

# Selective laser sintering (SLS) 3D printing process: Influence of model design on the properties of zolpidem tartrate tablets

Ivana Adamov<sup>1</sup>, Gordana Stanojević<sup>2</sup>, David Kočović<sup>2</sup>, Snežana Mugoša<sup>2</sup>,  
Branka Grujić<sup>3</sup>, Svetlana Ibrić<sup>1</sup>

<sup>1</sup>Department of Pharmaceutical Technology and Cosmetology, University of Belgrade – Faculty of Pharmacy, 11221 Belgrade, Serbia

<sup>2</sup>Institute for Medicines and Medical Devices of Montenegro, 81000 Podgorica, Montenegro

<sup>3</sup>Galenika AD, 11080 Belgrade, Serbia

## Introduction

Three-dimensional printing (3DP) is an innovative additive manufacturing technology in the field of pharmaceuticals that has the potential to provide small batches of patient-tailored medicines (Wang et al., 2021). One of the newest and most advanced 3DP techniques is selective laser sintering (SLS), a one-step manufacturing process that uses a laser to selectively sinter powder particles into layers and create a 3D structure of a solid dosage form. Depending on the 3D design of the object, the laser is focused to draw specific patterns on the surface of the powder. Once the first layer is sintered, a fresh layer of powder is sprinkled on top so that a new layer can be sintered (Allahham et al., 2020). The aim of this study was to formulate and investigate the influence of the model design on the properties of zolpidem tartrate (ZT) tablets produced by the SLS 3DP process.

## Materials and methods

ZT was kindly donated by Hemofarm AD, Serbia, while the matrix former agent PHARMACOAT® 603 (hydroxypropylmethylcellulose, substitution type 2910) was provided by Shin-Etsu Chemical Co, Japan. Candurin® Gold Sheen was purchased from Merck, Germany, and AEROSIL® 200 (colloidal silicon dioxide) was purchased from Evonik, Germany. The formulation (150 g) was prepared by mixing the drug (5%, w/w) and excipients. Candurin® Gold Sheen (3%, w/w), a golden pigment, was added to increase the absorption of laser energy and

improve printability, while only 0.5% (w/w) AEROSIL® 200 was sufficient to improve the flowability of the powder mixture. The prepared formulation was sieved (125 µm) and transferred to the SLS printer (Sintratec Kit, Switzerland). Autodesk Fusion 360 software version 2.0.8809 (Autodesk Inc., USA) was used to design the templates of the cylindrical 3D tablets (10.00 mm × 3.00 mm) with and without circular perforations (n = 9; 1.00 mm diameter). The 3D models were exported as a stereolithography file into the central 3D printer software Sintratec version 1.2.0. The tablets with (F603P) and without (F603) perforations were printed according to the process parameters given in Table 1.

The 3D-printed tablets (n = 10) were weighed on an analytical balance (Kern & Sohn, Germany) and measured with a digital calliper (Vogel, Germany). The drug content was determined by UV spectrophotometry (Evolution 300, Thermo Fisher Scientific, USA) at a wavelength of 238 nm, using a calibration curve method, in duplicate. The breaking force of the tablets (n = 6) was measured with a hardness tester (ERWEKA TBH 125D, Germany), while the disintegration time of the tablets (n = 3) was measured in a compendial ERWEKA ZT 52 disintegration time tester (Erweka, Germany) using 800 mL distilled water at 37 ± 0.5 °C. The dissolution test was performed using a USP-I Erweka DT 600 (Erweka, Germany) apparatus in 500 mL distilled water at 37 ± 0.5 °C until a plateau was reached. The basket speed was set at 100 rpm, aliquots (4 mL) were taken at time intervals of 15, 30, 45, 60, 120, 180 and 240 minutes, respectively, filtered through 0.45 µm filters (Millipore, USA) and the amount of ZT released was

determined spectrophotometrically at 238 nm. The measurements were performed in triplicate. X-ray powder diffraction (XRPD) was performed to investigate the physical state of the drug after the 3DP process (Malvern Panalytical, UK).

Table 1. 3D printing process parameters

Parameter	Value
Chamber Temperature (°C)	150
Surface Temperature (°C)	130
Laser Scanning Speed (mm/s)	250
Hatching Spacing (µm)	100

## Results and discussion

The tablets were successfully printed, with the printing time depending mainly on the geometry of the defined 3D model, on average 20 minutes for 6 dosage forms. All 3D-printed tablets were yellow due to the golden pigment, with a characteristic layered structure and a uniform cylindrical shape (F603:  $9.86 \pm 0.06$  mm  $\times$   $3.26 \pm 0.04$  mm; F603P:  $10.09 \pm 0.09$  mm  $\times$   $3.29 \pm 0.03$  mm). Tablets with perforations had a lower average weight (F603P:  $134.42 \pm 6.15$  mg) compared to tablets without perforations (F603:  $165.07 \pm 3.43$  mg), which was expected due to the different geometric structure of the developed 3D model. Specific patterns on the surface of the tablets, including a different number of perforations, could improve adherence in patients with visual impairment and reduce medication errors (Awad et al., 2020). The determined drug content was within 95-105% of the theoretical value for drug loading (F603:  $99.81 \pm 0.94\%$ ; F603P:  $98.63 \pm 2.66\%$ ), indicating that degradation of ZT did not occur during the SLS 3DP process. Similar results have been reported in the literature confirming the potential of SLS 3DP technique in the manufacturing of small batches of medicines (Fina et al., 2018). ZT was incorporated into 3D-printed tablets within the therapeutic dosage range (F603:  $8.24 \pm 0.08$  mg; F603P:  $6.63 \pm 0.18$  mg), and only by changing the design of the 3D model was it possible to achieve a lower dosage, making tailored dosing and individualization of therapy even more feasible. The obtained tablets showed acceptable mechanical properties, while the presence of perforations significantly contributed to lower resistance to crushing (F603:  $73 \pm 7$  N; F603P:  $24 \pm 7$  N) as well as faster disintegration of the tablets (F603:  $33.94 \pm 0.54$  min; F603P:  $17.53 \pm 2.19$  min). The influence of a complex model structure on the dissolution rate of the drug was also evident. The tablets with perforations (F603P) released the drug faster than the tablets without perforations (F603) (Fig. 1), which is consistent with the larger surface area to

volume ratio (Fina et al., 2018). A greater number of perforations provided immediate release of the drug while maintaining the therapeutic dose. This provides an opportunity to individualize therapy not only in terms of dose adjustment but also in terms of onset of action.

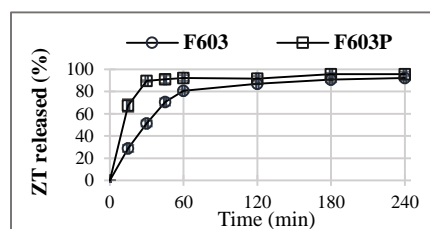


Fig. 1. Dissolution profiles of 3D-printed tablets

XRPD analysis showed that the degree of crystallinity of the ZT was significantly reduced, which was to be expected due to the high temperature to which the drug was exposed during the printing process (Fina et al., 2018).

## Conclusion

The role of the SLS 3DP technique in the production of complex dosage forms has recently been studied in detail and opens up a new perspective for the development and production of solid dosage forms with a special focus on the manufacturing of medicines tailored to the specific needs of patients and the individualization of therapy.

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