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Can Fused Deposition Modelling Enable the Manufacture of Uniform and Precise Dose Tablets? †

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Abstract: The consistency of a printer to manufacture tablets in a uniform and precise fashion is an important element when considering fused deposition modelling. Blends of polymer [poly(vinyl alcohol)] and drug (paracetamol) in different ratios were considered to evaluate the mass, drug content, dissolution performance, and thermal properties of tablets. Relative standard deviations below 5%, for most of the properties considered in the study, demonstrated the high uniformity between tablets within a batch and between batches. Overall, the study confirmed the ability of the technology to manufacture tablets in a reproducible way based on the selected properties.

Keywords: 3D printing; fused deposition modelling; poly(vinyl alcohol); paracetamol; solid dosage

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1. Introduction

Compounding has been used to obtain a medicine tailored to the specific needs of patients. However, poor compounding practices can result in patient injury and, eventually, death, due to contamination of the medicine or to potency errors [1]. The use of 3D printing has the ability to change the current approach on individualization of medicines. The aim of the present work was to evaluate how consistent fused deposition modelling (FDM) 3D printing can be in the manufacture of tablets based on different critical quality attributes (CQAs: mass, drug content, drug release, and thermal properties) when different blends of poly(vinyl alcohol) (PVA) and paracetamol (PAR) were applied.

2. Materials and Methods

2.1. Preparation of Filaments by Hot-Melt Extrusion (HME) and Tablets by FDM 3D Printing

To prepare feedstock material for FDM 3D printing, mixtures of PVA:PAR (90:10, 70:30, and 50:50 *w*/*w*) were extruded (at 0.3 kg/h, 1.75 mm die) in a co-rotating (100 rpm), fully intermeshing twin-screw extruder (Prism Eurolab 16, Thermo Fisher, Karlsruhe, Germany). Thereafter, filaments were fed to a MakerBot Replicator 2X Experimental 3D Printer (MakerBot, Brooklyn, USA), enabling the printing of 30 tablets (10 mm ϕ and 4 mm thick) of each blend in individual runs (intra-batch variability). To assess inter-batch variability, 2 batches were printed from each blend. The temperature was set at 180, 165, and 150 °C for PVA:PAR 90:10, 70:30 and 50:50, respectively, allowing constant flow out of the nozzle.

2.2. Characterization of Tablets

The mass of each tablet was determined immediately after manufacture. The drug content of tablets (n = 3) was checked in phosphate buffer pH 6.8 (spectrophotometer, λ = 244 nm, UV-1650PC, Shimadzu, Shimadzu Benelux, Antwerp, Belgium). The drug released from tablets was determined by dissolution tests (n = 3, phosphate buffer pH 6.8,

37.0 ± 0.5 °C, paddles at 100 rpm, VK 7010, Vankel Industries, Edison, NJ, USA) in samples collected at pre-set time points. The mean dissolution time enabled the comparison between different profiles. Thermal analysis (n = 2) was performed by differential calorimetry (Q2000, TA Instruments, Leatherhead, UK) at 10 °C/min on samples (~5 mg) in T_{zero} pans.

3. Results and Discussion

Results of the CQAs (Table 1) have shown that the Pharmacopoeia requirements for mass uniformity were reached for all formulations, with a variability intra-batch below 0.8%. Nevertheless, a difference of about 10 mg on the average mass was detected between batches of different blends. In this regard, the variation of the filament's diameter plays a major role in printing, especially on the mass deviation of the printed tablet [2]. Printed tablets presented a drug content between 95.5% and 100.6% of the expected value for paracetamol, reflecting the high precision of the process. Moreover, intra- and inter-batch variability was low, as required for the desired therapeutical effect on the patient.

Table 1. Critical quality attributes (CQA) of 3D printed tablets from different batches made of PVA:PAR.

CQA(Average ± Relative Standard Deviation)	Batch	PVA:PAR (% *w*/*w*)		
		90:10	**70:30**	**50:50**
Mass (mg ± %)	1	395.5 ± 0.5	383.5 ± 0.7	375.4 ± 0.5
	2	402.9 ± 0.4	393.5 ± 0.7	385.1 ± 0.8
Drug Content (mg ± %)	1	37.8 ± 1.0	114.0 ± 0.9	183.8 ± 0.2
	2	40.5 ± 1.5	117.0 ± 0.2	183.9 ± 0.9
Mean Dissolution Time (min ± %)	1	47.2 ± 0.9	27.1 ± 0.7	31.7 ± 10.4
	2	46.5 ± 6.1	30.4 ± 0.5	32.0 ± 6.6
Δ*C*p [(J/(g·°C)) ± %]	1	0.73 ± 3.7	0.48 ± 4.9	0.33 ± 3.7
	2	0.70 ± 1.4	0.49 ± 0.7	0.31 ± 2.3
Δ*H*melting [(J/g) ± %]	1	Not detected	3.48 ± 9.6	69.63 ± 2.5
	2	Not detected	3.68 ± 16.7	67.37 ± 4.2

Considering that FDM is a thermal process, and the dissolution behaviour can be influenced by the state of the solid drug, it was important to confirm whether the printed tablets have kept the value of the enthalpy of either amorphous or crystalline forms of PAR across manufacture. The melting event of tablets have shown that, at low PAR content, full conversion to the amorphous form was obtained, while at 50% PAR the drug remained mostly in the crystalline form, possibly due to the low temperature used, below the melting of the drug. Results have shown a consistent average of the heat capacity (ΔC_p) and enthalpy ($\Delta H_{melting}$) changes between batches and a relative standard deviation below 5% within the batches. However, the enthalpy of the melting event for tablets with 30% PAR showed high deviations within a batch, possibly due to the low crystalline fraction of PAR close to the sensitivity of the technique.

Overall, the study has proved the ability of FDM 3D printing to produce batches of tablets with low intra- and inter-batch variability, regardless the formulation considered.

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

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