

Effect of plasticizer content on the processability of paroxetine-loaded filaments by fused deposition modelling

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INTRODUCTION

Three-dimensional printing (3DP) is an innovative approach to manufacture personalized medicines, representing an excellent opportunity to make a significant technological leap over traditional pharmaceutical manufacturing processes. The incorporation of 3DP in the pharmaceutical compounding landscape is expected to promote flexibility, efficiency, safety, and quality of existing medicines. Fused deposition modelling (FDM), the most used 3DP technique, involves the production of a drug-loaded filament, obtained previously by hot-melt extrusion (HME), which is then melted and continuously deposited on a surface, layer by layer, building the 3D-printed dosage form [1].

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 [2]. Previous studies demonstrated that environmental conditions (especially, humidity) play a key role in the coupling of these technologies, since they impact on the moisture content of the filaments and, consequently, on their mechanical properties and processability [3]. Besides atmospheric humidity, it is crucial to study whether the composition of the polymeric formulation (e.g., plasticizer content) can influence the printability of the filaments.

This work aims to evaluate the impact of the plasticizer content on the quality and printability of paroxetine-loaded polymeric formulations for integrated HME-FDM, by assessing the water content of the filaments and their performance during the 3DP process.

MATERIALS AND METHODS

Paroxetine (PRX; Lusifar) was selected as a model drug; hydroxypropylcellulose (HPC, Ashland) as the polymeric matrix; dicalcium dihydrate phosphate (CaP; Budenheim), magnesium stearate (MgSt; Roic Pharma) and triethylcitrate (TEC; Sigma Aldrich) as adjuvants. The raw materials were pre-dried in a desiccator (11% RH) for 72 h.

Filaments containing PRX (30% w/w), HPC (54% w/w) and other excipients (16% w/w of a mixture made of CaP, MS and TEC), were produced by HME (Notzek Pro single screw

extruder, Notzek). Three different polymeric formulations were evaluated with 0%, 1% and 2.5% of TEC (plasticizer) with the proportional adjustment of the other formulation components. Moisture content and feeding/printing performance of filaments were evaluated for the different polymeric formulations, immediately after extrusion and after storage under specific conditions (room temperature/55% RH and desiccator at 11%RH).

Whenever possible, FDM 3D-printed tablets were produced (3D printer Delta WASP 20 40 Turbo 2, Wasp) from PRX-loaded filaments.

RESULTS & DISCUSSION

Preliminary studies revealed that the PRX-loaded filaments were not printable immediately after the extrusion process [3]. Indeed, at least 1 week under controlled environmental conditions (11% RH in a desiccator) is required for these materials to acquire suitable properties for the subsequent FDM process. Particularly, this holding time is needed to reduce the filaments' water content, so that they become less ductile and can be successfully fed into the 3D printer without printer feeding defects. In previous work, prior drying of the filaments was demonstrated as a good strategy to expedite the integrated HME-FDM manufacturing process by reducing atmospheric water content, without significant polymeric structural changes in filaments and without compromising the dissolution behavior of the PRX tablets [4].

However, it remains to be clarified whether the filaments' composition itself, in particular the plasticizer content, contributes to their water content and processability, independently from the atmospheric conditions. To this end, three different polymeric formulations containing different concentrations of plasticizer (TEC) were prepared. For each formulation, Figure 1 illustrates the variation of water content in the PRX-loaded products, throughout the manufacturing process and storage.

Consistently, the different physical mixtures (pre-extrusion step) presented a higher water content when compared to the filaments obtained after the extrusion process. This finding corroborates that the HME process promotes the reduction in water content, despite the short extrusion time.

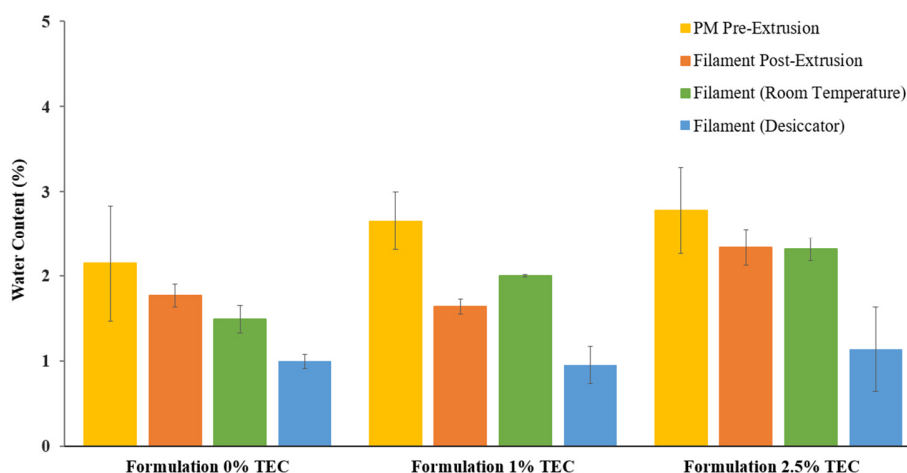


Figure 1: Moisture content (%) of PRX-based products according to the manufacturing process and storage conditions.

The plasticizer content exhibited a proportional correlation with the water content since higher moisture values were obtained for the formulations with a high concentration of TEC. Since the printability of PRX-containing filaments is favored by low water content (less flexibility of the filaments), it proves that plasticizer content should be reduced to the minimum amount that allows extrusion (the plasticizer helps to lower the T_g of the polymer, which facilitates the HME process).

As previously described, the storage of filaments under specific environmental conditions impacts on the water content [3]. This work demonstrates that it is also influenced by the plasticizer content in the polymer-based formulation. Storage of the filaments in a desiccator allows reduction of their water content, with the effect directly correlated with the percentage of TEC. In fact, a more significant decrease in the water content of filaments made of 2.5% of plasticizer and stored in a desiccator was observed when compared to the results obtained from formulation without plasticizer. It is related to the higher water content of filaments containing 2.5% of TEC immediately after their production and, consistently, this formulation also exhibited a higher moisture content after desiccator-mediated drying process. This finding supports that the plasticizing component can retain water molecules in the polymeric matrix and, consequently, make the filaments more ductile due to the higher moisture content. Conversely, storage the filaments under room conditions (20-25°C/55%RH) can originate a variable and unpredictable effect on their water content, regardless the plasticizer content. This is not surprising since it depends on the existing environmental conditions. Overall, the filaments without plasticizer were printable immediately

after HME, while the others were not. After storage in a desiccator (11%RH), all filaments were printable due to water loss.

CONCLUSION

The work reinforced the importance of the plasticizer content in PRX-loaded blends and in its subsequent processability, allowing optimization of the printing process, namely by reducing holding time, and anticipation of the most satisfactory composition of filaments.

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REFERENCES

- Zhang, J.; Feng, X.; Patil, H.; Tiwari, R.V. and Repka, M.A. Coupling 3D printing with hot-melt extrusion to produce controlled-release tablets. *Int. J. Pharm.*, 519, 186-197 (2017).
- Bandari, S.; Nyavanandi, D.; Dumpa, N.; Repka, M. Coupling Hot Melt Extrusion and Fused Deposition Modeling: Critical Properties for Successful Performance. *Adv. Drug Deliv. Rev.*, 172, 52–63 (2021).
- Figueiredo, S.; Fernandes, A.I.; Carvalho, F.G. and Pinto, J.F. Performance and stability of paroxetine tablets manufactured by fused deposition modelling-based 3D printing. *J. Pharm. Pharmacol.*, rgab138 (2021).
- Figueiredo, S.; Fernandes, A.I.; Carvalho, F.G. and Pinto, J.F. Exploring Environmental Settings to Improve the Printability of Paroxetine-Loaded Filaments by Fused Deposition Modelling. *Pharmaceutics*, 15, 2636 (2023).