Co-Extrusion as innovative method for Pharmaceutics

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INTRODUCTION

Hot melt extrusion is a process to produce a broad range of pharmaceutics: 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 formulation or even in combination of different release behaviors [1, 2].
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 only one single step. The most important parameter is a precise inner core and outer layer to achieve the desired drug content and release. For quality control Raman Microscopy is used.

MATERIALS AND METHODS

Hot Melt Extrusion Equipment

For co-extrusion one extruder is needed to produce each layer. For production of the inner core a co-rotating twin screw extruder with a screw diameter of 16 mm was used (Pharma 16, Thermo Fisher Scientific, Karlsruhe, Germany). For the outer layer a lower throughput is needed, therefore a co-rotating twin screw extruder with a screw diameter of 11 mm (Process 11, 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 will be controlled by the ratio of the mass flow of the inner and the outer phase. For co-extrusion the extruders are arranged in a 90° position, as shown in figure 1. Two gravimetric MiniTwin powder feeders are used (Brabender Technology, Duisburg, Germany) to achieve precise feed rates of the inner and the outer phase.

Materials

In the inner layer Itraconazol is 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 methacrylat copolymer (Eudragit® E, Evonik, Darmstadt, Germany) without API.

Thermal Analysis

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

Raman Spectroscopy

For characterization of the co-extrudates Raman Microscopy imaging is used (DXRxi, Thermo Fisher Scientific, Madison, USA). The Raman spectra were collected using a 532 nm laser with a 10 µm step size. For imaging a 10x magnification is used. The reference spectra of the single components were measured.

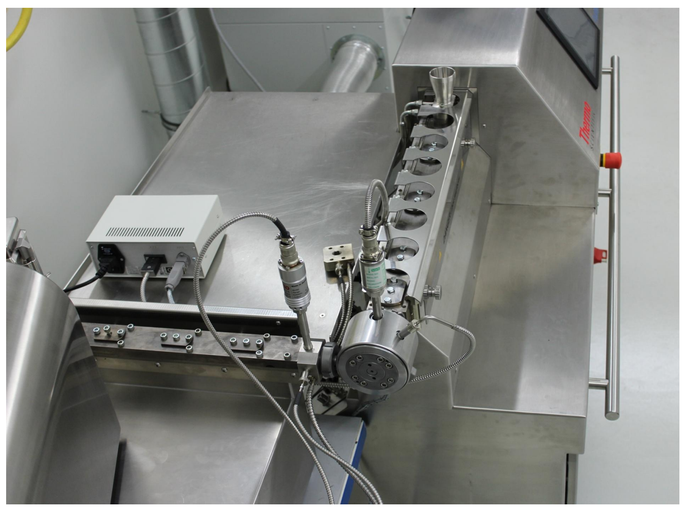

FIGURE 1: set up of twin screw extruders for co-extrusion

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 the bioavailability. The result of the DSC measurement in figure 2 shows only one glass transition of the sample of the inner core which means that a solid solution was achieved.

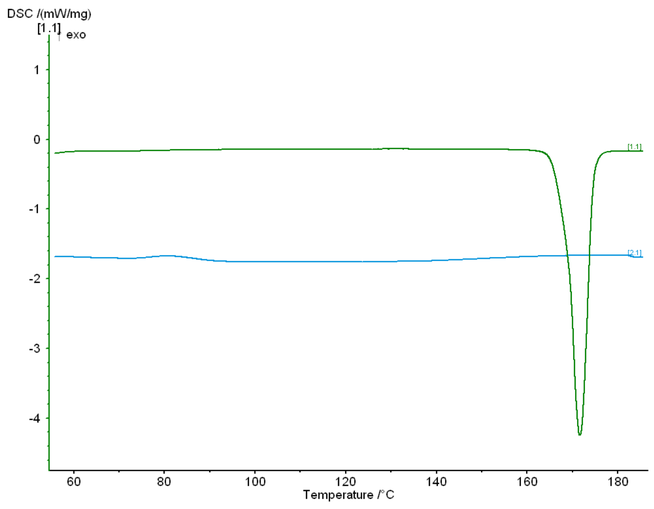

FIGURE 2: DSC scan of the crystalline Itraconazol (green) and the extruded product (blue)

Quality control measurements of the two layers

Only with microscopy the two different layers are hardly visible. To determine the shell thickness and the quality of the shell Raman microscopy imaging is used.
With the imaging the thickness of the layers are much easier to visualize, thus the thickness measurement is much easier. Also possible defects of the layers could be easily determined (Figure 3).
This method is also used to determine if there is any migration of the Itraconazol from the inner core in the outer shell, because this will lead to a change in the Raman spectra.

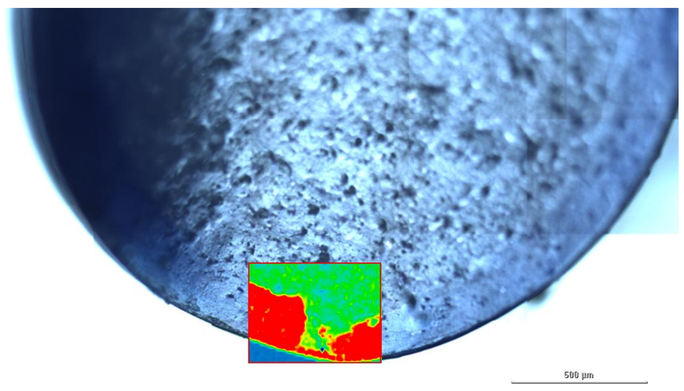

FIGURE 3: Cross section of a co-extrudate with a clear defect of the outer shell layer

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, show clearly 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 given by the used die insert. With varying feed rates different shell thicknesses are generated. With an increased feed rate for the inner core the outer shell is getting thinner. By double the feed rate of the inner core the thickness of the outer layer will be half the size (Figure 4 a and b).
Different process temperatures and therefore different viscosities of the different layers do not have an impact on the layer thickness. In 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 trial in figure 4b, but still the same layer thickness was observed.

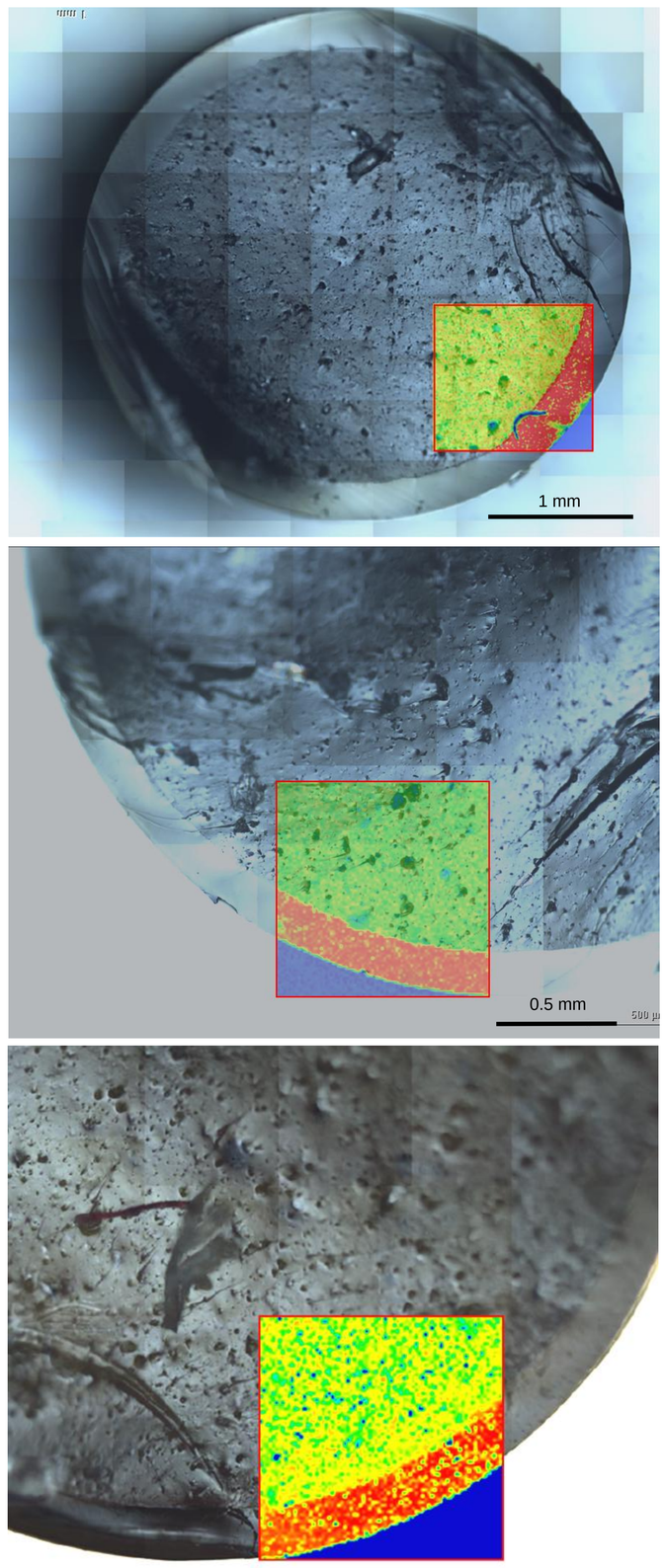

FIGURE 4 a-c: Cross section of co-extrudates, produces with different process parameters: from a to b the throughput of the inner core is doubled and as result the thickness of the shell is only half the size; from b to c the process temperature of the extruder producing the outer shell was increased of 25 K and the layer thickness stays the same.

CONCLUSION

Hot melt extrusion can be used to produce multi layer systems by co-extrusion to realize pharmaceutical dosage forms with different dissolution behavior for one API or for 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 a appropriate tool to determine the shell layer thickness and to visualize any 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 manufacturing technique for multilayer mini-matrices with dual drug release; European Journal of Pharmaceutics and Biopharmaceutics, 2013

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