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Research paper

Personalized 3D-Printed Gastroretentive Drug Forms with Metronidazole

Réka Révész[1,2], Akay Dogan Mengenli[1,2], Mónika Béres[3], Petra Arany[1], Ádám Haimhoffer[1,*]

[1]University of Debrecen, Faculty of Pharmacy, Department of Pharmaceutical Technology, H-4002 Debrecen, Rex Ferenc Str. 1.
[2]University of Debrecen, Doctoral School of Pharmaceutical Sciences, H-4032 Debrecen, Nagyerdei sqr. 98.
[3]University of Debrecen, Faculty of Medicine, Department of Medical Imaging, H-4032 Debrecen, Nagyerdei sqr. 98.
*Correspondence: haimhoffer.adam@euipar.unideb.hu;

Abstract

3D printing is increasingly recognized as a versatile manufacturing approach, enabling the production of devices that are difficult or costly to fabricate using conventional methods. In this study, we aimed to develop a hollow, 3D-printed capsule designed for incorporation of a molten matrix containing an active pharmaceutical ingredient, and to evaluate its potential for gastric retention through controlled drug release. Capsule shells were fabricated from polylactic acid using fused deposition modeling and subsequently filled with polyethylene glycol-based melts. Micro-CT was employed to assess internal structure and integrity. Drug release profiles were measured for different matrix compositions, and texture as well as compositional analyses were performed on both filled and unfilled capsules. Our findings demonstrate that the 3D-printed PLA shells provide sufficient mechanical strength and, depending on the matrix composition, enable controlled, zero-order drug release for up to five hours. These results highlight the potential of 3D-printed capsules as a customizable, gastro-retentive drug delivery system, offering opportunities for personalized therapies.

1. Introduction

Three-dimensional (3D) printing has become one of the most dynamically developing areas of healthcare innovation over the past decade. Technology was originally used in industrial and engineering applications but has now gained ground in many areas of healthcare. In addition to implants, prostheses, and dental devices, pharmaceutical technology is also increasingly using 3D printing solutions to create complex drug delivery systems [1–3]. With the development of personalized medicine, the possibilities

offered by 3D printing have become particularly valuable, as they enable the production of drug forms such as tablets and capsules that can be tailored to individual pharmacokinetic and pharmacogenetic characteristics [4,5]. The dose, rate of drug release, or structure of the formulation can be designed to increase treatment efficacy and reduce the risk of side effects.

One of the main advantages of drug carriers produced using 3D printing is the high degree of design flexibility. Thanks to computer modeling, the geometry, pore size, strength, and internal structure of the preparations can be precisely controlled, which is key to determining the release profile of the active ingredient [6,7]. The manufacturing process is particularly economical as it requires few raw materials and is fully automated, and even small batch production does not incur additional costs [8]. One of the best-known milestones in this field is Spritam®, the first 3D-printed drug containing levetiracetam, which was approved by the FDA in 2015 [6].

One of the 3D printing technologies is fused deposition modeling (FDM), which is based on thermoplastic polymers. The printing parameters of FDM technology, such as temperature, fill density, and shell count, allow for a degree of control over printing that is particularly advantageous in the development of drug delivery systems [9].

One exciting and intensively researched area of application for 3D-printed drug forms is the development of gastric retention (GR) systems [10]. These formulations are designed to remain in the stomach longer than average, allowing for the steady or delayed release of the active ingredient in an ideal environment. The use of GR systems is justified in the case of active ingredients whose solubility and stability are pH-dependent, or when the active ingredient needs to exert a local therapeutic effect, for example in the treatment of *Helicobacter pylori* infection [11,12]. The complex physiological characteristics of the stomach influence the time a drug spends in the stomach, which makes the design of GR systems a particularly complex task. Retention systems in the stomach can operate on the basis of several different mechanisms: these include high-density formulations that settle near the pylorus, expanding and swelling devices, solutions based on polymers that adhere to the gastric mucosa, and floating systems [13,14]. The latter have a lower density than the average density of stomach contents, so they float on the surface of the fluid and are able to retain the active ingredient in the stomach for a long time. These systems are particularly suitable for 3D printing, as the buoyancy and kinetics of the active

ingredient release can be controlled with high precision by fine-tuning the geometric parameters: wall thickness, number of shells, and fill percentage [13,15].

Previous research has demonstrated that 3D-printed floating capsules can be successfully used as longer-acting formulations that remain in the stomach. Several in vivo studies have confirmed that these devices remain in the stomach for up to 10-12 hours and provide predictable, uniform drug release [16,17]. The floating and dissolution rates are influenced by the capsule wall thickness, the number of shells, the filling ratio, and the properties of the selected polymer [18–20]. Based on the results of these studies, 3D-printed GR systems have significant potential for the future of personalized drug therapy.

The aim of our research is to develop a 3D-printed carrier with inherently low density, enabling gastro-retention. The carrier is also capable of holding molten formulations, allowing for personalized and controlled release of active ingredients.

2. Materials and methods

2.1 Materials

Polyethylene glycol, glycerin, strearic acid, polylactic acid and metronidazole were purchased from Molar Chemicals Kft. (Halásztelek, Hungary).

2.2 Methods

2.2.1 3D Printing and Filling of Capsule Bodies

The gastroretentive capsules were produced in collaboration with the Faculty of Engineering's 3D Technology Laboratory. The capsule shells were designed using computer-aided modelling and fabricated by FDM (Fused Deposition Modeling) 3D printing using PLA-based extruded filament. In designing the capsule, our objective was to create a low-density carrier that would remain below 1 g/cm³ even after being filled with the molten active ingredient content matrix. To achieve this, we developed a capsule architecture featuring a dual-layer shell with an inert, air-filled interspace (**Figure 1.**). This enclosed air compartment acts as a buoyant chamber, functioning similarly to an inflatable raft during the release of the active ingredient.

All samples were fabricated using a CraftBot Plus Pro 3D printer. The material used for printing was 1.75 mm PLA filament (polylactic acid). Prior to printing, the filament was stored in a dry environment to minimize moisture absorption. Models were

prepared in CraftWare slicing software using the following parameters: nozzle temperature: 200 °C; build plate temperature: 60 °C; layer height: 0.2 mm, print speed: 50 mm/s, Infill density: 20% (grid pattern), shell thickness: 1.2 mm (3 perimeters), cooling fan: 100% after the first three layers, retraction: 1.5 mm at 35 mm/s.

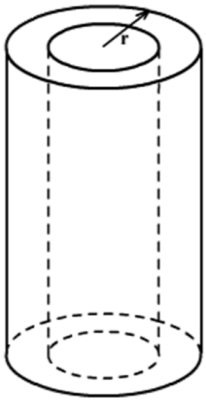

***Figure 1**.:* Schematic representation of the designed capsule, illustrating the double-wall structure and the enclosed air chamber.

The excipients were selected to enable the formation of a filament suitable for 3D printing, allowing the formulation to be printed directly into the capsule (**Table 1.**). However, during our experiments, we filled the capsules using extrusion and injection molding technologies. We melted 100 grams of each PEG-based matrix in a water bath (65 °C) and then filled the hollow capsules with a pipette. To prevent leakage, one end of each capsule was sealed with Parafilm. The amount of matrix introduced into each capsule was determined by measuring the capsule weight before and after filling.

Component	Sample A	Sample B
PEG	65%	55%
Glycerin	5%	5%
Metronidazole	30%	30%
Stearic acid	–	10%

***Table 1**.:* Two PEG-based matrix formulations were used as fillers.

The internal volume of the capsule was calculated using the cylindrical volume formula (M = 17.6 mm; r = 4 mm), resulting in 884.7 mm³ (0.8847 cm³). Using the measured mass and calculated volume, the density of the matrix was determined.

2.2.3 In Vitro Dissolution Study

Three random samples were taken for dissolution tests from every composition. 900 milliliters of hydrochloric acid media was used for the dissolution tests using a Hanson Vision G2 Elite8 dissolution tester (rotating paddle method, 75 rpm and 37 °C). Sampling was performed at 5, 10, 15, 30, 60, 120, 180, 240, and 300 minutes. The metronidazole content of the samples was quantified using a UV/VIS spectrophotometer (Shimadzu UV-1601, Shimadzu Corp., Kyoto, Japan) at 278 nm following dilution with pH 1.2 buffer. Dissolution profiles were evaluated graphically, assessing the fit to zero-order and first-order kinetic models. Model suitability was determined based on correlation coefficients. Floatation behavior was monitored visually at regular intervals.

2.2.2 Micro-CT Analysis

The internal structure of the capsule shells and matrix was examined using a SkyScan 1272 micro-CT instrument with the following parameters: resolution: 5 µm, pixel size: 1344x2016, excitation voltage: 50 kV; excitation current: 200 µA. Flat field correction and geometric correction were applied. Image reconstruction was performed using SkyScan NRecon software (v2.0.4.2), with radiation hardening correction, ring artifact reduction, and smoothing. The resulting images were saved in DICOM and BPM formats for further analysis.

2.2.4 Texture Analysis

A Brookfield CT3 (Toronto, Canada) texture analizer was used to following the structure changing during the dissolution. The initial filled dry samples and empty capsule shells were examined at room temperature without being immersed in the extraction medium. After dissolution, the samples were carefully removed from the liquid using a plastic sieve, and the water on the surface was gently drained off. Subsequently, the consistency analysis was performed using the following settings. During the measurement, the samples were placed on their sides on the metal sample holder table and compressed from above at a speed of 0.50 mm/s with a test piece (TA25/1000 acrylic cylinder, diameter: 50.8 mm, height: 20 mm). The test is performed until complete compression or until a resistance of 4500 grams is detected.

3. Results

3.1 3D Printing and Filling of Capsule Bodies

Based on the mass differences, the capsules were filled with 250 ± 10 mg of PEG-based molten matrix on average. Given the 30% metronidazole content of the formulations, each capsule contained 75 mg of metronidazole.

The capsule volume is 0.8847 cm^3, the apparent density of the PLA capsule shell was 520 mg/cm^3, which is lower than the density of water, enabling flotation. The filled capsules also remained buoyant with an apparent density of 775.6 and 766,0 mg/cm^3, still below the density of water at 37 °C (993.4 mg/cm^3).

3.2 Micro-CT Analysis

Micro-CT imaging was performed on both unfilled and matrix-filled samples. In **Figure 2**, the two structures on the left show side and top views of the unfilled capsule, demonstrating that the capsule shell consists of two layers with air entrapped between them. **Figure 3** further confirms that no gaps or discontinuities are present between the 3D-printed layers; the structure is completely sealed, preventing premature escape of the trapped air. Consequently, the prototype capsule shell exhibits low density, and its apparent density remains low even after filling.

The right side of **Figure 2** presents the capsules filled with the molten matrix. The matrix appears as a darker gray region and is shown to fill the internal cavity uniformly, with homogeneous distribution. The melt does not penetrate the outer cavities, thereby preserving the integrity of the double-shell structure.

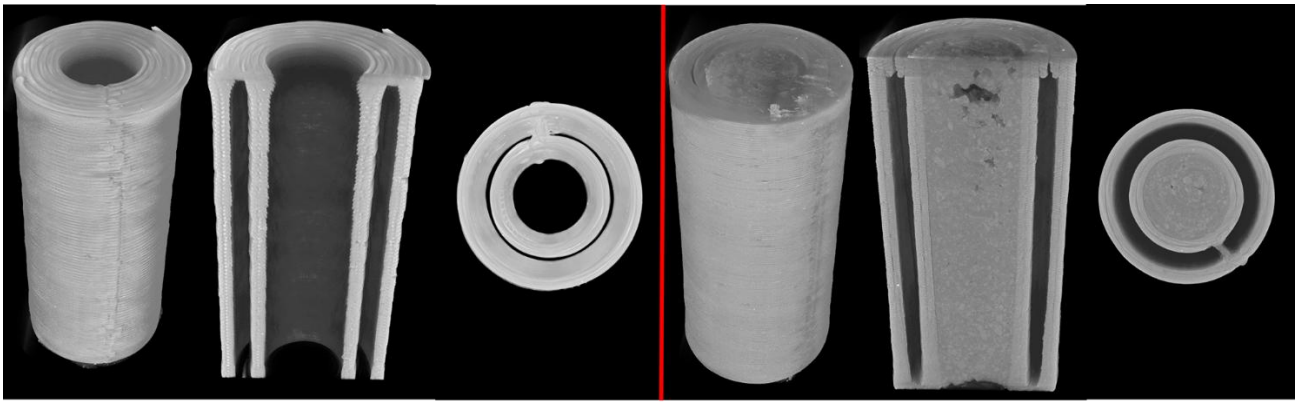

Figure 2.: Micro-CT images of empty (left) and matrix-filled (right) capsules.

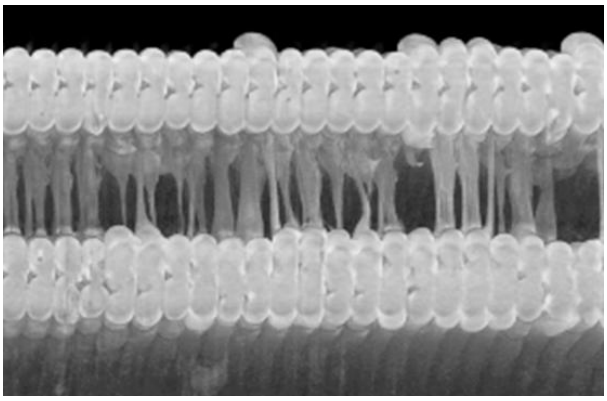

Figure 3.: Structural representation of the capsule shell.

3.3 In Vitro Dissolution Study

The in vitro dissolution study result is presented in **Figure 4**. The release of metronidazole in sample A was completed in approximately 2 hours in simulated gastric juice at 37 °C. The release rate was almost linear for 80 minutes, then gradually slowed down and reached a plateau level at around 120 minutes. However, in sample B, where the composition contained a retardant excipient, it was clearly observed that only a very small amount of the active ingredient, approximately 10%, dissolved in 5 hours.

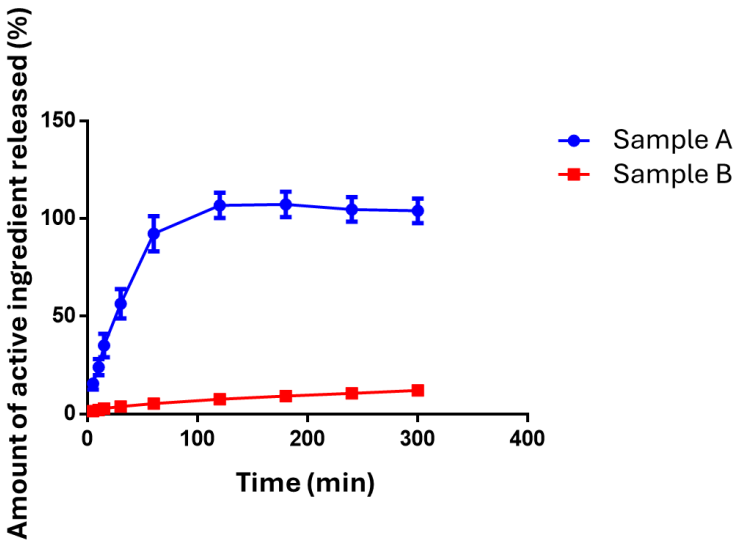

Figure 4.: Percentage of metronidazole released as a function of time.

The drug-release profiles were evaluated by assessing their fit to common kinetic models. For sample B, zero-order kinetics provided the best description of the release behavior, indicating a slow and constant release rate. In contrast, the release profile of

sample A was best characterized by first-order kinetics, showing a rapid initial release followed by a gradual plateau. The comparison of model fits is summarized in **Table 2.** below.

Kinetic model	Sample	Correlation coefficient (R^2)
Zero-order	A	0,8672
	B	0,9423
First-order	A	0,8870
	B	0,8169

Table 2. Fit of dissolution data to kinetic models.

3.4 Texture Analysis

Finally, mechanical properties of both unfilled and matrix-filled capsules were evaluated using a Texture Analyzer. Measurements were performed after dissolution at 25 °C and 37 °C. The results are presented in Figure 6. The measurements at 25 °C showed nearly identical mechanical behavior for both capsule types. However, at 37 °C the capsules exhibited noticeable dilation and became considerably softer compared to their behavior at 25 °C. This indicates that the capsule structure becomes slightly more fragile and more easily deformable at physiological temperature; nevertheless, it still withstands an applied force of 4.5 kg and remains sufficiently flexible.

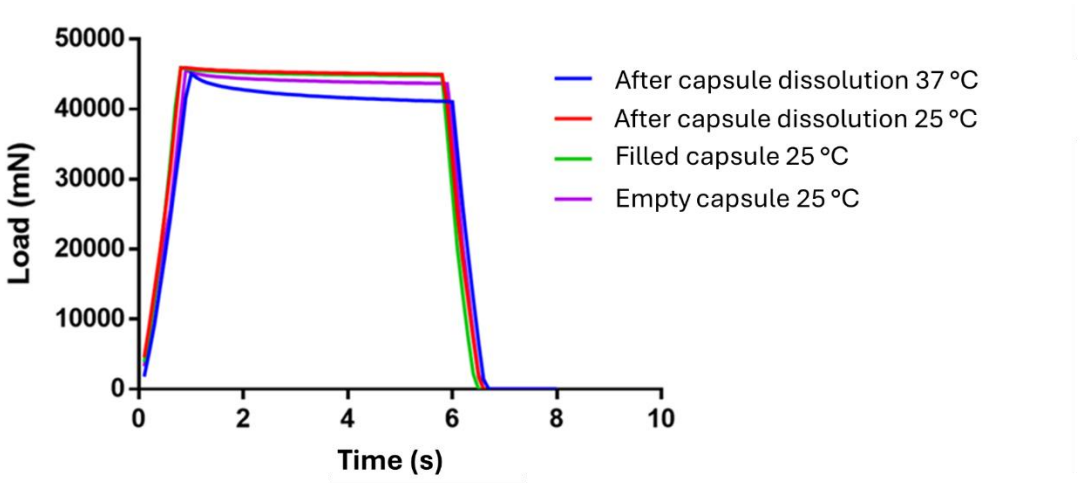

Figure 6.: Force–deformation curves of capsules measured with a Texture Analyzer.

4. Discussion

The aim of this study was to comprehensively evaluate the physical properties, internal structure, and drug-release characteristics of 3D-printed capsule shells filled with different molten matrices. The calculated apparent densities of the empty capsules are 520 mg/cm³, that is lower than the gastric fluid, confirming their continuous buoyancy during dissolution. In previous studies, similar raft-like 3D structures exhibited higher densities than the preparations developed in our work [16]. This is because we were able to further reduce the apparent density not only through the use of low-density filaments, but also by incorporating air-trapping features directly into the structural design. Micro-CT imaging clearly verified the double-walled PLA shell structure, showing complete closure between the layers. According to previous studies, the gaps between 3D printed structures provide adequate sealing against gases and liquids [21]. In the filled capsules, the PEG-based matrix occupied the internal cavity homogeneously, while the outer shell cavities remained empty, indicating that the melt was confined exclusively to the inner chamber. Drug-release studies demonstrated a pronounced effect of the selected excipients on metronidazole dissolution. In sample A, complete release occurred within approximately 120 minutes, whereas sample B, containing a retardant excipient, exhibited less than 10% drug release after 5 hours. For gastroretentive metronidazole matrices containing comparable amounts of retardant excipients, the literature typically reports drug release over approximately 12 hours [22]. In contrast, our formulation provides an even slower release, attributable to the 3D raft structure. The ‘sandwich effect’ created by the double-walled 3D design results in a markedly slower and more uniform release of the active ingredient [23]. Texture analysis revealed similar mechanical resistance among the capsules at room temperature. After dissolution at 37 °C, samples exhibited increased deformability and elasticity, softening under thermal influence yet maintaining structural integrity under a 4.5-kg load [24]. These results indicate favorable mechanical stability for gastric-retentive applications. Emptying of the capsule from the stomach is ensured by motility, which takes approximately 4 hours [25].

Overall, the findings demonstrate that 3D-printed PLA capsules exhibit favorable structural characteristics, stable buoyancy, and well-controlled drug-release behavior, supporting their potential for use in the development of personalized gastroretentive drug-delivery systems. Currently marketed gastroretentive formulations (e.g. floating

tablets, swellable matrices, mucoadhesive systems) are typically single-design, fixed-dose products manufactured using conventional tableting or encapsulation techniques. These systems offer limited flexibility. Unlike conventional systems that rely on gas-generating excipients to achieve buoyancy, flotation in the present design is ensured by a permanently enclosed air chamber, resulting in predictable and stable gastric retention. Furthermore, the functional separation between the PLA capsule shell and the drug-containing molten matrix allows independent optimization of mechanical stability, buoyancy, and drug-release kinetics. The digitally controlled design also enables modification of capsule geometry, wall thickness, and matrix composition, providing a high degree of personalization that is not achievable with existing commercial products. Finally, the feasibility of small-batch and on-demand manufacturing without additional tooling highlights the potential of this system as a flexible platform for personalized gastroretentive drug delivery.

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Data Availability Statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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