Macedonian pharmaceutical bulletin, 69 (Suppl 1) 105 - 106 (2023)
Online ISSN 1857 - 8969
DOI: 10.33320/maced.pharm.bull.2023.69.03.051
Short communication

Application of semi-solid extrusion (SSE) 3D printing for generating customized propranolol-loaded oral drug delivery systems

Kristiine Roostar[1], Karin Lombiots[1], Oleh Koshovyi[1], Jyrki Heinämäki[1], Niklas Sandler-Topelius[2], Urve Paaver[1]

[1]*University of Tartu, Faculty of Medicine, Institute of Pharmacy, Nooruse 1, 50411 Tartu, Estonia*
[2]*CurifyLabs Oy, Salmisaarenaukio 1, 00180 Helsinki, Finland*

Introduction

Modern 3D printing technologies hold great promises for the manufacture of customized ("tailor-made") medicines and personalized drug delivery systems (Seoane-Viaño et al., 2021; Vaz and Kumar, 2021). It is well known that a conventional "one-size-fits-all" concept is not suitable for all patient groups, and therefore pharmaceutical 3D-printing technologies are expected to make a revolutionary contribution to the new approach of personalized medicine.

Oral conventional dosage forms (i.e., tablets, capsules and granules) are still the most widely used pharmaceutical preparations in both in human and veterinary drug treatments. Such drug preparations are manufactured by means of established manufacturing technologies and excipients widely used in the pharmaceutical industry. Within past 10-15 years, however, a number of promising 3D printing technologies have been introduced for pharmaceutical applications. Semi-solid extrusion (SSE) 3D printing is one interesting method for pharmaceutical polymer-based printing applications due to its simplicity, a low operating temperature and suitability for preparing high drug-loaded preparations (Sjöholm et al., 2020).

Propranolol is a beta blocker used in the treatment of diseases such as high blood pressure, heart arrhythmias, performance anxiety and essential tremors. To date, only a few 3D-printed oral drug delivery systems for propranolol have been reported in the state-of-the-art literature.

The aim of the present study was to develop a novel customized 3D-printed oral solid drug preparation for propranolol, and to investigate the physical solid-state properties and performance (dissolution *in vitro*) of such 3D-printed systems. A SSE 3D printing was used as a printing method for generating such drug preparations.

Materials and methods

Propranolol hydrochloride (Thermo Scientific, Japan) was used as a drug substance. The particle size, shape and surface morphology of propranolol hydrochloride was studied by scanning electron microscope (SEM) (Fig. 1). For preparing a printing solution, an in-house polymer mixture (CuraBlend™, CurifyLabs, Finland) was used as a basic polymer platform for SSE 3D printing. The CuraBlend™ mixture was heated up to 42 °C to ensure a semi-solid state, and to enable mixing of it with a drug substance (propranolol) and essential key excipients. The semi-solid mixtures used for SSE 3D printing consisted of 99% (w/w) CuraBlend™ and 1% drug substance. The viscosity of the semi-solid mixtures was studied at 45 ± 5 °C with a Brookfield Ametek DVNext viscosimeter.

The 3D-printed drug preparations ("curablets") were prepared with a bench-top SSE 3D-printer (Curify Oy, Finland). The 3D-printing process took place at 42 °C and at an ambient room humidity. After printing, the drug preparations were kept in a refrigerator at +3-8 °C for 3-5 minutes, and subsequently packaged in a blister package for further studies.

The physical appearance, mass and mass variation, and dimensions (length, width and height) of 3D-printed drug preparations were studied. The physical solid-state

*kristiine.roostar@ut.ee

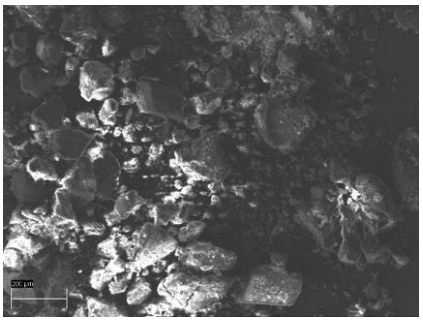

Fig. 1. Scanning electron microscopy (SEM) image of propranolol hydrochloride powder particles. Size-bar 200 µm.

properties of 3D-printed preparations were investigated with Raman spectroscopy (BWS415 i-Raman Miniature spectrometer, B&W TEK Inc., USA), IR spectroscopy (Prestige-21 IR spectrometer, Schimadzu Corp., Japan), X-ray powder diffraction, XRPD (Bragg-Brentano geometry D8 Advanced Bruker diffractometer equipped with a LynxEye detector, Bruker, AXS GmbH, Germany), and differential scanning calorimetry, DSC (DSC 4000, Perkin Elmer Ltd., USA). The *in-vitro* dissolution of the 3D-printed drug preparations were 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 baskets was 100 rpm.

Results and discussion

The viscosity of drug-loaded (1%) CuraBlend™ mixture was slightly lower (2623 ± 860 cP) compared to the viscosity of a reference CuraBlend™ mixture (without any drug) (3485 ± 199 cP) at 42 °C.

The SSE 3D-printed drug preparations ("curablets") were oval to round in shape, and the diameter of the preparations loaded with 3 mg, 4 mg or 5 mg of drug, was 0.5 cm, 1.5 cm and 2.0 cm, respectively (Fig. 2).

Fig. 2. Photograph of the 3D-printed drug preparations ("curablets") loaded with 3 mg, 4 mg and 5 mg of propranolol hydrochloride.

The weight and variability of the size (diameter) of "curablets" are shown in Table 1. The weight and diameter of the "curablets" prepared from the drug-loaded (1%) CuraBlend™ semi-solid mixtures were larger than the weight and diameter of the reference drug preparations printed from the CuraBlend™ mixture without drug.

Table 1. The average mass (m), diameter (d) and height (h) of 3D-printed drug preparations ("curablets") (n = 25). Reference "curablets" did not contain any drug substance. Standard deviation (SD) shown in parenthesis.

	3D-printed drug preparation					
	3 mg		4 mg		5 mg	
	Reference	CuraBlend™ Propranolol 1%	Reference	CuraBlend™ Propranolol 1%	Reference	CuraBlend™ Propranolol 1%
m (mg)	280 (8.0)	282 (8.3)	375 (10.6)	378 (7.6)	468 (13.1)	481 (20.8)
d (mm)	12.72 (0.25)	14.84 (0.73)	14.73 (0.33)	17.10 (0.76)	16.51 (0.36)	20.22 (0.96)
h (mm)	2.71 (0.10)	2.10 (0.16)	2.68 (0.10)	2.13 (0.14)	2.74 (0.11)	2.02 (0.13)

Conclusion

The addition of propranolol hydrochloride (1%) into a semi-solid CuraBlend™ slightly decreases the viscosity of the mixture. CuraBlend™ is well miscible with propranolol and enables to print homogenous drug preparations. The present "curablets" show small variation in weight and dimensions suggesting that the formulation is applicable for 3D printing. A SSE 3D printing is a feasible and rapid method for preparing customized propranolol-loaded "curablets" for oral immediate-release applications.

References

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

Vaz, V.M., Kumar, L., 2021. 3D printing as a promising tool in personalized medicine. AAPS Pharm.Sci.Tech. 22, 49, 1-20. https://doi.org/10.1208/s12249-020-01905-8