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Proceeding Paper

Selection of a Hydroxypropylcellulose Grade for 3D-Printable Paroxetine Formulations by Fused Deposition Modelling †

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Abstract: This work presents the preliminary development of paroxetine-based formulations containing hydroxypropylcellulose (HPC) polymers suitable for hot-melt extrusion coupled to fused deposition modeling (3D printing). Two grades of HPC (54% *w*/*w*), Klucel™ LF and Klucel™ GF, were tested in a polymeric formulation of paroxetine (30% *w*/*w*) and adjuvants (16% *w*/*w* of dicalcium dihydrate phosphate, magnesium stearate, and triethylcitrate; 10:1:5 ratio). Both formulations exhibited a release of almost 100% of paroxetine after 12 h, but the drug released from the Klucel™ LF formulation was quicker and closer to the formulations available in the market.

Keywords: hydroxypropylcellulose (HPC) grade; paroxetine (PRX); printability; 3D-printed tablet; fused deposition modelling (FDM); hot-melt extrusion (HME)

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1. Introduction

Three-dimensional printing (3DP) has recently been attracting the attention of the pharmaceutical community because it allows patient-centric design and production of dosage forms, according to the individual needs of a specific patient [1]. Fused Deposition Modelling (FDM), one of the most used 3DP techniques, relies on the previous production of a drug-containing thermoplastic polymeric filament. The FDM 3D-printer is fed with the filament, which is molten at high temperature, extruded, and continuously deposited on the printer plate, layer by layer, building the 3D-printed dosage form. Hot-melt extrusion (HME) is the most interesting method to manufacture the filaments, using existing pharmaceutical-grade polymers [2].

The success of FDM for medicine customization depends on several factors, such as the choice of the adequate polymeric matrix, according to the intended drug release profile. Recently, cellulose-derived polymers have been increasingly used for filament preparation by HME. Cellulose ethers encompass a category of polymers designed by the linking of cellulose to alkyl substituents, such as methyl (methylcellulose, MC), ethyl (ethylcellulose, EC) and propyl (hydroxypropylcellulose, HPC) groups.

Among the cellulosic polymers, HPC (Figure 1) has been extensively studied, in several works, for application in integrated HME-FDM 3DP [3]. Typically, HPC polymers exhibit plasticity and hydrophobicity, high solubility in water and organic solvents, and a low Tg (0–120 °C, which tends to decrease with increasing moisture due to the plasticizer effect of water).

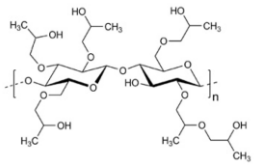

Figure 1. Chemical structure of HPC with a 2.5 degree of substitution. Reprinted with permission from Ref. [4]. 2017, Ashland Inc.

Since HPC polymers are marketed with different viscosities and molecular weight grades (Klucel™ ELF, EF, LF, JF, GF, MF, and HF; Table 1) they can be used in pharmacy to modulate the drug release profile [4]. In fact, the drug release rate depends on the polymer viscosity, which in turn is affected by the molecular weight and temperature.

Table 1. Properties and applications of typical pharmaceutical HPC polymers (adapted with permission from Ref. [4]. 2017, Ashland Inc.).

HPC Grade	Viscosity (mPa·s)	Molecular Weight (Da)	Usual Pharmaceutical Applications
Klucel™ HF Pharm	1500–3000	1,150,000	Controlled-release matrix
Klucel™ MF Pharm	4000–6500	850,000	Controlled-release matrix
Klucel™ GF Pharm [1]	150–400	370,000	Controlled-release matrix
Klucel™ JF Pharm	150–400	140,000	Controlled-release matrix
Klucel™ LF Pharm [1]	75–150	95,000	Immediate-release binder/Film-coating
Klucel™ EF Pharm	300–600	80,000	Immediate-release binder/Film-coating
Klucel™ ELF Pharm	150–225	40,000	Immediate-release binder/Film-coating

[1] Klucel™ GF and LF grades, marked in bold, were tested in this work. Klucel is a trademark of Ashland Inc.

As these matrix polymers have not been developed specifically for 3DP applications, it is crucial to evaluate their properties both alone and in the presence of the drug and adjuvants. Polymers can affect the characteristics of the final formulation, such as their aqueous solubility, erosion, and/or swelling properties. The mechanical and rheological properties of the filaments determine the quality and behavior (e.g., immediate or delayed release) of the final dosage form produced and are largely dependent on the matrix. Furthermore, drug release can be adjusted by the addition of excipients (e.g., disintegrants, surfactants, and/or pore builders) and by printing specimens with different infills or geometries [3].

Based on a comparative study of the drug dissolution profile, this work reports the selection of the most suitable grade of HPC polymer to modulate the release of paroxetine (PRX; used for the treatment of major depression, generalized anxiety, and related disorders) from 3D-printed tablets obtained by HME coupled to FDM 3DP.

2. Materials and Methods

PRX (Lusifar, Lisbon, Portugal) was used as a model drug; as matrix-forming polymers, hydroxypropylcellulose (HPC; Klucel™ LF and Klucel™ GF Pharm, Ashland Inc., Schaffhausen, Switzerland) were used. Magnesium stearate (MgS) (Roic Pharma, Terrasa, Barcelona, Spain), dicalcium dihydrate phosphate (CaP) (Budenheim, Rheinstrasse, Germany), and triethylcitrate (TEC) (Sigma Aldrich, Darmstadt, Germany) were used as excipients. Paroxetine film-coated tablets 20 mg (Tecnimede Group, Sintra, Portugal) were used as commercial references.

The extrusion of physical mixtures of the raw materials was performed in a single-screw extruder (Noztec Pro, Noztek, Shoreham, UK) at temperatures of 120 °C and 90 °C (barrel with two heating sections), at a constant screw speed (10 rpm). Two different polymeric formulations (HPC™ LF and HPC™ GF) were considered. Tablets were 3D-printed by FDM (3D printer Delta WASP 20 40 Turbo 2, Massa Lombarda, Italy) from PRX-loaded filaments, according to a digital template (3D Sprint Software v2.11, 3D Systems,

Rock Hill, SC, USA) and exported as a stereolithography (.stl) file into Cura (v15.04.2, Ultimaker B.V., Utrecht, The Netherlands). The tablets (10 mm diameter × 3 mm thick cylinders; 0.7 mm layer width × 1.4 mm wall thickness; 100% infill) were printed at a temperature of 200 °C and a 60 mm/s printing speed.

In vitro dissolution of the 3D-printed tablets was performed, and kinetic parameters, such as the time required for 50% drug release ($t_{50\%}$) and the dissolution rate (DR), were calculated [5].

3. Results and Discussion

Previous work demonstrated the feasibility of PRX-based formulations to be ex-truded by HME into filaments, which could be used to manufacture 3D-printed tablets by FDM. The polymeric formulation containing PRX (30% *w*/*w*), HPC (54% *w*/*w*), and excipients (16% *w*/*w* of CaP, MgS, and TEC) exhibited the most adequate behavior, among those studied, for coupling both technologies [6].

Nevertheless, it remained unclear which HPC polymer grade (Klucel™ LF and Klucel™ GF) was the most suitable to use. In terms of the manufacturing process (extrudability and printability), no significant differences were observed by the use of any of the HPC polymer grades considered. Thus, the selection criterion was directed towards the quality attributes of the 3D-printed dosage forms produced. In particular, it was defined that the best HPC candidate would be the one capable of producing a drug release profile closer to that of the commercial PRX tablets produced by tableting.

Both polymeric formulations containing Klucel™ LF and Klucel™ GF were used to produce filaments, and 3D-printed tablets were manufactured. A comparative study of the in vitro dissolution profile of both 3D-printed dosage forms was carried out (Figure 2), and the kinetic parameters were evaluated (Table 2).

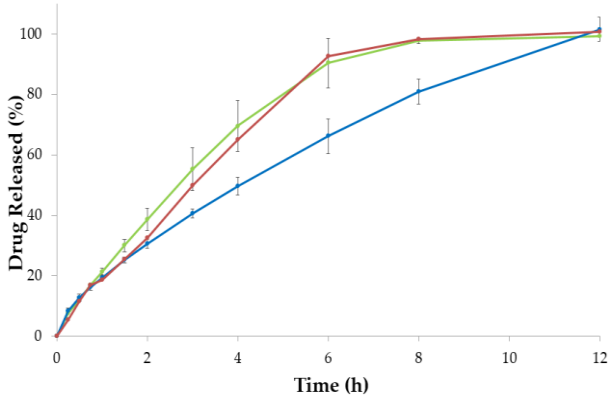

Figure 2. Dissolution profiles of the 3D-printed PRX tablets prepared with Klucel™ LF (green) and Klucel™ GF (blue); commercial tablets (red) were used as a reference (n = 3).

Table 2. Dissolution parameters of 3D-printed tablets produced by HME coupled to FDM.

Formulation	$t_{50\%}$ (min)	DR (mg·min^{-1})	f_2	Similarity
Klucel™ LF	2.681	0.184	71.46	Yes *
Klucel™ GF	4.027	0.174	48.20	No

* Criterion defined for f_2: 50–100; (n = 3).

The dissolution exhibited a profile typically associated with controlled release formulations, particularly useful in the treatment of psychiatric diseases and related to the use of the HPC polymer in both formulations, regardless of its grade. For the polymeric formulation composed of Klucel™ LF, the release of ≥85% of PRX was observed for ≈6 h of the test, reaching the steady state (release close to 100%) after 8 h. The release profile was superimposable to that of the commercial formulation obtained by a conventional tableting

process; the similarity of the dissolution profiles between both formulations was supported by an f_2 test, which exhibited a value higher than 50 (71, i.e., good similarity). This finding suggested that coupling HME and FDM technologies can produce 3D-dosage forms with drug release kinetics similar to those commercially available. Although the dissolution profiles were similar, the kinetics of drug release are amenable to adjustments leading to complete overlapping of the profiles, namely by modulating the polymer:PRX ratio or the adjuvants present in the formulation.

On the contrary, the polymeric formulation containing Klucel™ GF presented a slower PRX release rate, as inferred by higher $t_{50\%}$ values and lower DR results, when compared to the Klucel™ LF-based polymeric formulation. In this scope, the increase in the HPC viscosity associated with the higher molecular weight of Klucel™ GF, impaired the release of the drug. Likewise, the dissolution profile was not comparable with the commercial formulation, despite the f_2 factor being close to 50 (48, i.e., almost similar). In fact, more than 8 h were required for $\geq$85% of the PRX to be released from 3D-printed tablets composed of Klucel™ GF polymeric formulation (even though it reached 100% at the end of dissolution test). The potential for further extending drug action with this formulation is apparent and is the subject of future investigation.

Overall, this work supports the selection of the Klucel™ LF polymeric matrix as the best option, among those studied, to manufacture 3D-printed PRX tablets by integrated HME-FDM, as a therapeutic strategy in the treatment of psychiatric diseases. 3DP is proven to be capable of mimicking the drug release of commercial formulations with the added value of possible customization according to the patient needs.

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