

Preparation of medicines by three-dimensional printing and personalization of therapy in compounding pharmacies: a case study

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Introduction

Three-dimensional printing (3DP) has recently been attracting the attention of the pharmaceutical community since this technology gives the opportunity to personalize therapy according to patient's needs, re-centering medicines' design on the individual [1]. Fused Deposition Modelling (FDM), the most widely used 3DP technique, involves the prior production of a drug-containing polymeric filament by Hot-melt extrusion (HME), which is then melted and continuously deposited on a surface, layer by layer, building the 3D-printed dosage form [2].

The successful integration of HME and FDM requires that both extrudability of the raw materials and printability of the HME filaments fabricated are attained, properties which are influenced by the mechanical, rheological and thermal properties of materials. These properties are influenced not only by the composition of the filament (e.g., polymer matrix, additives and drug) and the processing parameters used, but also by the storage conditions of the filaments [3-5].

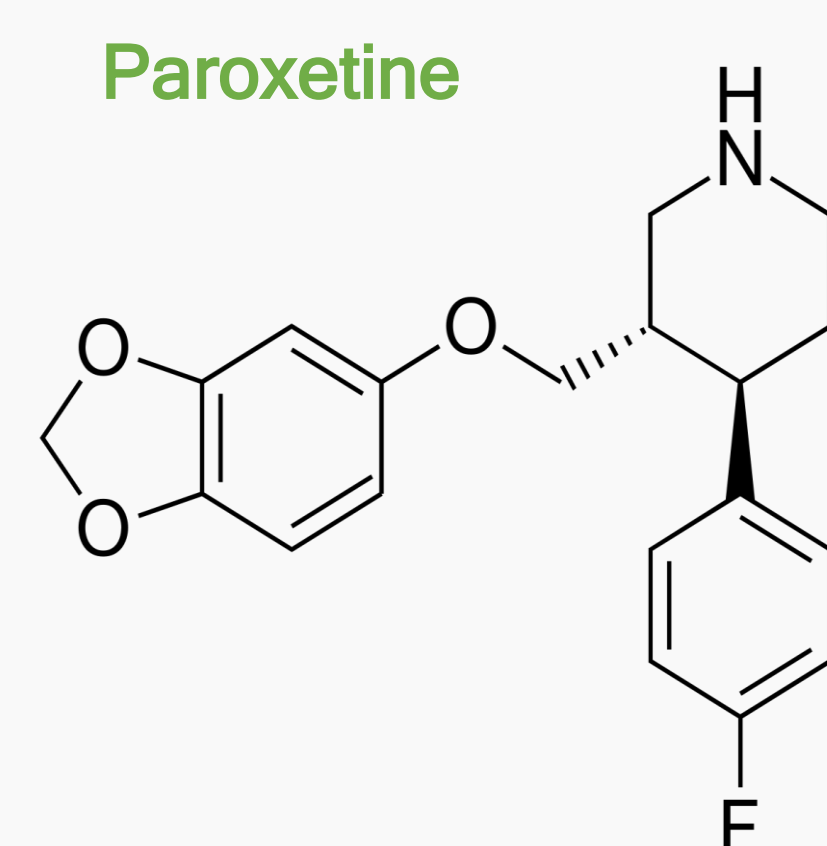
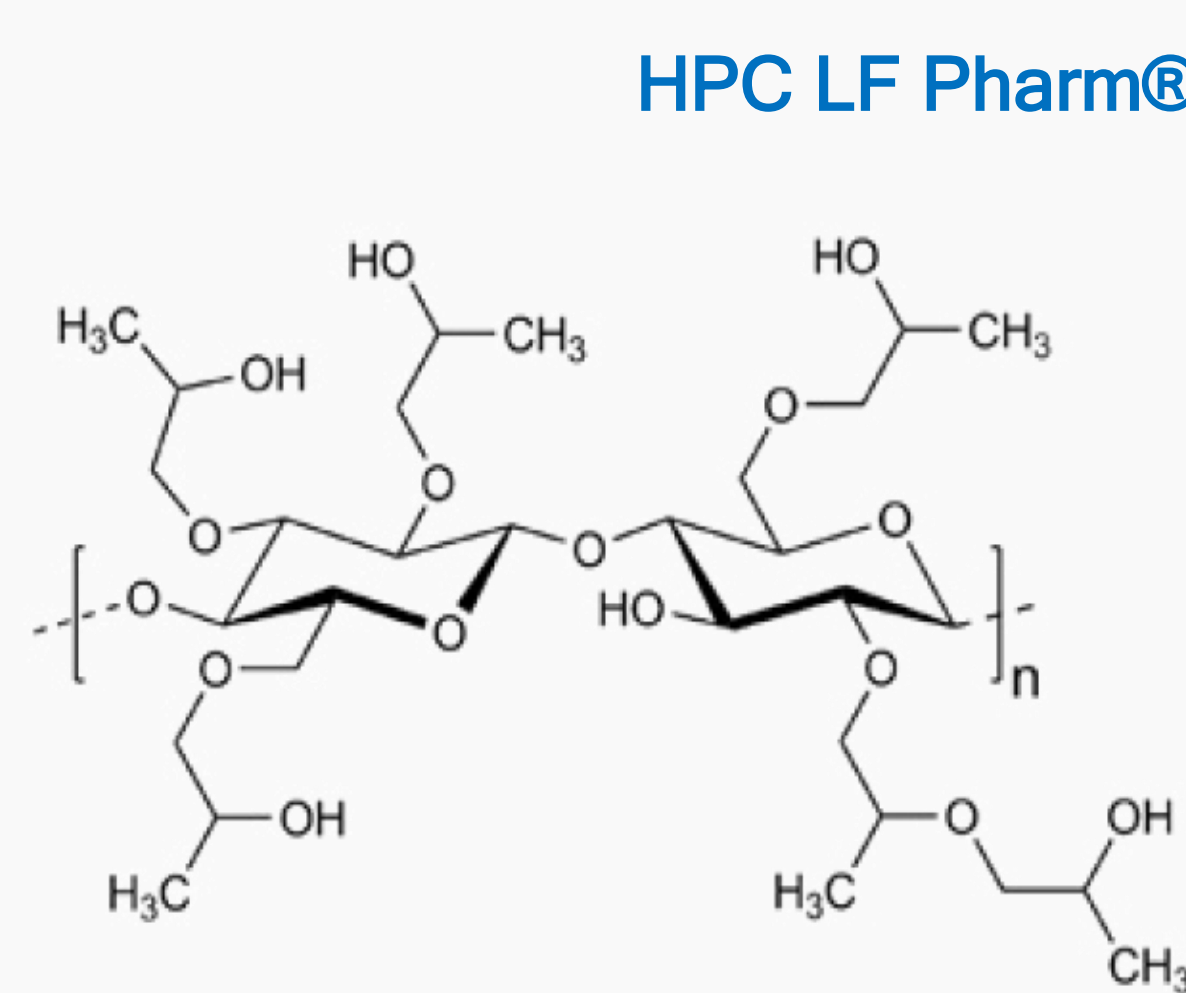
Aim

Based on a case study using paroxetine (PRX; used for the treatment of major depression, generalized anxiety and related disorders) as model drug, this work aims to identify the most relevant requirements impacting on the use of Fused Deposition Modelling (FDM) technology coupled to Hot-Melt Extrusion (HME) to manufacture compounded medicines.

This should be achieved by identifying the main challenges that a pharmacist will face prior to define the strategies to be considered for the successful implementation of this technology in the daily practice in compounding pharmacies.

Materials & Methods

Tablets were 3D-printed by FDM from PRX-loaded filaments, previously manufactured by HME. Filaments were subjected to a stability studies at different environmental conditions or were submitted to a heated-oven and microwave-mediated drying processes. Printability of tablets was assessed.



Formulation

HPC LF Pharm® (54% w/w) + Paroxetine (30% w/w)

Other excipients: 6% w/w of Calcium Phosphate, Magnesium Stearate and Triethylcitrate in a 10:1:5 ratio

Preparation of filaments

Filaments containing polymeric formulation were prepared by HME (Notzek Pro single screw extruder, Notzek) at temperatures of 120°C and 90°C, at a screw speed of 10 rpm.

Storage at different climatic conditions

AND

Drying by Oven or Microwave

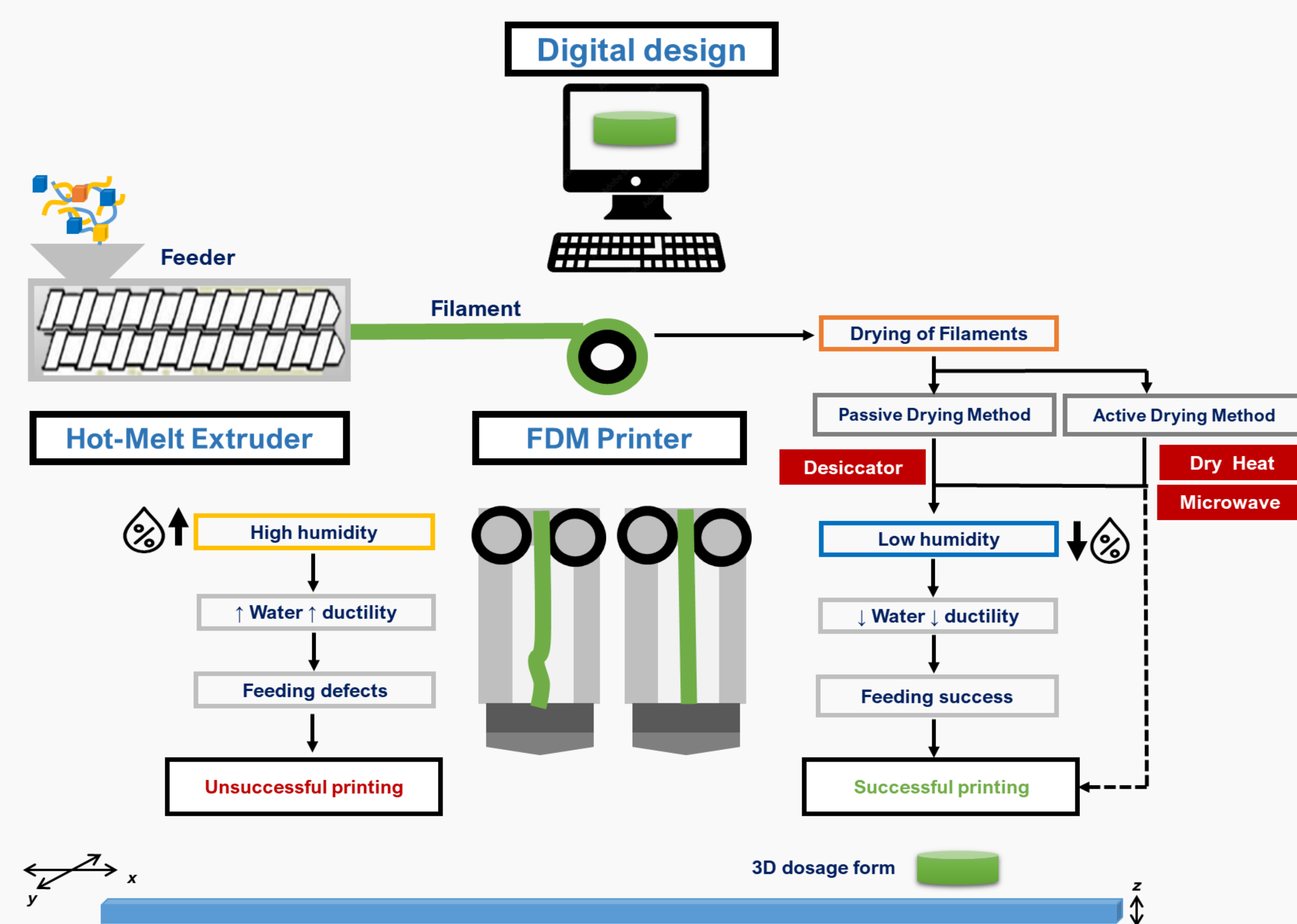
Evaluation of filaments

Feeding/printing performance of filaments were evaluated for the different time points and conditions of storage, as well as for the implementation of different drying processes.

Printing and Evaluation of 3D tablets

FDM 3D-printed tablets were manufactured (3D printer Delta WASP 20 40 Turbo 2, Wasp, Italy) with printing temperatures of 200°C (extrusion) /50°C (plate) and 60 mm/s printing speed.

Results



Experimental settings	T0 (days)	T1 (days)	T2 (days)	T7 (days)	T30 (days)
20°C/11%RH	No	No	No	Yes*	Yes*
25°C/60%RH	No	No	No	No	No
30°C/65%RH	No	No	No	No	No
40°C/75%RH	No	No	No	No	No
Hot-air Oven	No	No	Yes*	NP	NP
Microwave	No	Yes*	NP	NP	NP

NP: Not Performed

The storage of filaments under controlled environmental conditions was critical for the successful printing of tablets by 3DP FDM.

Stability Studies

These studies demonstrated the high ductility of the PRX loaded filaments for higher humidity conditions; and their inability to successfully feed the 3DP printer's gear.

Drying of Filaments

Under low humidity storage conditions, the filaments became stiffer and were adequately printed into tablets. Water removal was slow when carried out passively in a controlled atmosphere or accelerated by using active drying methods. The printability after microwave-mediated drying provided tablets with better quality attributes in comparison to hot-air oven drying.

Conclusions

This work supports that the prior production of the filaments with adequate properties for printing may be a limiting step for using FDM in compounding at the point-of-care. As an alternative, filaments may be manufactured in a facility that would centralize their manufacture, and supplied as intermediate materials to community pharmacies, which are expected to be able to convert different combinations of filaments into individualized medicines, based on prescriptions according to the patients' needs.

This approach repositions and strengthens the role of the pharmacy and the pharmacist in providing quality health care to the population.

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Acknowledgments

Fundação para a Ciência e a Tecnologia (PTDC/CTM CTM/30949/2017 (Lisboa 010145 Feder 030949). LEF - Infosaúde supported the participation in the 81st FIP World Congress of Pharmacy and Pharmaceutical Sciences.