Preparation and characterization of hot-melt extruded polycaprolactone-based filaments intended for 3D-printing of tablets

Laura Viidik , Jemina Vesala , Riikka Laitinen , Ossi Korhonen , Jarkko Ketolainen , Jaan Aruväli , Kalle Kirsimäe , Karin Kogermann , Jyrki Heinämäki , Ivo Laidmäe , Tuomas Ervasti

PII: S0928-0987(20)30407-3
DOI: https://doi.org/10.1016/j.ejps.2020.105619
Reference: PHASCI 105619

To appear in: *European Journal of Pharmaceutical Sciences*

Received date: 31 May 2020
Revised date: 4 October 2020
Accepted date: 19 October 2020

Please cite this article as: Laura Viidik , Jemina Vesala , Riikka Laitinen , Ossi Korhonen , Jarkko Ketolainen , Jaan Aruväli , Kalle Kirsimäe , Karin Kogermann , Jyrki Heinämäki , Ivo Laidmäe , Tuomas Ervasti , Preparation and characterization of hot-melt extruded polycaprolactone-based filaments intended for 3D-printing of tablets, *European Journal of Pharmaceutical Sciences* (2020), doi: https://doi.org/10.1016/j.ejps.2020.105619

Preparation and characterization of hot-melt extruded polycaprolactone-based filaments intended for 3D-printing of tablets

Laura Viidik[a], Jemina Vesala[b], Riikka Laitinen[b], Ossi Korhonen[b], Jarkko Ketolainen[b], Jaan Aruväli[c], Kalle Kirsimäe[c], Karin Kogermann[a], Jyrki Heinämäki[a], Ivo Laidmäe[a,d], Tuomas Ervasti[b]

[a]*Institute of Pharmacy, Faculty of Medicine, University of Tartu, Estonia*

[b]*School of Pharmacy, PromisLab, University of Eastern Finland, Finland*

[c]*Department of Geology, Institute of Ecology and Earth Sciences, Faculty of Science and Technology, University of Tartu, Estonia*

[d]*Department of Immunology, Institute of Biomedicine and Translational Medicine, Faculty of Medicine, University of Tartu, Estonia*

*Corresponding Author:*Laura Viidik, University of Tartu, Faculty of Medicine, Institute of Pharmacy, Nooruse Str. 1, 50411 Tartu, Estonia, Tel.: +372 56 609 319, Email: laura.viidik@ut.ee

Highlights

Arabic gum as plasticizer promotes the hot-melt extrusion of polycaprolactone-based filaments intended for 3D printing.

Inhomogeneity of a drug-polymer mass impairs the hot-melt extrusion of filaments and subsequent 3D printing.

Drug release can be regulated by modifying the geometry and texture of a 3D-printed tablet.

Abstract

Hot-melt extruded (HME) filaments are an essential intermediate product for the three-dimensional (3D) printing of drug delivery systems (DDSs) **by the fused deposition**

modelling (FDM) process. The aim of this study was to design novel polymeric 3D-printable HME filaments loaded with active pharmaceutical ingredients (APIs). The physical solid-state properties, mechanical properties, drug release and short-term storage stability of the filaments and 3D-printed DDSs were studied. Physical powder mixtures of polycaprolactone (PCL), plasticizer and API were manually blended, extruded by a single-screw extruder, and printed by a table-top FDM 3D-printing system. The composition of PCL and arabic gum (ARA) enabled the incorporation of 20%, 30% and 40% (w/w) of indomethacin (IND) and theophylline (THEO) into the HME filaments. The uneven distribution of API throughout the filaments impaired 3D printing. The HME filaments loaded with 20% IND or THEO were selected for the further analysis and printing tests (the ratio of PCL, ARA and IND or THEO was 7:1:2, respectively). The IND filaments were yellowish, mechanically strong and flexible, and they had a uniform filament diameter and smooth outer surface. The filaments containing THEO were smooth and off-white. The 3D-printed tablets fabricated from IND or THEO-loaded filaments showed sustained drug release *in vitro*. The drug release rate, however, significantly increased by changing the geometry of 3D-printed tablets from a conventional tablet structure to an unorthodox lattice ("honeycomb") structure. Overall, the combination of PCL and ARA provides an interesting novel polymeric carrier system for 3D-printable HME filaments and tablets.

Keywords

3D-printing, hot-melt extrusion, filament, polycaprolactone, arabic gum, drug release, fused deposition modelling

1. Introduction

Hot-melt extrusion (HME) is a widely used technique in manufacturing pharmaceutical oral dosage forms (Patil et al., 2016). A significant bottleneck associated with the use of

HME, however, is still the lack of a suitable polymeric carrier(s) for processing and delivering active pharmaceutical ingredients (APIs). HME process sets some strict requirements for a carrier polymer, since exceptional high temperatures are used in a fabrication process **(Goyanes et al., 2015a;** Kempin et al., 2018). The addition of plasticizer can increase the extrusion capacity of the carrier polymer (Desai et al., 2018). In addition, some APIs used in the formulation can act as a plasticizer, thus enhancing the process (Siepmann et al., 2006). The key HME process factors affecting the properties and performance of final extruded products are the extrusion temperature, screw speed and size, and feed rate (**Kallakunta et al., 2020**; Thiry et al., 2015).

The recent interest in exploiting three-dimensional (3D) printing technologies for pharmaceutical applications has provided also a significant extension for HME as a pharmaceutical fabrication method **(Awad et al., 2018; Azad et al., 2020; Dumpa et al., 2020; Giri et al., 2020; Melocchi et al., 2020, 2016;** Tan et al., 2018**; Vo et al., 2020; Yan et al., 2018)**. The HME filaments are used in a fused deposition modelling (FDM) assisted 3D-printing as an intermediate product. In a FDM-3D printing, HME filaments are molten and subsequently 3D-printed by means of layer-by-layer technique to form a pre-designed 3D-object. For ensuring the pharmaceutical quality of the final 3D-printed product, it is crucial that the HME filaments as intermediate products are uniform in terms of their geometrical, physical solid-state and pharmaceutical properties. To our best knowledge, the effects of HME filaments on the final properties of the 3D-printed drug delivery systems (DDSs) have not been systematically investigated and published up to date. **Novel approaches to FDM printing have also made possible to print without the intermediate HME process (Fanous et al., 2020; Goyanes et al., 2019).**

Polycaprolactone (PCL) is a biodegradable and water-insoluble polymer with a relatively low melting point of approximately 50-60 °C (Murphy et al., 2012). In the literature, PCL

has been reported as a suitable carrier polymer for a FDM-assisted 3D printing (**Beck et al., 2017; Fu et al., 2018; Goyanes et al., 2016;** Ramanath et al., 2008). To date, PCL has been applied as a carrier polymer for example in patient-specific 3D-printed antimicrobial wound dressings (Muwaffak et al., 2017), and more recently in biodegradable/ bioabsordable stents (Guerra and Ciurana, 2018). Natural gums, such as arabic gum, have been used as excipients in pharmaceutical dosage forms (Jani et al., 2009), but the use of these excipients in pharmaceutical HME and 3D printing is still limited.

The aim of the present study was to formulate and evaluate novel PCL-based HME filaments intended for a pharmaceutical FDM-3D-printing. The effects of three **different** dose model APIs (with different molecular weight, melting point and hydrophilicity) on the hot-melt extrusion of filaments and subsequently on the 3D-printing of tablets were investigated. The API-loaded filaments were extruded with a single-screw hot-melt extruder and 3D-printed into a tablet form with a table-top fused filament-based 3D printing system. The special attention was paid to the distribution of API and homogeneity of the HME filaments. The effects of geometry and texture of 3D-printed tablets on the drug release *in vitro* were also investigated.

2. Materials and methods

2.1 Materials

The base polymer in the extruded filaments was polycaprolactone (PCL, **inherent viscosity 0.82 dl/g,** Corbion Purac, Purasorb PC 08, USA). Polyethylene glycol, PEG (PEG 4000, Sigma-Aldrich, Germany), and arabic gum, ARA (Sigma-Aldrich, USA) were used as solid plasticizers. The APIs were chosen based on their different physical material characteristics and aqueous solubility. Indomethacin (IND, Acros organics,

United Kingdom), ibuprofen (IBU, Hangzhou Dayangchem CO. Ltd, China) and anhydrous theophylline (THEO, Sigma-Aldrich, Germany) were used for preparing physical mixtures (PMs) and HME filaments.

2.2 Preparation of PMs and HME filaments

The PMs used for a filament extrusion were manually prepared by using a "geometric dilution" protocol and a mortar and pestle. The powders were first manually ground by mortar and pestle before mixing. Three batches of IND, THEO and IBU were made with the content of API either 20%, 30% or 40%. All PMs contained 10% of the plasticizer, and the amount of PCL was varied in accordance to the API content. The filaments were extruded using a Filabot EX2 (Filabot, USA) single-screw hot-melt extruder. The most suitable extrusion temperature was screened and selected for each formulation. The extrusion speed was manually optimized during the process. The samples were stored in a dry cabinet (containing silica gel) at room temperature. The filaments intended for stability studies were stored at different conditions as described in chapter 2.9.

2.3 Differential scanning calorimetry

The thermal behavior of pure substances, PMs and HME filaments were studied by using the TA DSC2500 system (TA Instruments, USA). The samples of approximately 2-8 mg were placed in crimped aluminum pans with a pinhole on the lid. The samples were analyzed under a nitrogen purge of 50 ml/min, in the cooling unit a purge of 200 ml/min was used. The heating was conducted at 10 °C/min with a starting temperature at 25 °C. The end temperature was 170 °C for IND and IND extrudates, 150 °C for ARA, 75 °C for PCL, 280 °C for THEO, 270 °C for 20% THEO extrudate and 275 °C for 30% and 40% THEO extrudate.

2.4 X-ray powder diffraction

The powder samples, extruded filaments and 3D-printed tablets were studied by means of X-ray powder diffraction (XRPD) using a Bruker D8 Advance diffractometer with Ni filtered CuKα radiation, 0.3° divergence slit, two 2.5° Soller slits and LynxEye line detector, operated at 40 kV and 40 mA. Scanning steps of 0.019° 2θ from 3 to 55° 2θ and a total counting time of 175 s per step were used.

2.5 Homogeneity of HME filaments

For evaluating the homogeneity of filaments, 5-8 samples of 0.5 cm in length were cut and weighed from each experimental filament generated. **The sample size differed for practical reasons. The amount (length) of filament manufactured was not the same with the different materials, and therefore the samples were collected such a way that the result would present the whole filament as much as possible.** These samples were dissolved in 100 ml of acetonitrile by mixing in acetonitrile overnight. Aliquots (10 ml) were filtered (jet biofil 0,45 µm, Guangzhou Jet Bio-Filtration Co., China) and diluted (1:10) with a solution of acetonitrile and water (70:30 V/V). The concentration of API in the filaments was studied by high-performance liquid chromatography (HPLC) using a Gilson equipment consisting of 321 pump and 234 autoinjector (both from Gilson, France), 506C System Interface Module (Gilson, USA), and UV/Vis-151 detector (Gilson, France). A Gemini NX C18 250 mm x 4.60 mm HPLC colon (Phenomenex, USA) equipped with a SecurityGuard pre-colon (Phenomenex, USA) was used. The analytical wavelength used for IND and THEO was 270 nm and 210 nm, respectively. The mobile phase consisted of 70% of acetonitrile, 30% of water and 0,1% of trifluoroacetic acid (Sigma-Aldrich, USA) and the flow rate was adjusted to 1,2 ml/min

(Ojarinta et al., 2017). Standard curves were prepared using an acetonitrile/water 70/30 (V/V) solution.

2.6 Flexural strength of HME filaments

The mechanical properties of filaments were evaluated by a three-point bending test using a texture analyzer (AMETEK Brookfield CT3, USA) at room temperature. The filament samples were cut in 5-cm pieces, and their diameter was measured by a digital caliper. The distance between horizontal probes was 3 cm, trigger load was set at 10 g, and test speed was 1 mm/s. All measurements were carried out in triplicate.

2.7 3D-printing

The filaments were test-printed into cylindrical-shaped model tablets using a fused filament-based 3D printing system (System 30M, Hyrel 3D, USA; MK1-250 extruder). The printing temperature was altered depending on the formulation. A printer head moving speed was set at 30 mm/s and the temperature of a printing plate was adjusted for each formulation. To alter the drug release, the model tablets with equal weight but different surface area (**Figure 1**) were designed using a Solidworks software (Solidworks 2018, Dassault Systems, USA). The model printlets were manufactured by Zmorph 3D-printing system (ZMorph, Poland). The temperature in printing was held at 175 °C and a printing plate temperature was kept in the range of 35 °C and 40 °C for IND tablets. The corresponding temperature levels used with the THEO tablets were 190 °C and 40 °C, respectively. The filaments and prepared 3D printed samples were stored in a dry cabinet (containing silica gel) at room temperature before further analyses.

2.8 Drug release

Drug release of the 3D-printed tablets was studied *in vitro* by a Sotax AT6 dissolution tester (Sotax AG, Switzerland) using the USP Paddle method with a paddle rotation speed of 50 rpm. The volume and temperature of the dissolution media were 900 ml and 37 °C, respectively. The sample size was 5 ml and the samples were replaced by pure buffer solution immediately after sampling. The sampling time points were at 15 min, 30 min, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours and 24 hours. The release of IND from the tablets was studied in a phosphate buffer (pH 7.2; USP). For THEO, the dissolution media was HCl-buffer solution with sodium chloride (pH 1.2; USP). The dissolution tests were carried out in triplicate after one week from printing.

2.9 Physical stability of HME filaments

The physical appearance and potential solid-state changes of the HME filaments were studied for 3 months with the filaments stored at the elevated temperature of 40 °C and 75% relative humidity (RH), or alternatively in a refrigerator at 3-8 °C and 0% RH. The XRPD solid-state analysis of the fresh and stored HME filaments was performed as described previously.

2.10 Data analysis

All data are presented as mean ± standard deviation. Statistical analysis was performed by a two-tailed unpaired t-test. The tests were carried out using MS Excel.

3. Results and discussion

3.1 Formulation of HME filaments

Finding a suitable carrier polymer for HME process is crucial, since the polymer affects the stability and physicochemical characteristics of the final drug-loaded filaments. We selected PCL as a carrier polymer, since it is extrudable in HME process alone at 75 °C.

The HME filaments fabricated from PCL, however, were soft, somewhat uneven in thickness and not intact enough for handling. In our study, the main reason for adding a secondary excipient (to carrier polymer), was to improve the overall processability of given filaments. This can be achieved by the addition of a suitable plasticizer (Desai et al., 2018). For HME process, the plasticizer of choice would be a solid plasticizer, since liquid plasticizers could extensively decrease the viscosity and solidity of HME mass, and thus impairing extrusion and subsequent 3D printing. To date, there are only few studies in the literature reporting on the use of solid plasticizer(s) in the HME of polymeric filaments (Desai et al., 2018; Schilling et al., 2007; Wu and Mcginity, 2003). We investigated PEG 4000, and ARA as solid plasticizers in fabricating the HME filaments. Based on the results of our preliminary tests, a carrier polymer-plasticizer mixture of PCL and ARA was chosen for fabricating the HME filaments loaded with API. In comparison with the other solid plasticizers tested, ARA (incorporated with PCL) aided the most a HME process enabling the most uniform filament flow. As discussed before, pure PCL filaments were too soft for further processing. Addition of ARA helped to make the structure firmer, yet not making it brittle and unsuitable for any mechanical handling.

The compositions of the API-loaded filaments, HME process parameters and final filament properties are summarized in **Table 1**. For fabricating the HME filaments, the model API (IND, THEO or IBU) was loaded in the filaments at the concentration levels of 20%, 30% and 40%. The HME temperature was kept as low as possible for each formulation (**Table 1**). We found that the HME filaments loaded with IND or THEO can be fabricated at all three API concentrations without any limitations. The addition of IBU in the HME filaments, however, resulted in soft filaments with an uneven filament diameter and non-repeatable process. Therefore, the IBU-loaded filaments were excluded from further studies. The limitations associated with IBU filament formulations could be

explained by the significantly lower melting temperature of IBU (80 °C) (Lerdkanchanaporn and Dollimore, 1997) compared to approximately 160°C for IND (Tita et al., 2009) or 270 °C for THEO (Shaikh et al., 2019).

3.2 Physical appearance and homogeneity of HME filaments

3.2.1 Physical appearance

Figure 2 shows the appearance of the API-loaded HME filaments, and the characteristics of the filaments are described more detailed in **Table 1**. With the THEO-loaded filaments, the surface roughness apparently increased as the concentration of the API in the filaments was increased. The corresponding trend was not observed with the IND-loaded HME filaments. The IND-loaded filaments, however, were found to be more yellowish in color as the concentration of API was increased. The average diameter (n = 9) for IND20 filaments was 1.83 ± 0.15 mm and for IND40 filaments 1.78 ± 0.03 mm (**Table 1**). The present difference, however, was not statistically significant. With the THEO filaments, the trend goes perhaps surprisingly the other way round: THEO20 filaments had a diameter of 1.74 ± 0.07 mm and THEO40 filaments 1.88 ± 0.03 mm ($p < 0.05$). In both cases, the HME filaments with higher percentage of API had a more uniform filament diameter.

3.2.2 Homogeneity

The uniformity of HME filaments is one of the key parameters for the further development of successful 3D-printed DDSs (Govender et al., 2020). The concentrations of API in the HME filaments are shown in **Table 1. With both THEO- and IND-loaded filaments the actual API concentrations were lower than the corresponding theoretical values. From these, the THEO-loaded filaments were closer to the**

nominal value at all concentrations studied. The change in API concentration within the filament formulations studied is shown on **Figure 3**. With the IND-loaded filaments, the concentration of IND was decreased on the course of HME process. The corresponding trend was not observed with the THEO-loaded filaments, but the variation between the API concentrations is evident. The variation in the content of all APIs was the smallest with the filaments having the highest concentration of API. This heterogeneity could be explained by the inadequate degree of mixing of API and excipients prior to extrusion, or de-mixing during extrusion. As mentioned earlier, the particle size reduction of the components prior to HME could improve the homogeneity of the filaments. Another reason for the inhomogeneity of the IND-loaded filaments could be the cohesiveness of IND, which has been reported to cause challenges in a HME process (Holländer et al., 2016). We also found that the homogeneity of the HME filaments loaded with THEO was not very good. There are, however, no reports in the literature for such limitations with the HME filaments loaded with THEO.

3.3 Mechanical properties of HME filaments

Several studies in the literature have focused on describing the importance and evaluation of the mechanical properties of filaments intended for 3D-printing (Aho et al., 2019; Nasereddin et al., 2018). We used the established three-point bending test for investigating the mechanical properties of HME filaments (**Figure 4**). This evaluation method was considered as the test of choice for characterizing our filaments, since it provides information about the filament properties relevant to the process behavior in HME and resistant to flexural strength. The results of a three-point bending test showed that with both IND and THEO filaments the decrease in API content resulted in the filaments with higher resistance to deformation (**Figure 4**). This could be explained by the significantly higher ratio of polymer (PCL) to API in the binary mixture of filaments,

thus promoting the mechanical properties of HME filaments. This phenomenon could be expected, since PCL is shown to have plasticizing characteristics and it has been also used as a plasticizer (Olewnik-Kruszkowska et al., 2016). As seen in **Figure 4**, the mechanical strength (load) values for the IND filaments were quite equal in comparison with the corresponding values obtained with the THEO filaments (the difference in load values was not statistically significant). With the IND filaments, however, the values for the deformation (at break) were significantly higher than the corresponding values for the THEO filaments (**Figure 4**). This suggests the auto-plasticization characteristic of IND resulting in enhanced strain behavior of HME filaments. On the contrary, the limited deformation of THEO filaments suggests that THEO does not support the plasticization and formation of PCL filaments in a HME process. With the THEO filaments, the relatively large variation in the results of a three-point bending test could be explained by the uneven filament diameter observed with the THEO filaments.

3.4 3D printing of HME filaments

According to the state-of-the-art literature, the temperature in 3D printing should be set slightly higher than the temperature used in the HME of the polymeric filaments (Kollamaram et al., 2018). Therefore, it is important to select the temperature used in HME process as low as possible to minimize the potential negative effects on the final product in 3D printing. We found that all HME filaments loaded with a model API were applicable for the 3D printing of tablets with different geometries. The HME filaments loaded with 20% of IND showed very good 3D-printing properties, and the printing of tablets was performed without any drawbacks. When the concentration of IND was higher, the 3D printing was limited due to regular nozzle blockages. With the HME filaments loaded with THEO, the uneven filament diameter made the 3D printing of tablets somewhat complicated. While printing solid cylindrical-shape tablets or lattice

("honeycomb") tablets (**Figure 1**), no technical problems were met. Both types of 3D-printed tablets were successfully generated using the HME filaments of an API. The *in-vitro* drug release of the present 3D-printed tablets with different geometry and texture are described later (see section 3.5).

3.5 Physical solid state and storage stability

3.5.1 X-ray powder diffraction (XRPD)

The physical solid-state changes (XRPD) of the model APIs (IND, THEO) and the key excipients during HME and 3D-printing process are shown in **Figure 5.** The XRPD pattern of IND powder showed the characteristic major diffraction peaks for the γ-polymorph (**Figure 5A**). These results are in line with the results described in the literature (Aceves-Hernandez et al., 2009). The HME of IND-loaded filaments resulted in an apparent loss in crystallinity of the API (i.e., blunting of the corresponding XRPD reflections). After 3D printing, however, it is evident that IND is in an amorphous form (**Figure 5A**). The XRPD pattern of THEO powder (**Figure 5B**) showed the characteristic diffraction peaks of THEO, and this is in good agreement with the results described in the literature (Phadnis and Suryanarayanan, 1997). These characteristic reflections can be also observed in the XRPD diffraction patterns obtained with the PMs and HME filaments of THEO.

Figure 5 shows the physical stability of the API-loaded HME filaments stored for 3 months at the elevated temperature of 40 °C and humidity of 75% RH, or in a refrigerator at 3-8 °C and 0% RH. We found that the HME filaments loaded with IND or THEO changed its appearance and colour from off-white/yellowish to either darker (IND) or lighter (THEO) brownish paste-like slurry, when the filaments were stored at 40°C/75% RH for 3 months. In the slurry, there were some fiber-like and crystal structures

detectable. The crystal formation can be observed also in the XRPD diffraction patterns of the aged HME filaments presenting the characteristic diffraction peaks for IND and THEO (**Figure 5**). A slight shift in the diffraction peak positions can be observed, which could be due to the limitations in the sample preparation of the filaments for XRPD. When the IND or THEO-loaded HME filaments were stored in a refrigerator (3-8 °C and 0% RH) for 3 months, no physical solid-state changes were detected in the filaments (**Figure 5**). The colour of all aged filaments, however, was slightly changed to darker, but the shape and structure of the filaments were virtually the same as observed with the original filaments.

3.5.2 Differential scanning calorimetry (DSC)

The thermal behaviour of pure substances, HME filaments and 3D-printed tablets is presented in **Figure 6**. The DSC thermograms in **Figure 6A** showed the characteristic melting endotherm for IND (at onset temperature 160 °C) and THEO (270 °C), which is in good agreement with the literature (Holländer et al., 2016; Karmwar et al., 2011; Shaikh et al., 2019). As shown in **Figure 6A**, PCL as a semi-crystalline polymer presents a melting endotherm at onset temperature of approximately 55 °C. The DSC thermograms for the HME filaments (**Figure 6B**) show the characteristic melting endotherms for both IND and PCL, respectively. It is likely that amorphous IND within HME recrystallized during heating, as XRPD confirmed the presence of amorphous IND. However, a slight shift of the endothermic peak temperature of PCL (approximately 2.5 °C) was observed with the HME filaments compared to that obtained with pure PCL. This suggests potential interaction (but not necessarily incompatibility) of PCL with IND confirming also the previous results reported in the literature on the interaction between the API and polymer (Kempin et al., 2017). As seen in **Figure 6B**, the melting peak for

IND is more prominent in the DSC thermograms of HME filaments loaded with higher concentration (30% or 40%) of API. In the case of 3D-printed tablets (**Figure 6C**), the melting endotherm of PCL has been shifted towards lower temperature. The DSC thermogram of 3D-printed tablets with 40% of API presented a small characteristic melting peak for IND indicating that the API is at least partially in a crystalline form.

With the THEO filaments, the melting endotherm of PCL can be seen at 55 °C onset temperature (**Figure 6D**), and this peak was slightly shifted to lower temperature as the concentration of API in the filaments was decreased. Similar endothermic peak shift (PCL) was observed with the IND filaments, thus indicating potential interaction of PCL with the other components of the HME filaments (APIs, ARA). Also, the melting of THEO can be seen, confirming its crystallinity. **Figure 6E** shows the DSC thermogram of 3D-printed tablets of THEO. The deformed endothermic peaks for both PCL and THEO suggest the occurrence of some thermal-induced changes in the formulation. Overall, the present DSC thermal profiles are in good agreement with the XRPD results shown previously (**Figure** 5).

3.6 Drug release *in vitro*

The 3D-printed tablets fabricated from the API-loaded HME filaments presented an extreme sustained drug release behavior *in vitro*. The drug release of the 3D-printed tablets (cylinder-shape) loaded with IND was negligible (i.e., practically no drug was released within 24 hours), therefore these results are not presented. In case of the 3D-printed tablets (cylinder-shape) loaded with THEO (**Figure 7**), the amount of API **(theoretical loading 48.9 ± 3.7 mg)** released within 24 hours was somewhat higher, but the overall drug release was still very low (less than 5%). According to the literature, the PCL-based DDSs exhibit a prolonged drug release (Lao et al., 2008). The dissolution

results obtained in our study suggest that the present active-loaded 3D-printed tablets based on PCL are more applicable for implant drug-delivery applications than for oral administration. To accelerate the drug release, we made further 3D printing experiments with the HME filaments loaded with the model APIs.

We changed the geometry and texture of the 3D-printed tablets from cylindrical to "honeycomb" **(theoretical loading 48.3 ± 5.2 mg)** and found a significant increase in the amount of drug released compared to that obtained with conventional-shaped tablets (**Figure 7**). The weight of the novel "designed" tablets was kept as much as possible the same as with the conventional-shaped tablets (assuming that the amount of API in both tablets would be then identical as well). The drug release of the "honeycomb"-patterned 3D-printed tablets loaded with THEO was approximately 12% within 24 hours, while the drug release of the cylinder-shaped tablets was only 2% within the same time-period. Much larger outer surface area of the "honeycomb"-structured tablets greatly enhances the drug release from the 3D-printed tablets. The positive effect of the increased surface area on the drug release behavior has been reported also in the literature (Goyanes et al., 2015b). As the size, shape and texture of 3D-printed DDSs are easily to be modified, this could open up a true option for the patient-specific formulation of drug products and tailoring the drug release in accordance to patient needs in the future.

4. Conclusions

The combination of PCL and ARA proved to be a suitable polymeric carrier system for HME filaments loaded with API (such as IND or THEO). The present filaments are extrudable at a relatively low temperature and they have smooth surface and sufficient mechanical properties. Our study suggests that the filaments can be loaded up to 40% of API being still capable to be produced in a HME process. One important challenge

associated with the HME filaments, however, is the uniform distribution of API and overall homogeneity of the filaments. Furthermore, the physical stability of such HME filaments is limited, thus underlining the importance of proper storage conditions for the filaments. The HME filaments developed in this study can be successfully 3D-printed into tablets. The 3D printing enables also the modification of the size, shape and texture of the printed tablet. Our results suggest that the drug release of conventional cylinder-shape 3D-printed tablet can be significantly improved by modifying the tablet geometry and texture by means of 3D printing (i.e., a lattice "honeycomb" tablet form).

Funding

This study is funded by the Estonian Research Council projects IUT34-18 and PRG726, and by the Nordic POP (patient-oriented products), a Nordic University Hub project #85352 funded by NordForsk.

References

Aceves-Hernandez, J.M., Nicolas-Vazquez, I., Aceves, F.J., Hinojosa-Torres, J., Paz, M., Castano, V.M., 2009. Indomethacin polymorphs: Experimental and conformational analysis. J. Pharm. Sci. 98, 2448–2463.

Aho, J., Bøtker, J.P., Genina, N., Edinger, M., Arnfast, L., 2019. Roadmap to 3D-Printed Oral Pharmaceutical Dosage Forms : Feedstock Filament Properties and Characterization for Fused Deposition Modeling. J. Pharm. Sci. 108, 26–35. https://doi.org/10.1016/j.xphs.2018.11.012

Awad, A., Tren, S.J., Gaisford, S., Basit, A.W., 2018. 3D printed medicines : A new branch of digital healthcare. Int. J. Pharm. 548, 586–596. https://doi.org/10.1016/j.ijpharm.2018.07.024

Azad, M.A., Olawuni, D., Kimbell, G., Badruddoza, A.Z., Hossain, S., Sultana, T., 2020. Polymers for Extrusion-Based 3D Printing of Pharmaceuticals : A Holistic Materials – Process Perspective. Pharmaceutics 12, 124.

Beck, R.C.R., Chaves, P.S., Goyanes, A., Vukosavljevic, B., Buanz, A., Windbergs, M., Basit, A.W., Gaisford, S., 2017. 3D printed tablets loaded with polymeric nanocapsules : An innovative approach to produce customized drug delivery systems. Int. J. Pharm. 528, 268–279. https://doi.org/10.1016/j.ijpharm.2017.05.074

Desai, D., Sandhu, H., Shah, N., Malick, W., Zia, H., Phuapradit, W., Ram, S., Vaka, K., 2018. Selection of Solid-State Plasticizers as Processing Aids for Hot-Melt Extrusion. J. Pharm. Sci. 107, 372–379. https://doi.org/10.1016/j.xphs.2017.09.004

Dumpa, N.R., Bandari, S., Repka, M.A., 2020. Novel Gastroretentive Floating Pulsatile Drug Delivery System Produced via Hot-Melt Extrusion and Fused Deposition Modeling 3D Printing. Pharmaceutics 12, 52.

Fanous, M., Gold, S., Muller, S., Hirsch, S., Ogorka, J., 2020. Simplification of fused deposition modeling 3D-printing paradigm : Feasibility of 1-step direct powder printing for immediate release dosage form production. Int. J. Pharm. 578, 119124. https://doi.org/10.1016/j.ijpharm.2020.119124

Fu, J., Yu, X., Jin, Y., 2018. 3D printing of vaginal rings with personalized shapes for controlled release of progesterone. Int. J. Pharm. 539, 75–82. https://doi.org/10.1016/j.ijpharm.2018.01.036

Giri, B.R., Song, E.S., Kwon, J., Lee, J., Park, J., 2020. Fabrication of Intragastric Floating , Controlled Release 3D Printed Theophylline Tablets Using Hot-Melt Extrusion and Fused Deposition Modeling. Pharmaceutics 12, 77.

Govender, R., Abrahmsen-Alami, S., Folestad, S., Larsson, A., 2020. High Content Solid Dispersions for Dose Window Extension : A Basis for Design Flexibility in Fused Deposition Modelling. Pharm. Res. 37, 9.

Goyanes, A., Allahham, N., Trenfield, S.J., Stoyanov, E., Gaisford, S., Basit, A.W., 2019. Direct powder extrusion 3D printing : Fabrication of drug products using a novel single-step process. Int. J. Pharm. 567. https://doi.org/10.1016/j.ijpharm.2019.118471

Goyanes, A., Buanz, A.B.M., Hatton, G.B., Gaisford, S., Basit, A.W., 2015a. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. Eur. J. Pharm. Biopharm. 89, 157–162. https://doi.org/10.1016/j.ejpb.2014.12.003

Goyanes, A., Det-amornrat, U., Wang, J., Basit, A.W., Gaisford, S., 2016. 3D scanning and 3D printing as innovative technologies for fabricating personalized topical drug delivery systems. J. Control. Release 234, 41–48. https://doi.org/10.1016/j.jconrel.2016.05.034

Goyanes, A., Robles, P., Buanz, A., Basit, A.W., Gaisford, S., 2015b. Effect of geometry on drug release from 3D printed tablets. Int. J. Pharm. 494, 657–663. https://doi.org/10.1016/j.ijpharm.2015.04.069

Guerra, A.J., Ciurana, J., 2018. 3D-printed bioabsordable polycaprolactone stent : The effect of process parameters on its physical features. Mater. Des. 137, 430–437. https://doi.org/10.1016/j.matdes.2017.10.045

Holländer, J., Genina, N., Jukarainen, H., Khajeheian, M., Rosling, A., Mäkilä, E., Sandler, N., 2016. Three-Dimensional Printed PCL-Based Implantable Prototypes of Medical Devices for Controlled Drug Delivery. J. Pharm. Sci. 105, 2665–2676.

https://doi.org/10.1016/j.xphs.2015.12.012

Jani, G.K., Shah, D.P., Prajapati, V.D., Jain, V.C., 2009. Gums and mucilages : versatile excipients for pharmaceutical formulations. Asian J. Pharm. Sci. 4, 308–322.

Kallakunta, V.R., Sarabu, S., Bandari, S., Batra, A., Bi, V., Durig, T., Repka, M.A., 2020. Stable amorphous solid dispersions of fenofibrate using hot melt extrusion technology : Effect of formulation and process parameters for a low glass transition temperature drug. J. Drug Deliv. Sci. Technol. 58, 101395. https://doi.org/10.1016/j.jddst.2019.101395

Karmwar, P., Graeser, K., Gordon, K.C., Strachan, C.J., Rades, T., 2011. Investigation of properties and recrystallisation behaviour of amorphous indomethacin samples prepared by different methods. Int. J. Pharm. 417, 94–100. https://doi.org/10.1016/j.ijpharm.2010.12.019

Kempin, W., Domsta, V., Grathoff, G., Brecht, I., Semmling, B., Tillmann, S., Weitschies, W., Seidlitz, A., 2018. Immediate Release 3D-Printed Tablets Produced Via Fused Deposition Modeling of a Thermo-Sensitive Drug. Pharm. Res. 35.

Kempin, W., Franz, C., Koster, L., Schneider, F., Bogdahn, M., Weitschies, W., Seidlitz, A., 2017. Assessment of different polymers and drug loads for fused deposition modeling of drug loaded implants. Eur. J. Pharm. Biopharm. 115, 84–93. https://doi.org/10.1016/j.ejpb.2017.02.014

Kollamaram, G., Croker, D.M., Walker, G.M., Goyanes, A., Basit, A.W., Gaisford, S., 2018. Low temperature fused deposition modeling (FDM) 3D printing of thermolabile drugs. Int. J. Pharm. 545, 144–152. https://doi.org/10.1016/j.ijpharm.2018.04.055

Lao, L.L., Venkatraman, S.S., Peppas, N.A., 2008. Modeling of drug release from biodegradable polymer blends. Eur. J. Pharm. Biopharm. 70, 796–803. https://doi.org/10.1016/j.ejpb.2008.05.024

Lerdkanchanaporn, S., Dollimore, D., 1997. A Thermal Analysis Study of Ibuprofen. J. Therm. Anal. 49, 879–886.

Melocchi, A., Parietti, F., Maroni, A., Foppoli, A., Gazzaniga, A., Zema, L., 2016. Hot-melt extruded filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling. Int. J. Pharm. 509, 255–263. https://doi.org/10.1016/j.ijpharm.2016.05.036

Melocchi, A., Uboldi, M., Maroni, A., Foppoli, A., Palugan, L., Zema, L., Gazzaniga, A., 2020. 3D printing by fused deposition modeling of single- and multi-compartment hollow systems for oral delivery – A review. Int. J. Pharm. 579, 119155. https://doi.org/10.1016/j.ijpharm.2020.119155

Murphy, G.A., Leeke, M.J., Jenkins, S.H., 2012. A Comparison of the use of FTIR spectroscopy with DSC in the characterisation of melting and crystallisation in polycaprolactone. J. Therm. Anal. Calorim. 107, 669–674. https://doi.org/10.1007/s10973-011-1771-7

Muwaffak, Z., Goyanes, A., Clark, V., Basit, A.W., Hilton, S.T., Gaisford, S., 2017. Patient-speci fi c 3D scanned and 3D printed antimicrobial polycaprolactone wound dressings. Int. J. Pharm. 527, 161–170. https://doi.org/10.1016/j.ijpharm.2017.04.077

Nasereddin, J.M., Wellner, N., Alhijjaj, M., Belton, P., Qi, S., 2018. Development of a Simple Mechanical Screening Method for Predicting the Feedability of a

Pharmaceutical FDM 3D Printing Filament. Pharm. Res. 35, 151.

Ojarinta, R., Heikkinen, A.T., Sievänen, E., Laitinen, R., 2017. Dissolution behavior of co-amorphous amino acid-indomethacin mixtures : The ability of amino acids to stabilize the supersaturated state of indomethacin. Eur. J. Pharm. Biopharm. 112, 85–95. https://doi.org/10.1016/j.ejpb.2016.11.023

Olewnik-Kruszkowska, E., Kasperska, P., Koter, I., 2016. Effect of poly (ε -caprolactone) as plasticizer on the properties of composites based on polylactide during hydrolytic degradation. React. Funct. Polym. 103, 99–107. https://doi.org/10.1016/j.reactfunctpolym.2016.03.026

Patil, H., Tiwari, R. V, Repka, M.A., 2016. Hot-Melt Extrusion : from Theory to Application in Pharmaceutical Formulation. AAPS PharmSciTech 17, 20–42. https://doi.org/10.1208/s12249-015-0360-7

Phadnis, N. V., Suryanarayanan, R., 1997. Polymorphism in Anhydrous Theophylline - Implications on the Dissolution Rate of Theophylline Tablets. J. Pharm. Sci. 86, 1256–1263.

Ramanath, H.S., Chua, C.K., Leong, K.F., Shah, K.D., 2008. Melt flow behaviour of poly-e-caprolactone in fused deposition modelling. J. Mater. Sci. Mater. Med. 19, 2541–2550. https://doi.org/10.1007/s10856-007-3203-6

Schilling, S.U., Shah, N.H., Malick, A.W., Infeld, M.H., Mcginity, J.W., 2007. Citric acid as a solid-state plasticizer for Eudragit RS PO. J. Pharm. Pharmacol. 59, 1493–1500. https://doi.org/10.1211/jpp.59.11.0005

Shaikh, R., Walker, G.M., Croker, D.M., 2019. Continuous, simultaneous cocrystallization and formulation of Theophylline and 4-Aminobenzoic acid

pharmaceutical cocrystals using twin screw melt granulation. Eur. J. Pharm. Sci. 137, 104981. https://doi.org/10.1016/j.ejps.2019.104981

Siepmann, F., Brun, V. Le, Siepmann, J., 2006. Drugs acting as plasticizers in polymeric systems : A quantitative treatment. J. Control. Release 115, 298–306. https://doi.org/10.1016/j.jconrel.2006.08.016

Tan, D.K., Maniruzzaman, M., Nokhodchi, A., 2018. Advanced Pharmaceutical Applications of Hot-Melt Extrusion Coupled with Fused Deposition Modelling (FDM) 3D Printing for Personalised Drug Delivery. Pharmaceutics 10. https://doi.org/10.3390/pharmaceutics10040203

Thiry, J., Krier, F., Evrard, B., 2015. A review of pharmaceutical extrusion: Critical process parameters and scaling-up. Int. J. Pharm. 479, 227–240. https://doi.org/10.1016/j.ijpharm.2014.12.036

Tita, B., Fulias, A., Rusu, G., Tita, D., 2009. Thermal Behaviour of Indomethacin - Active Substance and Tablets Kinetic Study Under Non-Isothermal Conditions. Rev. Chim.

Vo, A.Q., Zhang, J., Nyavanandi, D., Bandari, S., Repka, M.A., 2020. Hot melt extrusion paired fused deposition modeling 3D printing to develop hydroxypropyl cellulose based fl oating tablets of cinnarizine. Carbohydr. Polym. 246, 116519. https://doi.org/10.1016/j.carbpol.2020.116519

Wu, C., Mcginity, J.W., 2003. Influence of methylparaben as a solid-state plasticizer on the physicochemical properties of Eudragit w RS PO hot-melt extrudates. Eur. J. Pharm. Biopharm. 56, 95–100. https://doi.org/10.1016/S0939-6411(03)00035-3

Yan, Q., Dong, H., Su, J., Han, J., Song, B., Wei, Q., Shi, Y., 2018. A Review of 3D

Printing Technology for Medical Applications. Engineering 4, 729–742.
https://doi.org/10.1016/J.ENG.2018.07.021

Figure 1. Examples of tablet geometries and textures used for 3D printing and drug release studies: lattice “honeycomb” tablet (left) and solid cylindrical tablet (right).

Figure 2. Hot-melt extruded (HME) filaments composing of polycaprolactone, arabic gum and 20% of (A) indomethacin, (B) theophylline, or (C) ibuprofen.

Figure 3. Changes in the concentration (%) of (A) indomethacin (IND) and (B) theophylline (THEO) throughout hot-melt extruded filaments.

Figure 4. Load-displacement curves of hot-melt extruded filaments loaded with theophylline (THEO) and indomethacin (IND) at two different drug concentrations (20% and 40%). The filaments were tested with a three-point bending test (n = 3). Each line represents one test sample.

Figure 5. XRPD diffractograms of model drugs, polycaprolactone (PCL), arabic gum (ARA) as a powder form, and the corresponding diffractograms for physical mixture (PM), hot-melt extruded filaments (EXT), 3D-printed tablet (3DP), and the filaments after a 3-month storage stability test. Key: (A) Indomethacin (IND) and (B) Theophylline (THEO).

Figure 6. DSC thermograms (exotherm up) of (A) pure materials, (B) hot-melt extruded (HME) filaments loaded with indomethacin (IND), (C) 3D-printed tablets of IND, (D) HME filaments loaded with theophylline (THEO), and (E) 3D-printed tablets of THEO.

Figure 7. Drug release profiles of 3D-printed tablets of **20%** theophylline (THEO) with different geometry and texture (n = 3).

Table 1. Composition, process parameters and properties of the drug-loaded filaments.

Batch	**PCL**	**ARA**	**API**	**API (%) measured**	**Extrusion temperature**	**Filament description**	⌀ (mm)
IND20	70%	10%	20%	13.3 ± 3.8	100...105°C	Light yellowish uniform filament, slightly rough surface	1.83 ± 0.15
IND30	60%	10%	30%	16.3 ± 4.8	100...105°C	Light yellowish uniform filament, slightly rough surface	
IND40	50%	10%	40%	33.9 ± 3.4	100...105°C	Light yellowish, slightly rough surface, more brittle	1.78 ± 0.03
THEO20	70%	10%	20%	19.1 ± 4.5	120...125°C	Off-white uniform filament, smooth surface	1.74 ± 0.07
THEO30	60%	10%	30%	29.6 ± 3.4	120...125°C	Off-white uniform filament, somewhat rough surface	
THEO40	50%	10%	40%	40.0 ± 3.9	120...125°C	Off-white uniform filament, visibly rough surface	1.88 ± 0.03
IBU20	70%	10%	20%	-	75…85°C	Light yellowish, non-uniform, rough surface	

IBU30	60%	10%	30%	-	-	-	
IBU40	50%	10%	40%	-	-	-	

Key: ARA- arabic gum; API- active pharmaceutical ingredient; ext- extruded HME filaments; IBU- ibuprofen; IND- indomethacin; THEO- theophylline; PCL- polycaprolactone.