Investigation of tablets made by injection moulding: R&D stage manufacturing and characterisation of Theophyllin-PEO-tablets

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Abstract

Purpose: To demonstrate injection molding of final dosage forms as a quick method to create test specimen for galenical development; to characterize melt extrudate solid dosage forms and determine if injection molding should be considered as a possible manufacturing step in producing a final tablet.

Methods: Polyethylene oxide was used as polymeric matrix and theophylline was used as model drug. Both materials were pre-blended, then extruded in a 16mm parallel twin screw extruder and the melt was collected to allow a quick transfer to the Minijet, a lab scale non-continuous injection moulding device where oblong-shaped tablets were produced from the melt. FT-NIR spectra were collected in reflective mode for later analysis.

Results: The manufacturing in small lab scale of injection moulded tablets is possible. The obtained tablets showed expected retardation in drug release depending on drug load and tablets showed deviations in drug content which can be confirmed by FT-NIR spectra analysis and has its roots in insufficient blend quality of PEO-theophyllin powder blend used. XRPD-diffractograms showed that approx. up to 5% of theophylline might be dissolve in the PEO but higher concentration lead to crystalline incorporated theophylline.

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.
As output of the melt extrusion process a melt is obtained. In plastics industry manifold solutions for the down streaming of the melt exist. Two down streaming possibilities for pharmaceutical purpose which could lead directly to a final shaped dosage form would be the calandering, where tablets could be obtained by pressing the melt between two calander rolls which contain half of a tablets each. Another possibility to obtain a final dosage form would be injection moulding. In the plastic industry this is a common used technology. Many things we daily use are made by this technique which developed to be a fast, reliable and low cost production opportunity which can be adopted as a continuous operation mode to the compounding step taken place in the hot melt extruder upfront. This paper is demonstrating for lab scale how tablets for galenical investigations can be manufactured and characterized.

Materials & Methods

For the extrudate polyethylene oxide was used as polymeric matrix. Sentry® WSR N10 was kindly donated by Dow Wolff Cellulosics, Midland, MI, USA. Theophyllin anhydrous was used as model drug in 0%, 5%, 10%, 15% and 20% concentration. Theophyllin 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 160°C. The screw profile contained two kneading sections for melting and mixing of the pre-blends used. At the end of the extruder a FT-NIR fibre-optics was mounted and connected to an Thermo Fisher Antaris MX FT-NIR device to collect spectra in reflective mode with 32 scans per spectrum. The melt was collected in molten form in the reservoir of the injection moulding device - the Thermo Fisher Minijet. After filling the Minijet reservoir, oblong-shaped tablets with a size of 12 x 7 mm were produced under defined injection conditions. The tablets were analyzed for weight, drug content, crystallinity and drug release.

FIGURE 1. Thermo Fisher Minijet

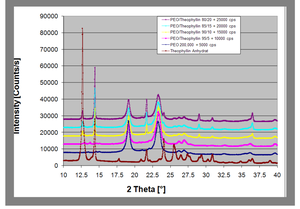
Table 1. Formulations and process data for injection moulding

	Formulation Data		Injection moulding process data			
Batch	PEO	Theophyllin	Pressure 1 [bar]	Pressure 2 [bar]	Temp. Reservoir [°C]	Temp. Mould [°C]
LJ001/15a	100	0	400	150	160	50
LJ001/15b	95	5	200	150	160	50
LJ001/15c	90	10	150	150	150	40
LJ001/15d	85	15	170	150	160	45
LJ001/15e	80	20	170	150	160	45

Results

Table 1 shows the formulations utilized. Figure 2 shows the XRPD-data taken from the tablets made by injection moudling. As can be seen, theophylline remains in a crystalline state except for the 5% concentration level where the typical peaks for the theophylline nearly disappear. Reason could be the transformation of theophyllin in amorphous form or the peaks in low 5% concentration are just hidden by the majority of polyethylene oxide. It is expected that theophylline does not dissolve in higher amounts in the polymer. Figure 3 supports this thesis, that also in case of 5% drugload theophyllin is not getting disolved as the appearance is getting from yellowish for the 100% plain polymer to white with a 5% drug load already and therefore does look the same as the higher concentrations. A thermal characterization of this via e.g. DSC has not been performed.

FIGURE 2. XRPD-Data of tablets



For the injection moulding process the pressure to Inject the melt could be reduced with increasing theophyllin content. In some tablets air inclusions could be observed which need to be optimized in further studies by varying process parameters for the injection moulding.

The drug content of the tablets shows deviations which were not expected as such but are investigated here and are explained. Basing on the weight of the tablets and the weighed-in formulation the expected drug content in mg was calculated,. The measured drug content of 6 tablets per formulation type shows differences in different extent. Reason is likely an insufficient pre-blending of the PEO with the theophyllin prior to extrusion.

FIGURE 3. Tablets with PEO matrix and different theophyllin loadings

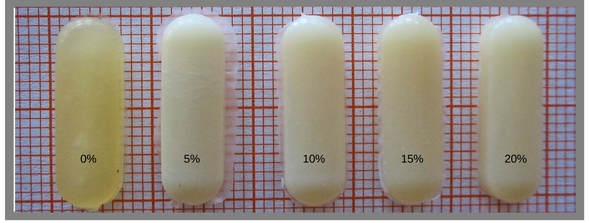


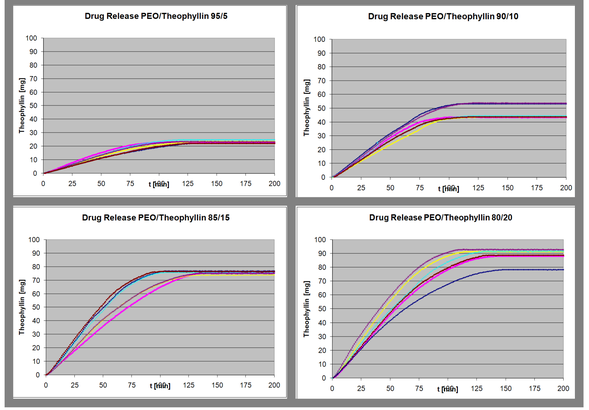
TABLE 2. Theophyllin content in injection moulded tablets and in extrudates (melt via FT-NIR)

	injection moulded tablets			Extrudates		
PEO/Theop.	Content expected [mg]	Content avg. Measured [mg]	rel. std. dev. [%]	Content expected [%]	Content FT-NIR predicted [%]	rel. std. dev. In predicted data [%]
100/0	0	N/A	N/A	0	N/A	N/A
95/5	22.37	23.37	3.64	5	5.33	47.96
90/10	45.4	47.09	9.65	10	14.14	9.67
85/15	68.33	75.65	1.28	15	15.89	2.01
80/20	91.75	88.58	5.49	20	16.07	1.69

A data model built from the collected FT-NIR spectra which was captured at the same time the melt was collected for the injection moulding confirms the trend in the deviations. The FT-NIR model developed for this study is basing on a PLS method. In cases where the measured drug content is below the expected drug content the FT-NIR model would predict a lower value as well. In cases where the measured drug content is above the expected drug content, the FT-NIR would predict a higher drug loading.

Evaluation of drug release shows that drug release is strongly dependent upon the constitution of the formulation. The greater the concentration of PEO within the tablets the lower the drug release becomes. The deviations in drug release of different tablets within one formulation (e.g. 80% PEO, 20% theophylline) is in conjunction with the relative standard deviations of the measured drug content. For the 90/10 formulation the highest relative std. deviation was measured, the same can be seen for the drug release. For the 95/5 formulation and for the 85/15 formulation the lowest rel. std. deviation is measured for the drug content and this conforms with the final drug release in both formulations.

FIGURE 4. Drug Release from injection moulded tablets with different drug loadings



The deviations in the drug content are a result of drug cluster formation in the powder blend. Further studies have to show if the cluster formation is a result of insufficient pre-blending or if cluster formation is a result of segregation effects during the introduction of material into the extruder.

Table 2 shows the relative std. deviation for the predicted theophylline content. Collection of FT-NIR data was a side aspect in this study only, and was used to confirm that the selection of correct collection mode (transmission or reflection) is important. As in this study the theophylline was the only reflectant to the FT-NIR light, the rel. std. deviation increases with decreasing theophylline content. A further study published on a poster titled "Inline Monitoring of a Hot Melt Extrusion Process by Near Infrared Spectroscopy" from Thermo Fisher is showing how to overcome such issues. Future studies will show how to optimize a set-up for FT-NIR process monitoring.

Conclusions

In a first study this poster shows the feasibility of manufacturing of tablets for galenical investigations. Future studies should show how to reach optimized conditions to achieve an optimized (low deviation) specimen for low volume characterization. Utilizing the Minijet injection moulding is a good tool to support early stage development phases.

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