

Formulation and evaluation of 3D-printed prednisolone-loaded tablets intended for veterinary applications

Marina Tihhonova¹, Andres Meos¹, Sari Airaksinen², Niklas Sandler-Topelius², Jyrki Heinämäki¹, Urve Paaver¹

¹University of Tartu, Faculty of Medicine, Institute of Pharmacy, Nooruse 1, 50411 Tartu, Estonia

²CurifyLabs Oy, Salmisaarenaukio 1, 00180 Helsinki, Finland

Introduction

The current established manufacturing processes in the pharmaceutical industry do not enable to produce tailor-made (personalized) drug products. Therefore, multisite pharmaceutical 3D-printing approaches have found uses in fabricating customized drug preparations for both human and veterinary drug therapy applications.

To date, many 3D-printing technologies have been introduced for preparing such customized pharmaceuticals. These methods include (but are not limited to) e.g., binder jetting, VAT photopolymerization, powder bed fusion, material extrusion, direct energy deposition, and sheet lamination (Seoane-Viaño et al. 2021). Among these technologies, semi-solid extrusion (SSE) 3D printing has been found as a suitable method for preparing customized oral solid drug preparations due to its simplicity. For example, a SSE 3D printing enables to prepare multi-drug loaded tablets, orodispersible tablets, and feasible oral solid drug preparations for veterinary uses. In addition, SSE 3D printing is the method of choice for adjusting the organoleptic properties (color and taste) of oral drug preparations, thus increasing patient compliance. A SSE 3D printing technology has found uses in hospitals and pharmacies (Beer et al., 2021), and more recently also in veterinary drug treatments (Sjöholm et al., 2020).

The aim of the present study was to design and prepare a novel immediate-release tablets for veterinary applications (pets) using a SSE 3D printing technology. The physicochemical and dissolution properties of the tablets were evaluated. Moreover, a short-term storage stability study (up to 3 months) was performed for the present 3D-printed preparations (printed tablets).

Materials and methods

Prednisolone, PRD (Thermo Fisher Scientific Inc., USA) was used as a drug substance. The printed tablets were prepared with a SSE 3D-printing system (Curify Oy, Finland) in CurifyLabs Oy, Finland. An in-house Curavet™ base was used as a polymeric platform for SSE 3D printing. Curavet™ base is composed of the mixture of polymers (microcrystalline cellulose, MCC and gelatin) and a number of other key excipients. The printed tablets consisted 0.5% or 1.0% of PRD, and the weight of the tablets were 0.25 g, 0.5 g or 1.0 g. The printed tablets were individually packed in blisters after printing.

The physical solid-state properties of printed tablets were investigated by means of Raman spectroscopy (B&W TEK Inc., USA) and IR spectroscopy (Prestige-21 Shimadzu Corp., Japan), and by X-ray powder diffraction, XRPD (Bragg-Brentano geometry D8 Advanced Bruker diffractometer equipped with a LynxEye detector, Bruker, AXS GmbH, Germany). The thermal properties were studied with a differential scanning calorimeter, DSC (DSC 4000, Perkin Elmer Ltd., USA). Drug content and drug release *in vitro* were determined by means of UV spectrophotometry (Shimadzu UV-1800, Shimadzu Corp., Japan), and high-performance liquid chromatography, HPLC (Shimadzu HPLC Prominence modular system, Shimadzu Europa GmbH, Germany) with a 250 x 4.6 mm (5 µm) HPLC column.

Dissolution of printed tablets was investigated in a Sotax AT 7 Smart dissolution test apparatus (Sotax AG, Switzerland) equipped with an Ismatec IPC 8 ISM 931 peristaltic pump (Cole-Parmer Instrument Company LLC,

USA) and Specord 200 Plus spectrophotometer (Analytik Jena GmbH, Germany). The dissolution medium was 900 ml of water (37 °C) and rotating rate of paddles was 100 rpm.

Results and discussion

The physical solid-state properties and dissolution of printed tablets were investigated about 1 week and 3 months after preparation. The tablets were kept in blisters in a refrigerator (+2-8 °C). Fig. 1 shows the surface morphology of printed tablets after 1 week. The XRPD results showed that PRD was in a sesquihydrate form. After removing the printed tablets from the blister, however, PRD was rapidly transformed from a hydrate form to a polymorph form II (XRPD).

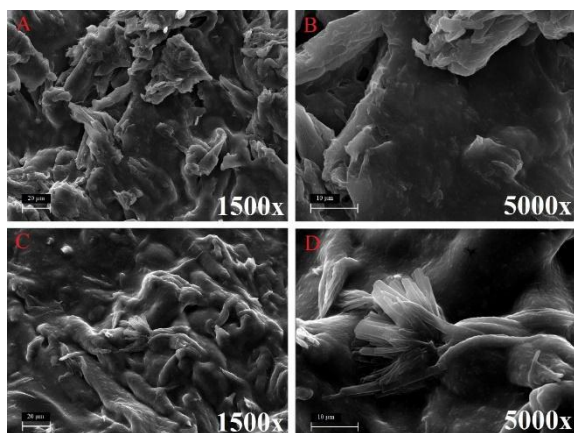


Figure 1. Scanning electron microscope (SEM) images of the surface view of the SSE 3D-printed tablets. Key: Reference printed tablets without drug (A, B) at the magnifications of 1500x (20 µm) and 5000x (10 µm), respectively. Drug-loaded printed tablets (C, D) consisting 1% of prednisolone (PRD), and weighing 1 g. Magnifications of 1500x and 5000x, respectively.

Fig. 2 shows the *in-vitro* dissolution of SSE 3D-printed tablets determined by HPLC. The drug release was dependent on the weight (size) of printed tablets. The dissolution of 1.0-g printed tablets was much faster (100% of PRD released within 15 min) than the dissolution of 0.25 g printed tablets (approx. 100% of PRD within 60 min). This was obviously due to the higher surface-area of 1.0 g tablets, thus leading to a faster disintegration of tablet. The results of a 3-month storage stability study showed that the drug (PRD) content in the printed tablets remains virtually at the same level as in the corresponding “fresh” (1-week) printed tablets and the present content results complied with the specifications set to the drug content.

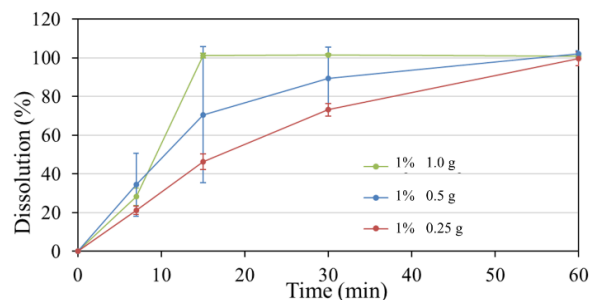


Figure 2. The *in-vitro* dissolution curves of SSE 3D-printed tablets containing 1% of prednisolone (PRD) (at 7.5 min, 15 min and 30 min, n = 2; at 60 min, n = 5-8). The weight of the tablets was 0.25 g, 0.5 g and 1.0 g. After 3D printing, the tablets were packed in blisters, and they were tested after 1 week (from the preparation). HPLC was used as an analytical method.

Conclusion

A SSE 3D printing technology enables to prepare immediate-release tablets of PRD for veterinary applications. The present printed tablets contain PRD in a sesquihydrate form. It is evident that a sesquihydrate form transformed to a PRD polymorphic II form, if the printed tablets are stored unpacked in an ambient room conditions. The release rate of PRD is dependent on the weight (size) of the printed tablets. A short-term storage of SSE 3D-printed tablets in blisters at an ambient room conditions does not affect the physical solid-state form of the drug (PRD) and drug content in the printed tablets.

Acknowledgements: The Authors would like to thank J. Aruväli, Prof. K. Kirsimäe and Dr. A. Lust for their valuable contribution to the present study.

References

- Beer, N., Hegger, I., Kaae, S., de Bruin, M. L., Genina, N., Alves, T. L., Hoebert, J. & Kälve mark Sporrang, S., 2021. Scenarios for 3D printing of personalized medicines case study. *Explor. Res. Clin. Soc. Pharm.* 4, 100073. <https://doi.org/10.1016/j.rcsop.2021.100073>
- Seoane-Viaño, I., Trenfield, S.J., Basit, A.W., Goyanes, A., 2021. Translating 3D printed pharmaceuticals: From hype to real-world clinical applications. *Adv. Drug Deliv. Rev.* 174, 553-575. <https://doi.org/10.1016/j.addr.2021.05.003>
- Sjöholm, E., Mathiyalagan, R., Prakash D.R., Lindfors, L., Wang, O., Wang, X., Ojala, S., Sandler, N., 2020. 3D-printed veterinary dosage forms – A comparative study of three semi-solid extrusion 3D printers. *Pharmaceutics* 12, 1239. <https://doi.org/10.3390/pharmaceutics12121239>