3D-Printing of paracetamol tablets by fused deposition modelling

Gabriela G. Pereira[1]; Ana I. Henriques[1]; Ana I. Fernandes[2]; Inês A. Santos[2]; João F. Pinto[1]

[1] iMed.ULisboa – Research Institute for Medicines, Faculdade de Farmácia, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal; jfpinto@ff.ulisboa.pt

[2] CiiEM, Instituto Universitário Egas Moniz, Quinta da Granja, Monte de Caparica, P-2829-511 Caparica, Portugal; aifernandes@egasmoniz.edu.pt

INTRODUCTION

Additive manufacturing technologies have recently been considered for the manufacture of solid dosage forms, in particular tablets. These technologies encompass a tridimensional construction of the tablet, known as 3D printing. Printed tablets are obtained through the deposition of mixtures of drug(s) and excipient(s) in layers to create a 3D structure (tablet) with tailored masses and shapes (Norman et al., 2017), thus amenable to personalized drug loading and release. In fact, the use of these novel technologies is promoting a paradigm shift towards the design and manufacture of customized medicines, *i.e.* produced according to individual patient's needs (Vijayavenkataraman et al., 2017). Such feature is particularly useful in paediatrics, geriatrics and oncology, amongst others uses, maximizing therapeutic outcomes.

This study was designed to develop and manufacture 3D printed tablets containing paracetamol (as a model drug) by fused deposition modelling (FDM).

MATERIALS AND METHODS

Paracetamol (AcoFarma, Spain), Hydroxypropyl cellulose (HPC − Klucel LF, USA), Soluplus® (BASF, Germany) and magnesium stearate (MS − Roic Farma SA, Spain).

Preparation of Filaments and 3D-Printed Tablets

Six different mixtures of HPC, Soluplus®, magnesium stearate (MS) and paracetamol (Table 1) prepared in a mortar (10 min) were hot-melt extruded (HME).

Mixture	Components (%)			
	HPC	Soluplus®	MS	Paracetamol
M1	54	15	1	30
M2	40	9	1	50
M3	54	14	2	30
M4	39.5	8.5	2	50
M5	52.5	12.5	5	30
M6	37.5	7.5	5	50

Table 1: Composition of the mixtures used to produce filaments

The extrusion (single screw, Notzek Pro, Notzek, Schoreham, UK) was carried out through a die (1.75mm) with temperature, in the 2 barrel sections, set at 100°C and 70°C, for all filaments.

Cylindrical tablets were fabricated from drug-loaded filaments by FDM (3D printer MakerBot Replicator 2X Desktop, MakerBot Inc., USA), according to a template made in AutoCad and exported as a stereolithography (.stl) file into Cura (Autodesk Inc., USA). The printer was set with a standard resolution, extrusion temperature of 200°C, extrusion speed of 20 mm/s, travelling speed of 150mm/s with 2 shells and layer height of 0.50 mm, for a 100% infill. At least 20 tablets from each filament (F1-F6) were prepared and analyzed.

Characterization of the Materials

The calorimetric behaviour of physical powder mixtures, filaments and tablets were analyzed by differential scanning calorimetry (DSC, heating rate of 10°C/min within the range -10°C and 250°C of 10-15mg samples placed in TA aluminium pans and pinhole hermetic lids, Q2000 DSC, TA Instruments, USA).

X-ray diffractometry (XRPD) was performed using an X'Pert PRO X-ray diffractometer (PANalytical, Almelo, the Netherlands) using a CuKα (λ=1.54 Å) source of radiation and with a defined voltage and current of 40kV and 30mA, respectively. The samples were analyzed using a step size of 0.017 °2θ with a counting time of 19.685 s in the range 7-35 °2θ.

Tablets were evaluated for mass, dimensions (caliper) and drug content (previously validated UV spectrophotometry, at 257 nm) after dissolution in NaOH 0.03M; drug loading of filaments was determined by the same method. Drug content (%) was calculated as the ratio between the amount of drug and the final tablet mass.

RESULTS

Polymeric filaments (diameter between 1.75 and 1.85 mm) were successfully prepared by HME from mixtures M1-M6.

Five from the six filaments could be printed using FDM to produce the 3D printed tablets, whose properties, such as mean weight, diameter and height are shown in Table 2.

3D-printed tablets	Weight (mg)	Diameter (mm)	Height (mm)	Drug content (%)
T1	658±48	5.91±0,07	2.90±0.022	94±2
T2	871±61	5.97±0,04	3.00±0.014	96±3
T3	295±30	5.95±0,05	3.00±0.024	104±5
T4	821±54	5.96±0,04	3.00±0.017	95±2
T5	809±47	5.98±0,02	3.00±0.029	97±1

Table 2: Properties of the 3D-printed tablets (n=10 for mass and dimensions; n=3 for content)

Figure 1 presents the thermal events observed for the different products obtained: physical mixtures (M1-M6), the HME filaments (F1-F6) and the 3D-printed tablets (T1-T5). Mixtures containing higher drug fraction show the endotherm for paracetamol, which decreased or was absent in the filaments. Heat used in the manufacture of the latter has contributed to the production of amorphous solid dispersions of paracetamol in the polymers. This was particularly evident when paracetamol was in a low fraction and polymers in high fractions in the formulation. Soluplus was equivalent to HPC in the preparation of dispersions. The transformation of filaments into tablets has promoted instability in the amorphous systems with the appearance of some crystalline paracetamol after partial recrystallization. In this respect, the increase in the MS fraction enabled the production of both filaments and tablets but promoted the instability of the amorphous dispersions. When tablets presented endotherms, they could be related to paracetamol that had suffered some degree of plasticization. Noteworthy is that FDM printing promoted instability of the amorphous dispersions.

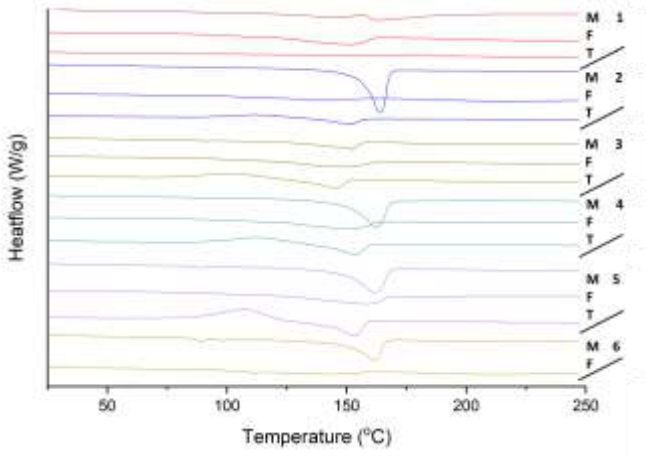

Figure 1: Thermograms from physical mixtures (M1-M6), filaments (F1-F6) and 3D-printed tablets (T1-T5)

Figure 2 shows the diffractograms of the different products complementing the data collected from the calorimetric studies and emphasizing the effect of heat on the production of amorphous tablets.

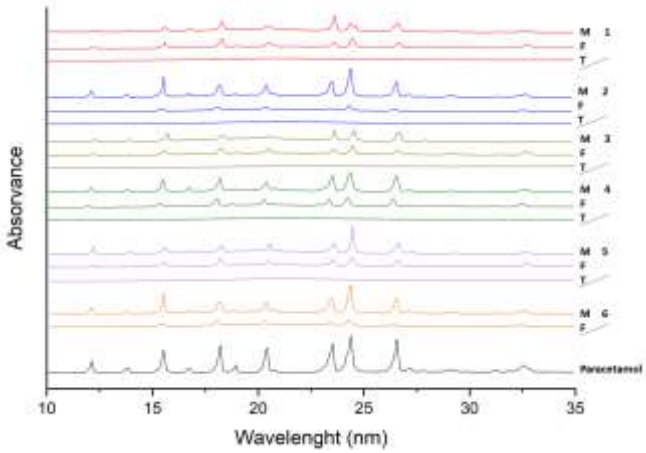

Figure 2: Diffractograms from physical mixtures (M1-M6), filaments (F1-F6) and 3D-printed tablets (T1-T5)

CONCLUSION

The paracetamol-loaded filaments obtained by extrusion were successfully produced with appropriate characteristics for use in FDM 3DP.

The use of heat in the production of both filaments and 3D-printed tablets promoted the production of amorphous dispersions.

The combination of polymers and stearate improved the extrudability of the physical mixtures with Soluplus appearing to provide better amorphous systems than HPC.

The processes still requires optimization, namely to improve the weight and drug content variation.

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