Evaluating mechanical properties of paroxetine-loaded filaments to enable printability by fused deposition modelling

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INTRODUCTION

Three-dimensional printing (3DP) has been recently identified as an opportunity to make a significant technological leap over traditional pharmaceutical manufacturing processes, namely regarding customization of medicines. Fused deposition modelling (FDM), the most commonly 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]. Since the filament is pulled by the printer feeding gears towards the heated nozzle where it softens to allow the accurate deposition on the building plate, evaluation of their mechanical properties is of the utmost importance. These properties are influenced not only by the polymeric formulation composition and the processing parameters used, but also by the storage conditions of the filaments [3-4].

This work aims to evaluate the impact of the environmental conditions on the quality and printability of paroxetine-loaded polymeric formulations for integrated HME-FDM, by assessing the mechanical properties of the filaments.

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.

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 in a 10:1:5 ratio) were prepared by HME (Notzek Pro single screw extruder, Notzek), stored in stability chambers (Fitoclima D1200PH, Aralab) and dessicator inside open plastic bags, and re-examined at pre-defined times. Mechanical properties, moisture content and feeding/printing performance of filaments were evaluated for the different time points and conditions of storage. Whenever possible, FDM 3D-printed tablets were produced (3D printer Delta WASP 20 40 Turbo 2, Wasp, Italy) from PRX-loaded filaments.

RESULTS & DISCUSSION

Preliminary studies revealed that the PRX-loaded filaments were not printable immediately after the extrusion process [5]. Indeed, at least 1 week under controlled environmental conditions (in a desiccator) is required for these materials to acquire suitable properties for the subsequent FDM process. Polymeric filaments were highly ductile after the HME process, so their remarkable flexibility causes printer feeding defects. These findings suggested not only the high influence of the environmental conditions (especially, humidity) on the mechanical properties of the filaments, but also the remarkable impact of these properties on the filaments' processability and subsequent success of 3DP.

Thorough assessment was made through a stability study carried out for 30 days, in which the filaments were introduced into open plastic containers inside a stability chamber (25°C/60%RH, 30°C/65%RH and 40°C/75%RH) or in a desiccator (20°C/11%RH). Regarding the printing performance, only the filaments stored in a desiccator were successfully printable after 1 week from the start of the study. On the contrary, the filaments maintained inside the stability chambers (all conditions) did not reveal an adequate mechanical behaviour for proper performance during FDM 3DP since they were too pliable, thus preventing printer feeding (Table 1).

Stability Conditions (Temp./Humidity)	**Time** (Day)			
	0	**1**	**7**	**30**
20°C/11%RH	No	Yes*	Yes*	Yes*
25°C/60%RH	No	No	No	No
30°C/65%RH	No	No	No	No
40°C/75%RH	No	No	No	No

Table 1. Printability of filaments over time and storage conditions.

***Printing temperatures of 200°C (extrusion) /50°C (plate) were used when the 3DP process was successful.

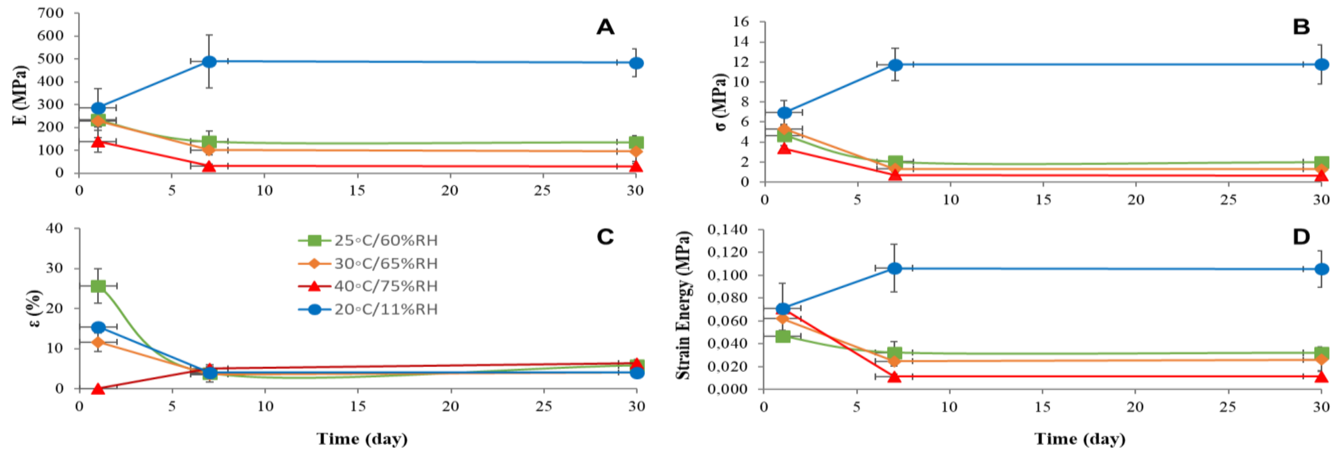

Figure 1: Mechanical properties of filaments over time and storage conditions.
(A) Young's modulus, **(B)** stress at maximum load, **(C)** strain at break and **(D)** energy strain.

Concurrently, the evaluation of filaments' performance during printing was correlated with their water content and mechanical properties (Fig. 1). When the filaments were stored in climatic chambers, in high humidity (>60%RH), they became successively more ductile due to moisture absorption (water content of the filaments increased during the stability study for all conditions; data not shown). Water promoted plasticization of the filaments, and breakage only occurred after significant deformation (Fig. 1A), making them inapt to feed the printer. These findings are consistent with the decreased stiffness and stress at maximum load (Fig. 1B), obtained for mechanical tests. The strain energy (Fig. 1D) undergoes a considerable reduction throughout the study, especially under severe conditions (40°C/75%RH). Results are in line with previous HPC-based filaments, which with high moisture uptake at high relative humidity, also failed to be printable [4].

Conversely, storage at reduced humidity (20°C/11%RH) resulted in water loss and was the most suitable condition since it reduced the initial ductility of the filaments (with an increase in stiffness), allowing proper feeding in the 3D printer head, after 1 week of production. The reduction of the ductile behaviour of the filaments is inferred not only from the increase of the stiffness and stress under load (with higher strain energy) parameters, but also by the decrease of strain at break (Fig. 1C).

These findings emphasize that moisture plays a significant role in the mechanical behaviour of filaments, which is a decisive factor for the success of 3DP process by FDM technology. As previously reported, filaments should, neither be excessively stiff because they will not be properly bent onto spools, nor excessively brittle to allow filaments to be properly loaded into the printer head without breaking [2].

CONCLUSION

This work reinforces the importance of the mechanical properties of PRX-loaded filaments in their processability, and correlates these factors to environmental conditions. This study is crucial to optimize the manufacturing process and to anticipate the most satisfactory storage conditions for these materials. In the future, complementary strategies to speed up the printability of filaments will be explored.

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