

Influence of the Infill Geometry of 3D-Printed Tablets on Drug Dissolution †

Nuno Venâncio ¹, Gabriela G. Pereira ² , João F. Pinto ²  and Ana I. Fernandes ^{1,*} 

¹ CiiEM, Interdisciplinary Research Center Egas Moniz, Instituto Universitário Egas Moniz, 2829-511 Almada, Portugal; nuno.venancio2000@gmail.com

² iMed.Ulisboa—Research Institute for Medicines, Faculdade de Farmácia, Universidade de Lisboa, 1649-003 Lisboa, Portugal; garrastazugp@farm-id.pt (G.G.P.); jfpinto@ff.ul.pt (J.F.P.)

* Correspondence: aifernandes@egasmoniz.edu.pt; Tel.: +351-212946823

† Presented at the 5th International Congress of CiiEM—Reducing Inequalities in Health and Society, Online, 16–18 June 2021.

Abstract: Patient-centric therapy is especially important in pediatrics and may be attained by three-dimensional printing. Filaments containing 30% *w/w* of theophylline were produced by hot-melt extrusion and printed using fused deposition modelling to produce tablets. Here, preliminary results evaluating the effect of infill geometry (cross, star, grid) on drug content and release are reported.

Keywords: 3D-printing; theophylline; tablets; infill geometry; dissolution

1. Introduction

Additive manufacturing, also known as 3D-printing (3DP), is gaining relevance in the manufacturing of personalized medicines, mainly of tablets (TAB), using fused deposition modelling (FDM). This technique requires prior drug incorporation in the matrix (e.g., thermoplastic polymers) and the production of filaments (FIL) through hot-melt extrusion (HME). FIL are in turn fed into the 3D-printer, molten and deposited layer-by-layer to build the dosage form [1]. The extrudability and printability of FIL depend on the raw materials (adjusted qualitatively and quantitatively, as required) and the processing conditions [1]. Since both HME and FDM rely on the fusion of the matrix, the heat stability of the drug is paramount.

The customization of medicines in pediatrics is critical, as one needs to repeatedly adjust the dose according to age, body weight or surface area as the child grows and to achieve well-defined drug release kinetics. This work evaluates how the infill geometry of 3D-printed TAB impacts drug content and release.

2. Materials and Methods

Theophylline (TEO; Sigma Aldrich) was chosen as a model drug (m.p. 270–274 °C). The thermoplastic matrix comprised hydroxypropylcellulose (HPC; m.p. 371 °C; Ashland), Soluplus® (SLP; BASF), and magnesium stearate (MgS; Roic Farma).

Drug-loaded FIL (30:54:15:1 % *w/w*—TEO:HPC:SLP:MgS) were obtained by HME, (ϕ 1.5 mm nozzle; temperature 130 ± 5 °C) using a single-screw extruder (Noztek Touch, Noztek); drug-free FIL were used as controls. TAB were printed (extrusion temperature: 220 °C; extrusion speed: 90 mm/s; travelling speed: 150 mm/s; number of shells: 2; infill geometry: cross, star, and grid (without top and bottom); layer thickness: 0.20 mm) with a FDM 3D printer (Delta WASP 20 40 Turbo 2, Wasp); TAB dimensions and infill were designed with 3D Sprint Software (3D Systems).

Physical mixtures of materials, FIL and TAB were characterized by infrared (FTIR; Bruker), differential scanning calorimetry (DSC; TA Instruments), and X-ray diffractometry (XRPD; X'Pert PRO PANalytical). Dissolution of the TAB was evaluated for up to 24 h,



Citation: Venâncio, N.; Pereira, G.G.; Pinto, J.F.; Fernandes, A.I. Influence of the Infill Geometry of 3D-Printed Tablets on Drug Dissolution. *Med. Sci. Forum* **2021**, *5*, 15. <https://doi.org/10.3390/msf2021005015>

Published: 20 July 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

using the paddle method ($n = 3$; 50 rpm, 900 mL HCl; $37 \pm 0.5^\circ\text{C}$; Erweka DT600). TEO was quantified by HPLC ($\lambda = 272 \text{ nm}$; HP 1100) [2].

3. Results and Discussion

Initial experiments have shown that the qualitative and quantitative composition of the chosen polymeric matrix possesses adequate plasticity and lubrication, enabling successful HME and FDM 3DP.

The uniformity of drug distribution in the FIL (samples from ends and middle of the extrudate) was ascertained as $98.15 \pm 3.35\%$ of the theoretical amount of TEO, also confirming drug stability during HME. Moreover, the heating of TEO at the printing temperature did not reveal degradation peaks in HPLC. TEO suffered partial amorphization caused by HME, a phenomenon strengthened during the FDM printing of the TAB, as ascertained by disappearance of the drug peaks in DSC and XRPD.

To evaluate the impact of geometry on dissolution, TAB of different infill geometry (cross, star, and grid, without a top and bottom; Figure 1) were 3D-printed and characterized (Table 1).

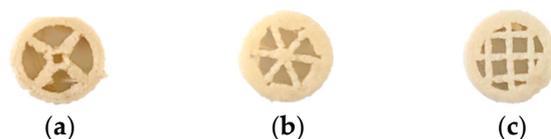


Figure 1. Infill geometry of the 3D-printed TAB: (a) cross; (b) star; (c) grid.

Table 1. Features of 3D-printed TAB ¹.

TAB Infill Geometry	Diameter (mm)	Height (mm)	Mass (mg)	Drug Content ² (mg)	Drug Recovery ³ (%)
Cross	12.00 ± 0.50	3.03 ± 0.02	196.80 ± 4.32	19.83 ± 1.74	33.54 ± 1.92
Star	12.50 ± 0.50	3.01 ± 0.01	246.10 ± 6.30	28.23 ± 1.07	37.72 ± 0.31
Grid	12.25 ± 0.73	3.03 ± 0.01	243.20 ± 9.14	27.44 ± 0.27	37.52 ± 0.42

¹ Results are mean \pm standard deviation; $n = 10$ for diameter, height, and mass; $n = 3$ for content. ² Amount of TEO quantified per tablet.

³ Expressed as percentage of the theoretical amount of TEO considering the TAB mass.

TAB dimensions, mass, and drug content were uniform. The star and grid TAB were equivalent; the cross showed significantly lower mass. Drug content was consistently below the theoretical value, but no degradation or interaction of TEO with the matrix was found by FTIR. Spontaneous micellization of the polymeric matrix (e.g., SOL) may account for the unavailability of the drug for quantitation.

In vitro drug release did not reveal significant differences related to infill geometry between the star and grid shapes since the surface area of exposure to the dissolution media did not seem to have a sufficient enough difference to impact the dissolution profile. For the cross geometry, the larger void spaces account for the higher accessibility of water to the structure, as well as slightly faster and more complete drug dissolution ($\approx 100\%$ at 3 h); the star and grid show higher mass and thicker walls, so the matrix effect on slowing drug release is more marked ($\approx 95\%$ after 4–5 h).

Further in-depth studies are warranted to fully understand and characterize the systems and to explore the impact of geometry on dissolution.

Acknowledgments: This work was supported by Fundação para a Ciência e a Tecnologia [grant number PTDC/CTM-CTM/30949/2017 (Lisboa 010145 Feder 030949)].

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Pereira, G.C.; Figueiredo, S.; Fernandes, A.I.; Pinto, J.F. Polymer selection for hot-melt extrusion coupled to fused deposition modelling in pharmaceuticals. *Pharmaceutics* **2020**, *12*, 795. [[CrossRef](#)] [[PubMed](#)]
2. Okwuosa, T.C.; Pereira, B.C.; Arafat, B.; Cieszynska, M.; Isreb, A.; Alhnan, M.A. Fabricating a shell-core delayed release tablet using dual FDM 3D Printing for patient-centred therapy. *Pharm. Res.* **2017**, *34*, 427–437. [[CrossRef](#)] [[PubMed](#)]