



## Co-extrusion as an innovative method for pharmaceuticals

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### Introduction

Hot melt extrusion is a process to produce a broad range of pharmaceuticals. It can be used for oral applications, implants, or patches. In oral solid dosage forms, it can be either used to increase the bioavailability of poorly soluble active pharmaceutical ingredients (API) in immediate and sustained release formulations or even in combination with different release behaviors.<sup>1,2</sup>

To produce a combination of different release profiles and/or different drugs in fixed-dose combinations, it can be extruded in a multi-layer system. With co-extrusion, the production of an inner core and an outer shell will be realized in one single step. The most important parameter is a precise diameter of the inner core and thickness of the outer layer to achieve the desired drug content and release. For quality control, Raman imaging microscopy is used.

### Materials and methods

#### Hot-melt extrusion equipment

For co-extrusion, one extruder is needed to produce each layer. For the production of the inner core, a co-rotating twin-screw extruder with a screw diameter of 16 mm was used (Thermo Scientific™ Pharma 16 Twin-Screw Extruder, Thermo Fisher Scientific, Karlsruhe, Germany). For the outer layer, lower throughput is needed. Therefore, a co-rotating twin-screw extruder with a screw diameter of 11 mm (Process 11 Twin-Screw Extruder, Thermo Fisher Scientific, Karlsruhe, Germany) was used. The co-extrusion die was equipped with an insert of 4 mm for the total diameter. The thickness of the outer layer was controlled by the ratio of the mass flow of the inner and outer phases. For co-extrusion, the extruders are arranged in a 90° position, as shown in Figure 1,

with the Process 11 Twin-Screw Extruder orientated from left to right. Two gravimetric MiniTwin powder feeders were used (Brabender Technology, Duisburg, Germany) to achieve precise feed rates of the inner and the outer phase.

### Materials

In the inner layer, Itraconazol was used as a model drug (BASF, Ludwigshafen, Germany) with Lactose (GranuLac®, Meggle, Germany) and PVP/PVA Copolymer (Kollidon® VA 64, BASF, Ludwigshafen, Germany) as a carrier. The outer layer consists of a cationic methacrylate copolymer (Eudragit® E, Evonik, Darmstadt, Germany) without API.

### Thermal analysis

To determine the solid state of the inner core, dynamic scanning calorimetry (DSC) was used (DSC 204 F1 Phoenix; Netzsch-Gerätebau GmbH, Selb, Germany).

### Raman spectroscopy

For characterization of the co-extrudates, Raman microscopy imaging is used (Thermo Scientific™ DXR3xi Raman Imaging Microscope, Thermo Fisher Scientific, Madison, USA). The Raman spectra were collected using a 532 nm laser with 10 mW power and a 10 µm step size. For imaging, a 10x magnification is used. The exposure time was 0.0025 s, and the number of exposures was 100. The reference spectra of the single components were measured.



Figure 1: Setup of twin-screw extruders for co-extrusion.

## Results

### Determination of the solid state

The crystalline Itraconazol should be transferred into a solid solution by the hot melt extrusion process to increase the solubility and, therefore, consequently, the bioavailability. The result of the DSC measurement in Figure 2 shows only one glass transition of the sample of the inner core.

### Quality control measurements of the two layers

To determine the shell thickness and the quality of the shell, Raman chemical imaging was used.

With Raman imaging microscopy, it is possible to visualize the thickness of the layers, making thickness measurements much easier to perform than light microscopy. Also, any defects in the layers can be easily determined (Figure 3).

This method is also used to determine if there is any migration of the Itraconazol from the inner core to the outer shell, which would result in a change in the Raman spectra of the outer shell.

### Impact of extrusion parameters on the co-extrudate

During a stable process, the appearance of the co-extrudate is very homogeneous, and the surface is without any defects. The Raman microscopy images given in Figure 4 clearly show that the shell has a very homogeneous thickness, and there is no migration of the Itraconazol into the outer layer.

The total diameter of the strand is defined by the die insert used. By varying feed rates, different shell thicknesses are

generated. With an increased feed rate for the inner core, the outer shell becomes thinner. By doubling the feed rate of the inner core, the thickness of the outer layer will be half the thickness (Figures 4a and b).

Different process temperatures and, therefore, different viscosities of the different layers do not have an impact on the layer thickness. In the case of the co-extrudate shown in Figure 4c, the process temperature of the extruder for the outer layer was increased 25 K compared to the co-extrudate process in Figure 4b, resulting in no change in outer layer thickness.

## Conclusion

Hot-melt extrusion can be used to produce multi-layer systems by co-extrusion to produce pharmaceutical dosage forms with different dissolution behavior for one API or fixed-dose combinations of different APIs.

The outer shell thickness is very homogenous and can be varied easily by varying the throughput.

Raman microscopy imaging is an ideal tool to determine the shell layer thickness and to visualize any chemical and physical defects of the outer shell.

## References

1. Crowley et al.: Pharmaceutical applications of Hot melt extrusion; Drug Development and Industrial Pharmacy, 2007
2. Dierickx et al.: Co-extrusion as a manufacturing technique for multilayer mini-matrices with dual drug release; European Journal of Pharmaceutics and Biopharmaceutics, 2013

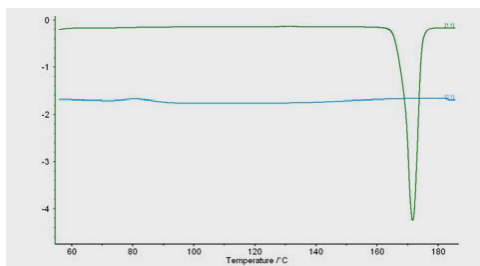


Figure 2: DSC scan of the crystalline Itraconazol (green) and the extruded product (blue).

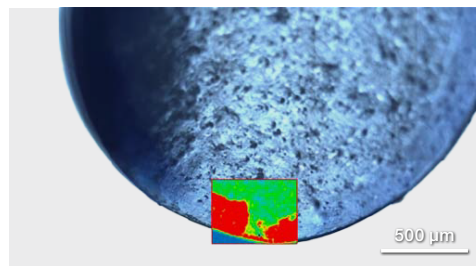


Figure 3: Cross section of a co-extrudate with a clear defect of the outer shell layer.

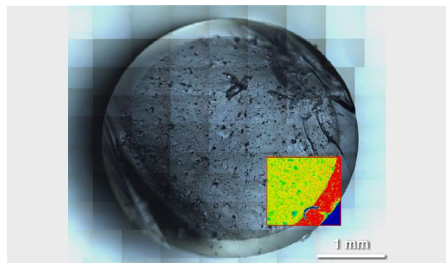


Figure 4A\*

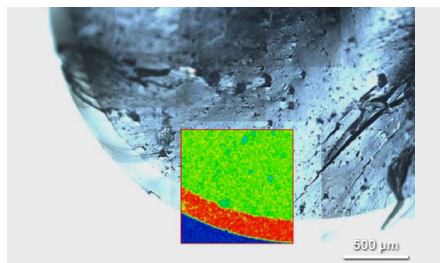


Figure 4B\*

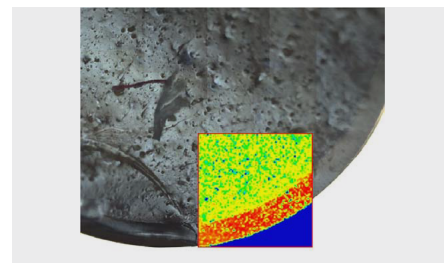


Figure 4C\*

\*Cross section of co-extrudates, produced with different process parameters: from a to b the throughput of the inner core is doubled and as a result the thickness of the shell in b is only half the size; from b to c the process temperature of the extruder producing the outer shell was increased by 25 K, and the layer thickness stays the same.

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