Drug-loaded poly(ε-caprolactone) for 3D printing of personalized medicine: A rheological study

Johanna Aho, Natalja Genina, Magnus Edinger, Johan P. Botker, Stefania Baldursdottir, and Jukka Rantanen

University of Copenhagen, Department of Pharmacy, Copenhagen, Denmark

ABSTRACT

Feed filament properties important for successful fused deposition modeling 3D printing of personalized dosage forms were investigated using indomethacin as a model drug and poly(ε-caprolactone) as a matrix polymer, with weight/weight ratios of 10/90, 30/70, and 50/50 %. First, these were melt-mixed and extruded into filaments with varying compositions using a co-rotating twin-screw extruder. The rheological properties of the extruded filaments were investigated and compared to those of the pure poly(ε-caprolactone). The viscosity of the 10/90 and 30/70 mixtures was lower than that of the pure polymer, whereas the viscosity of the 50/50 mixture was significantly higher, showing characteristics typical for concentrated dispersions. Disk-shaped model dosage forms were successfully printed from all the studied drug-polymer mixtures.

INTRODUCTION

Today's pharmaceutical industry is operating by a "one size fits all" principle, allowing very little tailoring of a product between different patients[1]. In reality, the patients' response to drugs and administered dose can vary significantly, depending on factors such as the gender, age, lifestyle, ethnic background, or a possible pathological state. In the medicine of the future, the aim is to treat the patients employing a personalized approach, selecting the most suitable drug in a precisely defined therapeutic dose according to the individual requirements, determined using highly sophisticated diagnostic tools[2]. Manufacturing of such personalized drugs, including, for example, combination drugs, tailored variable doses, or drugs aimed for different administration routes, demands a new kind of flexibility from the process and the equipment. 3D printing offers an interesting option as a flexible small-batch manufacturing platform typically required for personalized dosage forms[3-5].

Fused deposition modeling (FDM) is a 3D printing technique where the raw material is fed into the heated printer nozzle as a filament, by counter-rotating pulling wheels. The filament melts as it enters the nozzle, and the yet solid part acts as a piston pushing the molten material through the nozzle orifice. The nozzle moves in the *xy*-plane at a set speed, while the printing platform moves down allowing adding the material layer by layer to form the structure instructed by the CAD drawing file input[6].

The printability using the FDM method is affected by the feed material properties: Firstly, in the pulling wheels at the filament feed, where the filament has to be ductile enough to allow some bending, and hard enough not to be squeezed by the wheels. Secondly, a steady flow has to be ensured through the nozzle: A too viscous material or large filler particles or their agglomerates may clog the nozzle, whereas too runny

material may drool out spontaneously from the nozzle tip. In addition to the mechanical and melt flow properties, the thermal properties play an important role in cooling and solidification of the printed structure[7].

This work presents a pre-study for 3D printing, focusing on the rheological properties of drug containing feed filament for printing dosage forms using indomethacin (IND) as a model drug and poly(ε-caprolactone) (PCL) as a model thermoplastic polymer matrix material.

EXPERIMENTAL

MATERIALS

Poly(ε-caprolactone) CAPA™ 6500 (M_w= 50 000 g/mol, T_m= 58-60 °C, and T_g= -60 °C, reported by the polymer supplier Perstorp, UK), purchased from Makerbot in filament form, was used as a model matrix polymer. Indomethacin γ-form (T_m= 160 °C) was used as a model drug. IND and PCL were mixed in w/w ratios of 10/90, 30/70, and 50/50.

METHODS

The physical drug-polymer mixtures were melt mixed and extruded into filaments using a lab-scale co-rotating twin-screw extruder (Xplore Intruments, The Netherlands). The mixtures were first homogenized at T=100 °C in re-circulation mode for 5 min at a screw speed of 30 RPM, after which they were extruded at 5 RPM through a 1.5 mm circular die into a filament and cooled at ambient conditions.

The rheological properties of the extruded filaments were investigated in steady-state rotational shear (SSRS) and small-amplitude oscillatory shear (SAOS), using AR2000 rheometer (TA Instruments, New Castle, DE, US) with 25 mm parallel plate setup and environmental test chamber.

The printability was tested by producing model disks (diameter 9 mm, thickness 1.5 mm) from the extruded filaments with each composition using a MakerBot Replicator 2, (Makerbot, New York, NY, US) 3D printer. The printer nozzle temperature was set to 100 °C and the printer head speed to 90 mm/s.

Evaluation of the shear rate in the printer nozzle

In order to estimate the feed filament viscosity in the 3D printing process, the volume flow rate through the printer nozzle was calculated from the pre-set nozzle speed v_n, i.e., the speed at which molten material is deposited from the nozzle. The volume flow rate Q can be calculated using the radius of the nozzle exit, r_n:

$$Q = \pi r_n^2 v_n \quad (1)$$

The corresponding apparent shear rate at the nozzle wall can be then calculated as:

$$\dot{\gamma}_{wa} = \frac{4Q}{\pi r_n^3} \quad (2)$$

With the printer nozzle radius of 0.2 mm and speed of 90 mm/s, $\dot{\gamma}_{wa}$=1800 s^{-1}.

RESULTS

Rheology

For pure PCL, 10/90, and 30/70 mixtures the empirical Cox-Merz rule was found valid (Fig.1.), thus, estimations of the shear viscosity at high shear rates, encountered in the FDM on the basis of SAOS measurements. The decrease of viscosity (plasticization) compared to the pure PCL further indicates that most of the IND content is likely to be dissolved in PCL at the studied temperature[8]. No clear Newtonian plateau could be observed in SSRS for the 50/50 mixture, and the viscosity at low shear rates was roughly two-fold compared to the pure PCL. These observations indicate that the solubility of IND in PCL was exceeded and the undissolved IND content caused the mixture to have flow properties to approach concentrated dispersions. The steady-state

shear viscosity and complex viscosity did not show a good overlay, thus the Cox-Merz rule was not valid. Therefore, the flow properties at high shear rates encountered in the printing process are likely to deviate from the measured complex viscosity and cannot be directly evaluated from the SAOS results.

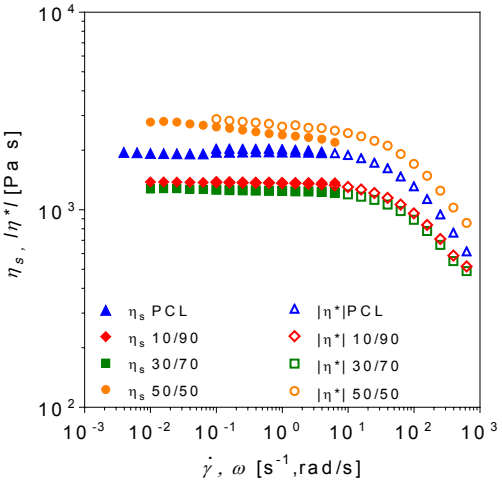

Figure 1. Shear and complex viscosity of PCL and extruded IND-PCL mixtures

Printability

All the custom-made extrudates proved to be printable at the same pre-set conditions as the pure PCL. However, the poor controllability of the filament thickness during extrusion led to some variation in the dimensions and surface quality of the printed objects (Fig.2.).

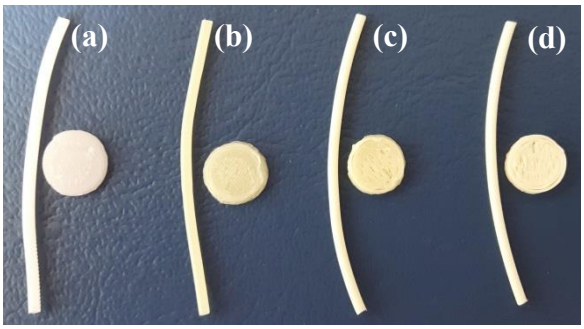

Figure 2. Extruded filaments and the model disks (diameter 9 mm, thickness 0.5 mm) printed from them: (a) PCL, (b) 10/90, (c) 30/70, (d) 50/50.

Indomethacin is a white powder in its crystalline state, but turns yellow when it is amorphous or molecularly dispersed. Thus, the pale yellow color of the extrudates and printed tablets is indicating that at least a part of the indomethacin is amorphous and/or dissolved in PCL.

CONCLUSIONS

The rheological properties of the extruded IND-PCL filaments were compared to those of the pure PCL. The 10/90 and 30/70 mixtures had a lower viscosity than the pure polymer, whereas the viscosity of the 50/50 mixture was significantly higher, showing dispersion-like rheological behavior. All the studied mixtures were successfully printed using FDM 3D printing technique.

Further work will include the assessment of FDM 3D printability using different pharmaceutically relevant polymers as matrix materials, and the characterization of rheological, as well as mechanical and thermal properties of the drug-polymer mixtures.

ACKNOWLEDGMENTS

Funding from the Danish Council for Independent Research (DFF), Technology and Production Sciences (FTP), project 12-126515/0602-02670B is acknowledged.

REFERENCES

1. Alomari, M., Mohamed, F.H., Basit, A.W., and Gaisford, S., (2015), "Personalised dosing: Printing a dose of one's own medicine", *Int. J. Pharm.*, **494**(2), 568-577.

2. "Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development", U.S.D.o.H.a.H. Services, Editor. 2013, FDA. p. 61.

3. Goyanes, A., Buanz, A.B.M., Basit, A.W., and Gaisford, S., (2014), "Fused-filament 3D printing (3DP) for fabrication of tablets", *Int. J. Pharm.,* **476**(1–2), 88-92.

4. Skowyra, J., Pietrzak, K., and Alhnan, M.A., (2015), "Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing", *Eur. J. Pharm. Sci.,* **68**, 11-17.

5. Hollander, J., Genina, N., Jukarainen, H., Khajeheian, M., Rosling, A., Makila, E., and Sandler, N., (2016), "Three-Dimensional Printed PCL-Based Implantable Prototypes of Medical Devices for Controlled Drug Delivery", *J. Pharm. Sci.*,

6. Gross, B.C., Erkal, J.L., Lockwood, S.Y., Chen, C.P., and Spence, D.M., (2014), "Evaluation of 3D Printing and Its Potential Impact on Biotechnology and the Chemical Sciences", *Anal. Chem.,* **86**(7), 3240-3253.

7. Turner, B.N., Strong, R., and Gold, S.A., (2014), "A review of melt extrusion additive manufacturing processes: I. Process design and modeling", *Rapid Prototyping Journal*, **20**(3), 192-204.

8. Aho, J., Edinger, M., Botker, J., Baldursdottir, S., and Rantanen, J., (2016), "Oscillatory Shear Rheology in Examining the Drug-Polymer Interactions Relevant in Hot Melt Extrusion", *J. Pharm. Sci.,* **105**(1), 160-167.