how these new processing methods affect formulation components, and to verify the distribution of the components within the fin al drug product. Raman imaging microscopy is a smart ways of analysis to ensure product quality. It not only provides a way to identify and verify components but it also provides visual representations of spatial distributions. This visual analysis can be extended to include images based on differences is state such as, solvation or degree of crystallinity.

In this case study Raman imaging microscopy proofed to be a good and reliable method to analyze the complex condition found in co-extrudates with a minimum effort. It was capable to make firm statements about the physical layer integrity as well as about the absence of significant API migration between the different layers. Also for the inexperienced user it is an easy to apply tool to get a good understanding of the final drug product quality.