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3D printing by fused deposition modeling of capsular devices for oral pulsatile release based on swellable/erodible polymers

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INTRODUCTION

Injection molding (IM) was recently used to prepare innovative Drug Delivery Systems (DDSs) in the form of functional containers [1-3]. Here the polymeric layers of traditionally coated DDSs were replaced with self-operating capsule shells filled with different drug preparations. Starting from hydroxypropyl cellulose (HPC), swellable/erodible capsule shells able of imparting a lag phase to the release of their contents were manufactured (Chronocap™ system) and then successfully enteric-coated [4]. For improving the potential of Chronocap™ for chronotherapeutic and site-specific release applications, a fine-tuning of the lag phase, by means of composition or design changes, should be attained. In this respect, development of new formulations, molds and a revision of molding processes would be needed, which may prove especially challenging [5].

Three-dimensional (3D) printing and, in particular, Fused Deposition Modeling (FDM) technique, were recently proposed for the production of personalized medicines [6]. Starting from computer-aided design (CAD) files, FDM allows the manufacturing of solid objects of almost whatever shape based on the addition, under a defined pressure and layer by layer, of thermoplastic materials supplied in the form of filaments which are generally produced by hot melt extrusion (HME) [7]. On the other hand, thanks to its real-time prototyping capabilities, FDM could be also exploited as a rapid tool to accelerate the development of molded products: it could speed up the screening of formulations, their transition to manufacturing and the evaluation of design characteristics found critical for these devices.

PURPOSE

To prepare swellable/erodible capsular devices for oral pulsatile release via 3D printing by Fused Deposition Modeling (FDM), starting from in-house produced filaments based on hydroxypropyl cellulose (HPC), and to explore the prototyping ability of the developed FDM process for the manufacturing of such devices by injection molding (IM).

EXPERIMENTAL

Materials: hydroxypropyl cellulose (HPC, Klucel® LF, Aqualon, USA); polyethylene glycol 1500 (PEG, Clariant Masterbatches, I), acetaminophen (Ataby, TK).

Equipment: 3D printer, MakerBot Replicator 2 (MakerBot®, USA).

Methods:

FILAMENT PREPARATION: HPC was stored 24 h in oven at 40 °C; when required it was mixed in a mortar with PEG 1500 (2, 5, 10% by weight calculated with respect to the dry polymer). Hot-melt extrusion (HME) was carried out in a twin-screw extruder (Haake MiniLab II, Thermo Scientific, USA) equipped with an aluminum rod-shaped die (ø 2.00 mm). Extruded rods were calibrated and rolled up on a spool using a purposely-assembled device.

RELEASE PERFORMANCE: capsule shells filled with 80 mg of acetaminophen (n=3) were tested in an adapted disintegration *apparatus* (800 mL distilled water, 37±0.5 °C, 31 cycles/min). Each unit, inserted in a sinker, was positioned in a tube of a basket-rack assembly. Fluid samples were withdrawn and assayed by spectrophotometer (248 nm). Lag time was calculated as the time to 10% release ($t_{10\%}$).

RESULTS

To asses the potential of the FDM in the manufacturing of capsular devices for oral pulsatile release, the following steps were undertaken:

i) preparation HPC-based filaments

HPC based filaments were prepared by HME using a purposely-designed calibrating device (**Fig. 1**).

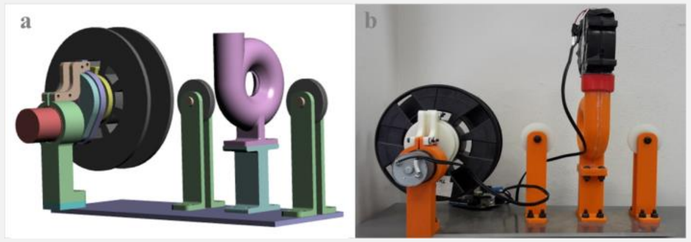

Fig. 1: in-house made pulling/calibrating device (b) and relevant sketch (a)

Extrusion parameters (*e.g.* screw speed) and pulling conditions (*e.g.* motor speed) were set up to obtain continuous filaments.

HPC, % w/w	PEG, % w/w	Extrusion T, °C	Screw speed, rpm	Pulling device speed, rpm
90	10	150	60	35
95	5	150	60	35
98	2	160	50	30
100	0	165	50	30

Starting from the formulation already developed for Chronocap™ (HPC + 10% w/w PEG) [2,4], the amount of PEG was progressively reduced, thus increasing the filament stiffness. Filaments that complied with requirements (*i.e.* ø 1.75 mm ± 5%) were prepared with all the formulations, starting from extruded rods of 2 mm diameter.

ii) 3D printing of oral pulsatile release capsular devices

Starting from the design of the mold formerly developed for Chronocap™ [2], CAD files for 3D printing the bodies and caps of the capsule shells were created (**Fig. 2**). The size of the gap between cap and body was defined to enable their efficient matching and the locking of the resulting capsule shell.

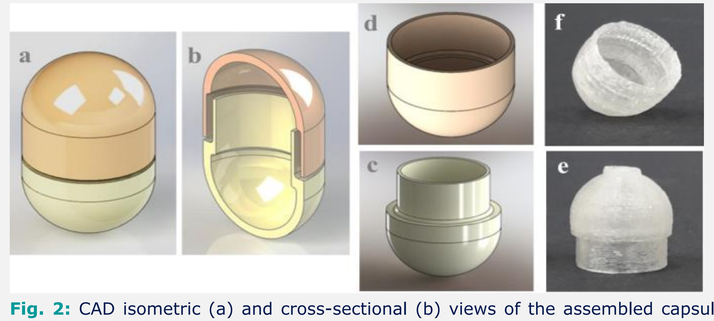

Fig. 2: CAD isometric (a) and cross-sectional (b) views of the assembled capsule shell; CAD isometric views and photographs of a printed body (c and e) and cap (d and f).

By defining a suitable printing temperature (*i.e.* 180 °C), HPC bodies and caps were obtained with 5 min printing time each.

Thickness, µm (cv)					
cap			body		
	1	481.0 (7.2)		1	469.2 (6.9)
	2	702.8 (5.8)		2	669.8 (6.4)

No support material was used for printing, while the raft was designed so that it could easily be removed by cutting.

3D printed HPC-based capsular devices showed a typical pulsatile-release profile, with a mean lag phases of 68.6 min, after which the drug liberation was complete in less than 10 min (**Fig. 5**), which was consistent with that of analogous capsule shells prepared by IM.

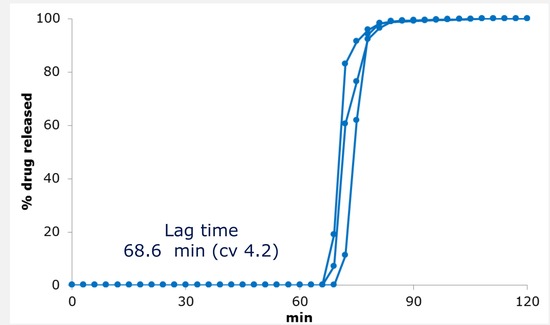

Fig. 5: release profiles of HPC capsular devices produced by FDM

CONCLUSION

HPC based filaments suitable for FDM were produced and exploited to print swellable/erodible capsular devices with the desired pulsatile release performance. The application potential of FDM in the real-time prototyping of IM processes was assessed.

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