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Study of the stability of acetaminophen extrudates for 3D printing prepared by hot melt extrusion when stored at different relative humidites

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CENTRO DE INVESTIGAÇÃO INTERDISCIPLINAR EGAS MONIZ

INTRODUCTION

3D printing technology (3DP) offers the greatest potential to revolutionize the future of pharmaceutical manufacturing. Of the many techniques available, fused-deposition modelling (FDM) (Fig. 1) has been the most used technique supporting the potential of the technology to prepare unit dosage forms [1]. Fused deposition modeling (FDM) (Fig 1) is a technique based on the deposition of successive layers of thermoplastic materials after softening / melting [2]. The challenges related to the use of the technique are mainly related to the scarcity of adequate filaments composed of pharmaceutical grade materials (e.g. polymers with appropriate characteristics) and processing related parameters (e.g. moisture exposure and content) that besides extrusion, enable printing [3].

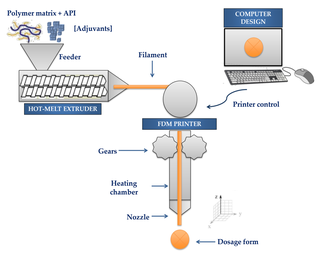

Fig. 1-Schematic of a FDM assemblage.

METHODS

Six different mixtures of HPC, Soluplus®, magnesium stearate and paracetamol (Table 1) were processed by HME and the filaments stored for 0, 7, 14 and 30 day in desiccators (11, 53, 75 and 93% RH / 24°C). The extrusion was carried out through a die with the temperatures in the barrel set at 100 (section 1) and (section 2) for all filaments. Printing was carried out at 200°C at a rate of 90mm/s and travelling at 150mm/s for a 100% infill and a 0.20mm layer thickness. Physical mixtures, filaments and tablets were characterized for thermal behavior by calorimetry (DSC, heating rate of 10°C/min within the range -10°C and 250°C, for 10-15mg samples placed in aluminum pans), crystallinity, drug content and printability. 10 tablets from each filament were prepared and analyzed.

Table 1: Mixtures (M1-6) made of different raw materials (%) considered in the work

	HPC	Soluplus	MgSt	Paracetamol
M1	54.0	15.0	1.0	30.0
M2	40.0	9.0	1.0	50.0
M3	54.0	14.0	2.0	30.0
M4	39.5	8.5	2.0	50.0
M5	52.5	12.5	5.0	30.0
M6	37.5	7.5	5.0	50.0

RESULTS

At day 0, filaments M1-M5 allowed printing. These filaments had the expected content of paracetamol (98-101%) (Table 2) mostly in an amorphous phase (Fig.2), by comparison to the initial physical mixture. The fraction of crystallinity found was likely due to partial recrystallization of paracetamol. Tablets did not show degradation of paracetamol, even though they have undergone a second process of extrusion, as imposed by the technique of printing.

The analysis carried out on days 15 and 30 were performed only on filaments stored at 11%RH, which could be printed. Table 3 presents the data from the printed tablets which presented a high mass and drug content uniformities between samples. This suggests that moisture is a key factor to allow filaments to be printed.

Paracetamol present in filaments that were stored at 11%RH remained stable at day 30 of the study, based on the thermal analysis data (Fig. 3). Also, it was possible to print 10 tablets under the same conditions, as before, from the F1-F6 filaments. Table 3 presents the data for tablet mass and drug content stressing the need to control filament storage humidity to ensure not only their printability but also the integrity of the drug during the entire storage period.

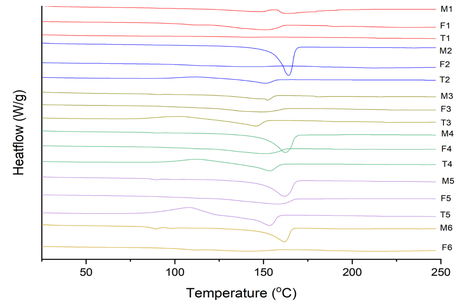

Fig 2: Thermograms from physical mixtures (M1-M6), filaments (F1-F6) and 3D-printed tablets (T1-T5).

Table 2: Physical properties of the 3D printed tablets from filaments.

Samples	Mass (mg)	Diameter (mm)	Thickness (mm)	Drug content (%)
1	65.8±4.8 *	5.91±0.07	2.50±0.022	98.36±2.35
2	87.1±6.1	5.97±0.04	3.00±0.014	97.70±3.01
3	29.5±3.0 *	5.95±0.05	1.50±0.014	104.13±2.14
4	82.1±5.4	5.96±0.04	3.00±0.017	98.15±2.20
5	80.9±4.7	5.98±0.02	3.00±0.029	99.08±0.98

*smaller tablets printed for dose adjustment (n=10)

Table 3: Physical properties of the 3D printed tablets at days 15 and 30 of storage.

	Day 15		Day 30	
Samples	Mass (mg)	Drug content (%)	Mass (mg)	Drug content (%)
1	71.78±5.80	99.01±2.25	73.53±5.20	100.02±2.10
2	76.38±1.03	99.80±2.23	78.88±8.14	97.89±2.65
3	83.21±5.27	100.09±1.13	75.97±5.45	99.06±1.09
4	81.31±7.01	101.55±2.20	87.52±5.42	99.59±5.27
5	76.78±3.17	97.08±1.98	77.93±1.11	98.87±1.89
6	73.71±6.46	101.05±1.59	73.75±1.07	99.05±1.87

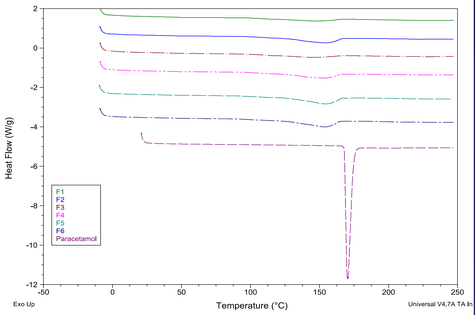

Fig 3: Thermograms from paracetamol and filaments (F1-F6) storage after 30 day at 11% RH

AIM

This study aims to evaluate the performance of filaments stored under different humidities on printing tablets with the required characteristics.

CONCLUSIONS

Filaments loaded with paracetamol were successfully printed delivering tablets with the preset properties, provided they were used at day 0 (M1-M5) or throughout 30 day, when stored at 11% RH (M1-M6).

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