Development of Non-biodegradable Filaments for 3D-printed Implant Inserts
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Introduction
The 3D-printing technique fused deposition modeling (FDM) offers a high potential for manufacturing of individualized drug delivery systems (DDS) regarding shape, dose and release behavior [1]. Hence, it is of interest for the fabrication of implants customized to the target site. The present study aimed for a filament development for 3D-printed implant inserts via hot melt extrusion (HME). The influence of pore former concentration on the mechanical properties and drug release should be investigated as well as the content uniformity to ensure high quality and desirable dissolution properties of filaments and implant inserts. Finally, an approach for a 3D-printed implant should be designed to show the importance of the individualization of such sustained-release DDS.

Materials and Methods

HME of Filaments
Four different powder blends (> 300 g) containing 10 % triamcinolone acetonide (TA, Farmabios, Italy), 0, 5, 15 or 25 % hypropemollose (HPMC, Metolose® 60SH, Shin-Etsu, Japan), ethyl cellulose (Aqualon® N10, Ashland, USA), 10 % triethyl citrate (CITROFOL® Al Regular, Jungbunzlauer, Switzerland) and 0.4 % anhydrous colloidial silica (Aerosil 200 VV Pharma, Evonik, Germany) were used for filament fabrication via HME. Each powder blend was extruded using a 400-D-co-rotating twin-screw extruder (PharmaLabs HME 16, Thermofisher Scientific, USA) with a feed rate of 5 g/min and an extrusion speed of 35 rpm at 170°C/90°C through a 1.75 mm die. Produced filaments were cooled on a conveyer belt (Model 846102.001, Brabender, Germany) with a speed of 44-48 mm/s to obtain a uniform diameter of 1.7 mm, which was measured by an in-line diameter measurement module (Laser 21025, Sikora, Germany).

Content Analysis of Filaments
Samples (~ 370 mg) were dissolved and diluted in ethanol 90 % (w/w). TA concentration was spectrosopically determined at 238 nm (Lambda 25 spectrometer, Perkin-Elmer, USA, n=6).

Determination of Mechanical Properties
The mechanical properties were determined using a texture analyser (TA.XT plus, Stable Micro Systems, UK). Testing regime and data evaluation was performed according to Korte and Quodbach [2]. Hence, a tensile test (n=6) and a three-point bend test (3PB, n=6) were applied.

3D-Printing
Printing was performed using an FDM-Printer (modified Prodlim XXL pro; Prodlim, Netherlands) at 165 °C and a printing speed of 12 mm/s. Inserts were printed with a rectangular infill of 85 %.

Dissolution of Filaments
TA-release of filaments (6 x 2.5 cm, n=3) was conducted in 1000 mL phosphate buffer pH 7.4 using USP Apparatus I (basket, 37°C, 100 rpm, DT 756 Erweka, Germany) over 7 days. Release was spectrosopically measured at 241 nm (UV 1800, Shimadzu, Germany).

Results and Discussion

Filament Characterization
Filaments with a uniform diameter of 1.72 ± 0.06 mm were obtained (Figure 1, left). The content varied between 95.0 and 100.3 ± 2 %. The TA content might have been reduced in some cases due to adhesion on the used equipment during the HME process.

Mechanical Properties
Young’s moduli (YM) and the distance at break of extruded filaments were determined in a tensile and 3-point bend test as the mechanical resilience is a crucial factor to ensure a constant conveyance of the filament inside the FDM-print head. All produced formulations exceeded the in literature specified thresholds for printability (Figure 1, right).

Filaments without HPMC were stiffer in longitudinal direction in comparison to HPMC-loaded ones, expressed in the highest YM. Addition of HPMC led to more elastic filaments, possibly caused by different visco-elastic properties of blends. The influence of the HPMC concentration on the YM was negligible. The impact on the distance at break was distinct. With increasing HPMC-load the distance at break decreased and thus brittiness.

It can be summarized that all extrudates have a desirable stiffness (expressed in a high YM) and have a suitable resilience against transversally applied stress (expressed in a high distance at break). Therefore, printability should be given, which was confirmed in printability studies.

Dissolution Study
Since a release rate over 3 months is desirable from TA implants, HPMC was added as pore former in different concentrations to identify a suitable concentration.

Preliminary dissolution studies of filaments showed, that with increasing HPMC concentration the drug release from the non-erodible EC-matrix increased as expected (Figure 2). Without or with only 5 % pore former the dissolution of TA was too slow for the targeted release duration. Whereas the release from formulations with 25 % HPMC is potentially too high. Filaments with 15 % HPMC revealed the most promising release properties, due to the possibility of influencing the profile by adapting shape or infill of printed implant insert.

Printing of Implants
Inserts for implants were designed to create units with a constant surface area within the implant. The implant consists of a drug-free customizable part and a drug-loaded insert. The insert can be individualized regarding dose and drug release by changing the specific surface area (Figure 3). First TA-loaded inserts for implants were printed successfully using self-extruded filaments.

CONCLUSION

The development of non-biodegradable printable filaments with EC as sustained release polymer, HPMC as pore former and TA as active pharmaceutical ingredient was successful. Obtained filaments were suitable regarding their mechanical resilience and thus printability. The addition of HPMC as pore former was effective to find a suitable filament formulation for printing of inserts and therefore to result in a suitable drug release. Nevertheless, dissolution studies over a longer period are necessary for further evaluation and kinetic determination. First implant inserts were printed successfully. The insert approach provides the opportunity to customize the shape by keeping the drug-loaded part and thus releasing profile constant.

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References:

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