

ORIGINAL RESEARCH ARTICLE

Semisolid extrusion 3D-printed self-emulsifying β -sitosterol suppositories with structure-modulated release for potential rectal delivery

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Abstract

Localized rectal delivery is a promising strategy for ulcerative colitis, as it may increase drug exposure at inflamed sites in the distal colorectum while reducing systemic exposure. However, many natural anti-inflammatory small molecules, including β -sitosterol, are hydrophobic and have poor aqueous dispersibility, limiting their formulation and therapeutic use. Conventional rectal dosage forms typically have fixed structures, making it difficult to tailor drug-release behavior. To address these challenges, a β -sitosterol-loaded self-emulsifying lipid suppository was fabricated using semisolid extrusion (SSE) three-dimensional (3D) printing, and the ability of the internal architecture to modulate early in vitro drug release was investigated. The Gelucire® 44/14-based matrix exhibited shear-thinning behavior and temperature-dependent softening, enabling SSE 3D printing. Upon contact with an aqueous medium, the printed suppositories formed submicron dispersions. Liquefaction and self-emulsification times ranged from 18.27 to 24.27 min and from 4.33 to 8.54 min, respectively. A representative formulation had a droplet size of 370.67 ± 39.09 nm and a polydispersity index of 0.27 ± 0.04 . Fourier transform infrared, differential scanning calorimetry, and X-ray diffraction analyses indicated good drug-matrix compatibility and reduced β -sitosterol crystallinity, suggesting partial solubilization within the lipid matrix. With the matrix composition and external geometry held constant, in vitro release was adjusted by varying the internal pore architecture and nominal infill density. Lower-infill-density structures promoted faster medium penetration and earlier β -sitosterol release, whereas higher-infill-density structures slowed release by increasing structural resistance and diffusion-path tortuosity. These results demonstrate the feasibility of using SSE 3D printing to produce structure-modulated rectal dosage forms containing poorly water-soluble natural compounds.

Keywords: Semisolid extrusion; Three-dimensional printing; Ulcerative colitis; Self-emulsification; Suppository; Structure-modulated release

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1. Introduction

Ulcerative colitis (UC), a major subtype of inflammatory bowel disease, is characterized by chronic, recurrent inflammation and ulceration of the colorectal mucosa.¹ This condition not only markedly impairs patients' quality of life but also increases the risk of colorectal cancer.² Currently, the clinical management of UC primarily relies on aminosalicylates, glucocorticoids, and immunosuppressants. However, long-term systemic administration is often associated with significant adverse effects, treatment resistance, and high relapse rates, underscoring the urgent need for safer and more effective therapeutic strategies.³ In recent years, natural phytosterols, particularly β -sitosterol, have attracted considerable attention owing to their reported anti-inflammatory and immunomodulatory effects, and have shown potential for alleviating intestinal mucosal inflammation and injury.⁴⁻⁷ The clinical translation of β -sitosterol is limited by its low oral bioavailability, mainly due to poor aqueous solubility and limited intestinal absorption.⁸ Therefore, the development of advanced drug delivery systems that can overcome these limitations is crucial to fully realize the therapeutic potential of poorly water-soluble natural small molecules.

Given that inflammatory lesions in UC often involve the distal colorectal mucosa,⁹ local rectal administration can bypass hepatic first-pass metabolism and reduce systemic exposure, enabling high drug concentrations at inflamed sites.¹⁰ However, most available rectal formulations, including conventional suppositories, are designed with fixed doses and relatively simple solid structures. This standardized approach fails to account for substantial interpatient differences in disease severity, lesion extent, and therapeutic response, thereby limiting the broader application of localized therapies in precision medicine.

In recent years, three-dimensional (3D) printing has emerged as a promising strategy for the on-demand fabrication of personalized drug delivery systems, owing to its high geometric design flexibility.¹¹⁻¹⁶ Although fused deposition modeling-based 3D printing has been explored for suppository fabrication,¹⁷ its high processing temperatures severely limit the incorporation of thermosensitive drugs, while the inherently rough surface of the printed products may compromise patient compliance during rectal administration. In contrast, semisolid extrusion (SSE) 3D printing enables mild processing under near-room-temperature conditions, making it particularly suitable for lipid-based matrix systems.¹⁸ Moreover, self-emulsifying lipid systems can spontaneously form submicron oil-in-water dispersions in physiological environments, thereby improving the

dispersibility and dissolution of hydrophobic drugs.^{19,20} However, current studies on SSE 3D-printed suppositories have largely focused on simple solid architectures, with dose adjustment primarily achieved by altering the overall volume or formulation composition.²¹ Previous studies on 3D-printed suppositories have mainly focused on formulation composition, material selection, and external geometry, while self-emulsifying drug delivery systems have generally regulated drug release through formulation modification. However, whether internal infill architecture can serve as an independent design parameter for modulating drug release, while maintaining identical formulation composition and external geometry, remains insufficiently explored.

To address these challenges, we developed β -sitosterol-loaded self-emulsifying lipid suppositories using SSE 3D printing, with β -sitosterol used as a model poorly water-soluble natural anti-inflammatory compound. A lipid-based pharmaceutical excipient (Gelucire[®] 44/14; Gattefossé, France) was used as the main lipid excipient to support mild extrusion processing and spontaneous emulsification upon contact with aqueous media. In addition to improving drug dispersion, this system was designed to test a central design question: whether the internal architecture of a printed lipid suppository could modulate drug release without altering the formulation composition. By varying pore geometry and infill density while maintaining identical external geometry and matrix composition, we investigated how structural features influence medium penetration, matrix softening, and β -sitosterol release. The printability, rheological behavior, thermal response, solid-state characteristics, self-emulsification performance, mechanical properties, and *in vitro* release behavior of the printed suppositories were evaluated. This study demonstrates that internal architecture can serve as a practical design variable for structurally modulated *in vitro* release, providing a structural design reference for the further development of architecture-tunable rectal dosage forms.

2. Materials and methods

2.1. Materials

β -Sitosterol (75% purity) was purchased from Xi'an Binghe Biotechnology Co., Ltd. (China), and the β -sitosterol reference standard (98% purity; Lot No. KB3379511) was obtained from Shanghai Yuanye Biotechnology Co., Ltd. (China). Analytical-grade methanol and acetonitrile were purchased from Thermo Fisher Scientific Co., Ltd. (China). Gelucire[®] 44/14 was provided by Shanghai Jiafashi Biotechnology Co., Ltd. (China). Stearic acid and mannitol were purchased from Tianjin Damao Chemical

Reagent Factory (China). Mixed fatty acid glycerides were obtained from Chengdu Lutianhua Kesen Co., Ltd. (China), and coconut oil was kindly provided by Beijing Fengli Jingqiu Trading Co., Ltd. (China). All other reagents were analytical grade.

2.2. Design of three-dimensional printing models

The external geometry of the suppositories was designed as a standard torpedo shape using Shapr3D software (V5.910.9193.0, Shapr3D, Hungary). To minimize the influence of external dimensions on drug release behavior, all models were designed with identical external parameters, including a height of 20 mm and a base diameter of 8 mm. After construction, the models were exported in STL format for subsequent printing. Unlike the external geometry, the internal infill structure was not predefined during computer-aided design modeling. Instead, it was automatically generated by the slicing software integrated into the 3D printing system (BioScaffolder 3.2, GeSiM, Germany). By adjusting the slicing parameters, the internal pore architecture and structural density could be controlled, thereby enabling investigation of the effects of internal architecture on formulation performance. Based on differences in lattice geometry and nominal infill density, four internal architectures were designed: low-density quadrilateral (QL), low-density hexagonal (HL), high-density quadrilateral (QH), and high-density hexagonal (HH). The low-density models (QL and HL) were assigned a nominal infill density of 30%, whereas the high-density models (QH and HH) were assigned a nominal infill density of 60%. Representative model illustrations are shown in Figure 1, and detailed design

parameters, including nominal infill density, infill spacing, infill offset, and layer rotation angle, are summarized in Table 1. The terms “low density” and “high density” refer to the nominal infill density set in the slicing software rather than experimentally measured porosity. Therefore, the four models should be interpreted as representative architectural configurations generated by combined variations in infill pattern, spacing, and layer rotation angle, rather than as a full-factorial design intended to isolate individual structural parameters.

2.3. Semisolid extrusion three-dimensional printing of β -sitosterol suppositories

Gelucire[®] 44/14, coconut oil, stearic acid, mixed fatty acid glycerides, mannitol, and β -sitosterol were used to prepare the printable paste. The formulation consisted of Gelucire[®] 44/14 (62.65%, w/w), mixed fatty acid glycerides (11.75%, w/w), coconut oil (7.83%, w/w), stearic acid (7.83%, w/w), mannitol (6.81%, w/w), and β -sitosterol (3.13%, w/w). All components were weighed according to the specified composition and heated and melted at 60 °C. The mixture was stirred at 900 rpm in a glass beaker using a magnetic stirrer until a homogeneous paste formed. The resulting β -sitosterol-loaded suppository paste was then transferred into a 10 mL dispensing syringe and precooled at 4 °C to achieve a printable state with suitable viscoelasticity. The prepared paste was loaded into a conical extrusion needle with an internal diameter of 0.35 mm, and the syringe–needle assembly was mounted on an SSE 3D printer (BioScaffolder 3.2, GeSiM GmbH, Germany). The printing parameters were as follows: printing temperature: 35 °C; layer height: 0.2 mm; and printing speed: 7 mm/s. The

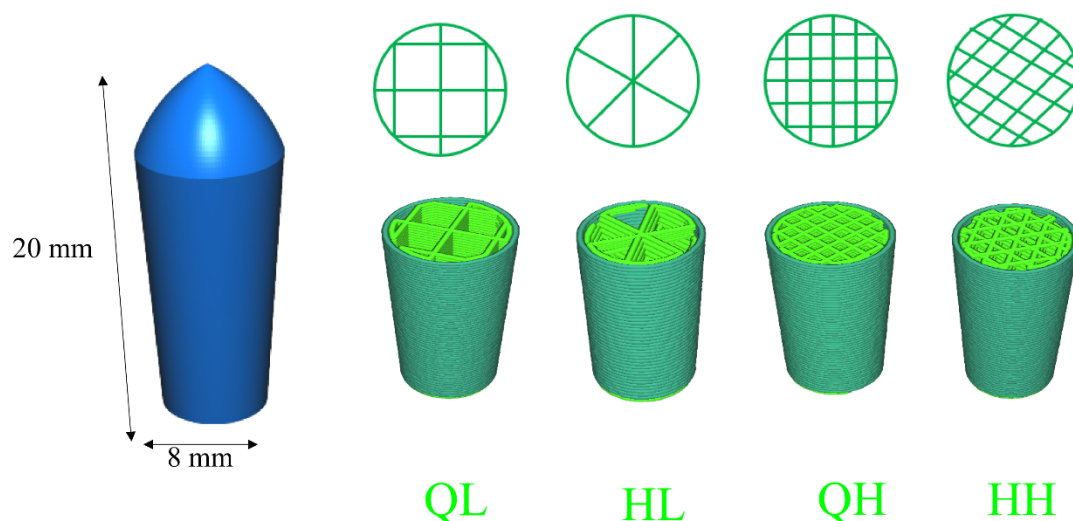


Figure 1. Three-dimensionally printed suppository models with different internal fillings

Abbreviations: HH: High-density hexagonal; HL: Low-density hexagonal; QH: High-density quadrilateral; QL: Low-density quadrilateral.

Table 1. Design parameters of suppository internal architectures

Design type	Infill pattern	Infill density (%)	Infill offset (mm)	Infill spacing (mm)	Layer rotation angle (°)
QL	Quadrilateral	30	0.1	2	90
HL	Hexagonal	30	0.1	4	60
QH	Quadrilateral	60	0.1	2	60
HH	Hexagonal	60	0.1	1	90

nominal β -sitosterol dose was calculated as the β -sitosterol equivalent based on the stated purity of the raw material.

2.4. Characterization of 3D-printed β -sitosterol suppositories

2.4.1. Rheological characterization

The rheological properties of the β -sitosterol-loaded suppository system were characterized using a rotational rheometer (MCR 302e, Anton Paar, Austria). To identify the linear viscoelastic region (LVR), a strain sweep test was first conducted over a strain range of 0.01–100% at 20 °C and 1 Hz. Based on the identified LVR, temperature sweep tests were performed at a constant strain of 0.05% and a frequency of 1 Hz from 20 °C to 50 °C. Frequency sweep measurements were then conducted at 20 °C and 0.05% strain from 0.1 to 10 Hz to evaluate the viscoelastic behavior of the formulation. Yield behavior was further analyzed using stress-sweep testing, and the yield stress and corresponding critical strain were determined.

2.4.2. Differential scanning calorimetry

Differential scanning calorimetry (DSC) analysis was performed using a thermal analyzer (STA 449 F3, Netzsch, Germany). Samples were heated from 20 °C to 200 °C at 5 °C/min under a nitrogen atmosphere (30 mL/min). The thermal behavior of β -sitosterol, the excipients, and the 3D-printed formulation was compared to assess potential drug–excipient interactions and changes in the crystalline state.

2.4.3. X-ray powder diffraction

Changes in the solid-state properties of β -sitosterol after preparation and 3D printing were analyzed using a 9 kW X-ray powder diffractometer (SmartLab, Rigaku, Japan). Test samples included pure β -sitosterol, Gelucire® 44/14, a physical mixture of the formulation components at the corresponding formulation proportions, and SSE 3D-printed suppositories. To ensure sample uniformity, both Gelucire® 44/14 particles and printed suppositories were gently ground into fine powder before testing. Measurements were performed using copper K α radiation

($\lambda = 1.5406 \text{ \AA}$) at 40 kV and 30 mA over a 2θ range of 2°–50° with a step size of 0.02° and a scanning rate of 2°/min. The diffraction patterns were compared to evaluate the physical state of β -sitosterol within the lipid matrix.

2.4.4. Fourier transform infrared spectroscopy

Fourier transform infrared (FTIR) spectra were collected using a spectrometer (Nicolet iS10, Thermo Fisher Scientific, United States of America [USA]) over a range of 4000–500 cm^{-1} at a resolution of 4 cm^{-1} with 24 scans. β -Sitosterol, Gelucire® 44/14, coconut oil, and the 3D-printed formulation were analyzed. The spectra were compared to assess potential intermolecular interactions, including hydrogen bonding, between the drug and the lipid matrix.

2.4.5. Scanning electron microscopy

The morphology of the 3D-printed suppositories was observed using a scanning electron microscope (SEM; Gemini 360, ZEISS, Germany). Samples were longitudinally sectioned, mounted on conductive carbon tape, and sputter-coated with gold to a thickness of 25 nm before imaging. SEM images were acquired using a secondary electron detector at an accelerating voltage of 10 kV.

2.4.6. Transmission electron microscopy

Transmission electron microscopy (TEM) analysis was performed using an S-Twin microscope (G2 F20, FEI, USA). A 50 mg suppository sample was dispersed in 100 mL ultrapure water and stirred at 100 rpm to allow self-emulsification. A drop of the diluted dispersion was deposited onto a carbon-coated copper grid, negatively stained with 1% (w/v) phosphotungstic acid solution, and dried before imaging. TEM images were acquired to evaluate droplet morphology and the dispersion state.

2.4.7. Characterization of self-emulsification behavior and physicochemical properties of the dispersion

The self-emulsification behavior of the formulation was evaluated by dispersing the sample in 100 mL ultrapure

water under magnetic stirring at 100 rpm. The droplet size, polydispersity index (PDI), and zeta (ζ)-potential of the resulting dispersion were determined using an analyzer (NanoBrook Omni, Brookhaven Instruments, USA) based on dynamic light scattering (DLS). To determine the self-emulsification time, 50 mg of the sample was added to 100 mL of ultrapure water at $37\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$ under magnetic stirring at 50 rpm. The time required to form a visually homogeneous dispersion was recorded as the self-emulsification time. All measurements were performed in triplicate and expressed as mean $\pm$ standard deviation (SD).

2.4.8. Determination of the mechanical properties of suppositories

The mechanical strength of the suppositories was evaluated using a texture analyzer (TA.XTplus, Stable Micro Systems, UK) equipped with a 2-mm cylindrical probe and operated in compression mode. Prior to testing, each suppository was placed horizontally on the test platform, and compression was applied perpendicular to its longitudinal axis. A localized indentation test was performed along the suppository body using a cylindrical probe with a diameter of 2 mm. The pre-test, test, and post-test speeds were set at 0.1, 1, and 10 mm/s, respectively. Compression was continued until the deformation reached 80% of the initial suppository height. All measurements were conducted at $25\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$. Because probe displacement increased linearly with time at a constant compression speed, the mechanical response was expressed as force–displacement curves rather than force–time curves. Each formulation was tested in triplicate ($n = 3$), and the maximum indentation force was recorded as an indicator of mechanical resistance. This compression test was designed to evaluate the structural integrity and mechanical robustness of the suppositories during handling and insertion before administration, rather than to replicate the *in vivo* mechanical environment of the rectum.

2.4.9. Determination of liquefaction time

The liquefaction time of the suppositories was determined using a disintegration tester (RBY-4, Tianjin Xinzhou Technology Co., Ltd., China). Distilled water at $37\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$ was used as the medium. Each suppository was placed in the basket and covered with a perforated disc to prevent floating, and the time required for complete softening or disintegration was recorded as the liquefaction time. All measurements were performed in triplicate and are expressed as mean $\pm$ SD.

2.4.10. Determination of drug content

The drug content of the suppositories was determined

using high-performance liquid chromatography (HPLC; Waters system, Waters Corporation, USA). A single suppository was dispersed in 100 mL phosphate-buffered saline (PBS; pH 7.4) containing 0.5% (w/v) sodium dodecyl sulfate (SDS) and stirred at 100 rpm and $37\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$ for 2 h. The resulting solution was filtered through a 0.22- μm membrane before analysis. HPLC analysis was performed using a Waters system equipped with an Ecosil 120-5-C18 column (5 μm , $4.6 \times 250\text{ mm}$). The mobile phase consisted of methanol/acetonitrile (90:10, v/v) and was delivered at a flow rate of 1.0 mL/min. The injection volume was 10 μL , and the detection wavelength was 204 nm. All measurements were performed in triplicate and expressed as mean $\pm$ SD. Prior to sample analysis, the HPLC method was validated according to the International Council for Harmonisation Guideline Q2 (Revision 2) for specificity, linearity, precision, repeatability, and solution stability.²² The method exhibited good linearity over the concentration range of 0.875–80 $\mu\text{g/mL}$ ($R^2 = 0.9996$), with relative SD (RSD) values of 0.20%, 1.82%, and 1.60% for instrumental precision, repeatability, and solution stability, respectively. The validated method was subsequently used to quantify β -sitosterol in the *in vitro* release study.

2.4.11. In vitro drug release assay

In vitro drug release was evaluated in 100 mL PBS (pH 7.4) containing 0.5% SDS at $37\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$. This medium was used as a methodological release medium rather than as a fully biorelevant simulation of rectal fluid. A relatively limited release volume was selected to avoid using an excessively large dissolution volume for a formulation intended for local rectal or distal colorectal delivery, and 0.5% SDS was added to maintain sink conditions, reduce the risk of saturation of the release medium, and ensure reliable quantification of poorly water-soluble β -sitosterol.^{23–25} At predetermined time points (20, 30, 45, 60, 90, and 120 min), 5 mL release medium was withdrawn and filtered through a 0.22- μm membrane. An equal volume of fresh release medium was immediately added to maintain a constant volume. β -Sitosterol concentration was quantified using HPLC. The cumulative release percentage (Q_t , %) was normalized to the experimentally determined drug content of the corresponding suppository architecture rather than a fixed theoretical dose. The cumulative amount of β -sitosterol released was corrected for the drug removed at each sampling point, and the cumulative release percentage was calculated as shown in Equation 1:

$$Q_t(\%) = \frac{\text{Cumulative amount of } \beta\text{-sitosterol released}}{\text{Actual drug content of the corresponding suppository}} \times 100\% \quad (1)$$

2.5. Statistical analysis

All experiments were performed in triplicate unless otherwise stated. Data are presented as mean $\pm$ SD. Statistical analysis and graphing were performed using OriginPro 2021 (OriginLab Corporation, USA).

3. Results and discussion

3.1. Rheological behavior of the lipid paste and three-dimensional printing mechanism

An ideal 3D-printed suppository matrix should balance printability during extrusion with softening behavior at physiological temperature. During printing, the material should exhibit sufficient flowability to overcome extrusion resistance and should rapidly recover structural strength after deposition to maintain the stacked morphology. After administration, the formulation should undergo moderate softening or melting at the physiological rectal temperature of approximately 37 °C to facilitate drug release.²⁶ Based on this design rationale, a self-emulsifying lipid matrix was constructed using Gelucire® 44/14 as the main component.^{27,28} Mannitol was incorporated as a hydrophilic excipient to modulate the material properties,²⁹ allowing the formulation to satisfy the dual requirements of extrusion-based printing and temperature-responsive softening for rectal administration. The rheological behavior of the system was then characterized to evaluate its suitability for printing and softening under physiologically relevant conditions.

The shear-rate sweep results (Figure 2A) showed pronounced shear-thinning behavior of the lipid paste.³⁰ As the shear rate increased, the apparent viscosity decreased markedly, indicating that the material could flow under the high-shear conditions inside the nozzle. Upon shear reduction, viscosity recovery may contribute to post-deposition shape retention. This reversible rheological behavior supports continuous extrusion and structural maintenance during printing. The stress sweep results (Figure 2C) further revealed the yield behavior of the system. Within the LVR below the yield point, the storage modulus (G') remained higher than the loss modulus (G''), indicating that the system maintained a stable gel-like network. When the applied stress exceeded the yield stress, G' decreased rapidly and fell below G'' , suggesting a transition from elastic-dominated to viscous-dominated behavior, accompanied by the onset of flow.³¹ This yield transition enables the paste to transform from a solid-like state to a flowable state under external force and recover structural stability after deposition, thereby supporting extrusion and maintaining shape fidelity. The frequency sweep results (Figure 2D) indicated the structural stability of the paste under dynamic perturbation. Over the

frequency range of 0.1–10.0 Hz, G' remained relatively stable and was consistently higher than G'' , indicating that the system was dominated by elastic behavior and had sufficient structural strength.³² This viscoelastic property may help the printed layers resist deformation caused by gravity or minor mechanical disturbances during layer-by-layer stacking. The temperature sweep results (Figure 2B) further demonstrated the temperature-responsive behavior of the system. In the range of 33.0 °C–37.0 °C, G' remained higher than G'' , indicating that the system retained structural rigidity. For example, at 33.1 °C, G' reached 10.0×10^4 Pa, which was higher than G'' (3.8×10^4 Pa), suggesting adequate morphological stability during storage and administration. As the temperature approached 37.0 °C, both moduli decreased markedly; G' and G'' decreased to 3.0×10^4 Pa and 2.5×10^4 Pa, respectively, indicating marked softening of the matrix.³³ This temperature-induced softening near the physiological rectal temperature is consistent with the design requirement that suppositories soften after rectal administration to promote drug release.

3.2. Effect of printing orientation on the shape fidelity of suppositories produced by semisolid extrusion three-dimensional printing

After confirming the rheological suitability of the lipid paste for SSE printing, the printable paste was further processed into suppositories with defined external morphology and well-preserved internal architecture. For torpedo-shaped suppositories, printing orientation is particularly important because the curved and axisymmetric geometry can markedly affect the initial contact area between the deposited material and the printing platform.³⁴ When printed horizontally, the curved outer surface of the suppository contacted the flat platform through an extremely narrow contact region. Under the combined effects of gravity, minor mechanical disturbances during printing, and the weight of subsequently deposited layers, this unstable contact region gradually flattened. As a result, the originally smooth, curved surface was partially flattened, resulting in unintended edges or sharp corners at the contact region. Such geometric distortion may compromise the structural integrity of the printed suppository and reduce its surface smoothness, thereby affecting patient acceptability during rectal administration.

To reduce these orientation-related distortions, a vertical printing strategy was adopted using the selected formulation and SSE processing conditions. In this orientation, layer deposition proceeded along the longitudinal axis of the suppository, allowing the structure to be built on a stable basal region rather than relying on a curved sidewall for platform support. The combination of

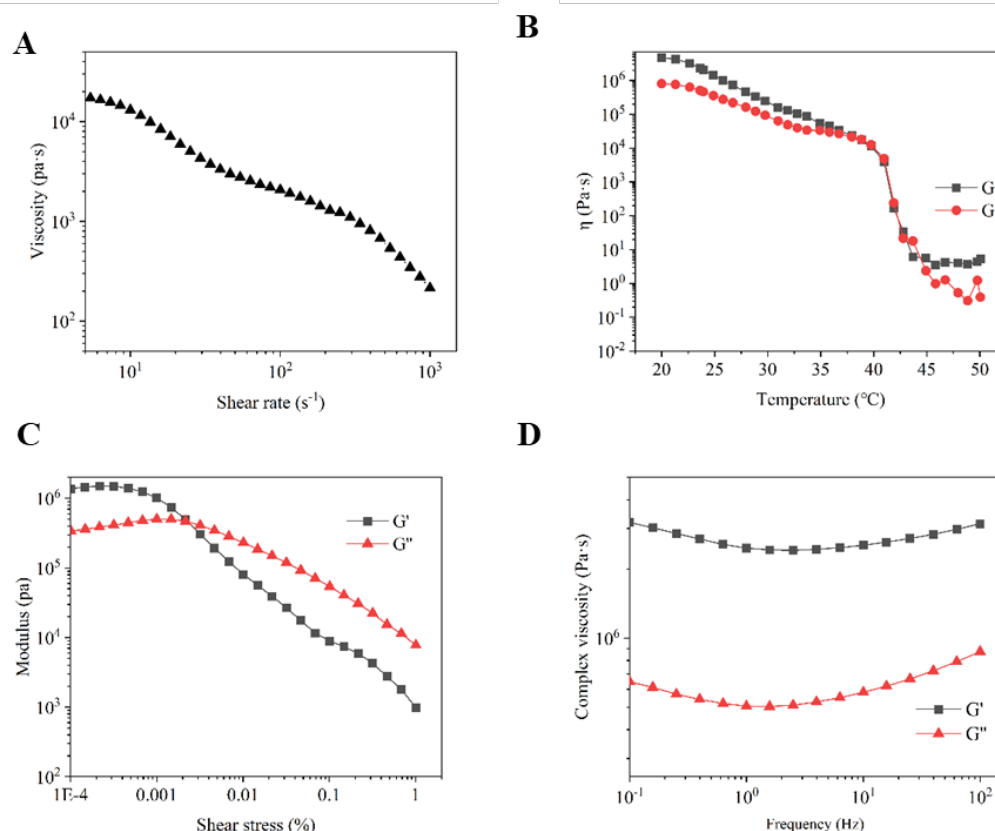


Figure 2. Rheological characterization of the three-dimensional printing paste. (A) Apparent viscosity as a function of shear rate. (B) Temperature-dependent changes in storage modulus (G') and loss modulus (G''). (C) Stress sweep analysis showing the yield transition. (D) Frequency sweep analysis showing the viscoelastic stability of the paste.

the printable lipid paste and vertical deposition improved layer-stacking stability and reduced deformation during printing. As shown in Figure 3, the vertically printed β -sitosterol suppositories exhibited regular torpedo-shaped external contours without obvious flattening, edge formation, or structural collapse. Cross-sectional images further showed that both quadrilateral and hexagonal infill patterns were well reproduced, indicating satisfactory fidelity of the internal architecture. These results suggest that the selected formulation–process combination was suitable for the vertical fabrication of SSE 3D-printed lipid suppositories and provided a reliable basis for subsequent evaluation of architecture-dependent drug loading, mechanical properties, and *in vitro* release behavior.³⁵

3.3. Effects of internal architecture on quality attributes and mechanical properties of printed suppositories

Following the successful establishment of vertical printing, the effects of internal infill geometry and nominal infill density on the quality attributes of the printed

suppositories were further evaluated (Table 2). Because the external geometry was kept constant across all designs, changes in formulation weight and drug content mainly reflected differences in internal architecture and nominal infill density. Increasing the nominal infill density tended to increase the total printed mass and β -sitosterol loading. Among the tested designs, the HH structure showed the highest average weight (447 ± 2.72 mg) and drug content (10.42 ± 0.45 mg), whereas the QL structure showed the lowest weight (340 ± 14.02 mg) and drug content (7.78 ± 0.34 mg), consistent with its lower designed infill density. In contrast, the base diameter remained close to the designed value of 8 mm for all formulations, with only minor variations among different infill structures. These results indicate that the internal architecture can be used to tune suppository mass and β -sitosterol dose while maintaining the overall external dimensions of the suppositories.

Indentation testing further showed that internal architecture affected the local mechanical response of the 3D-printed suppositories (Figure 4). The maximum

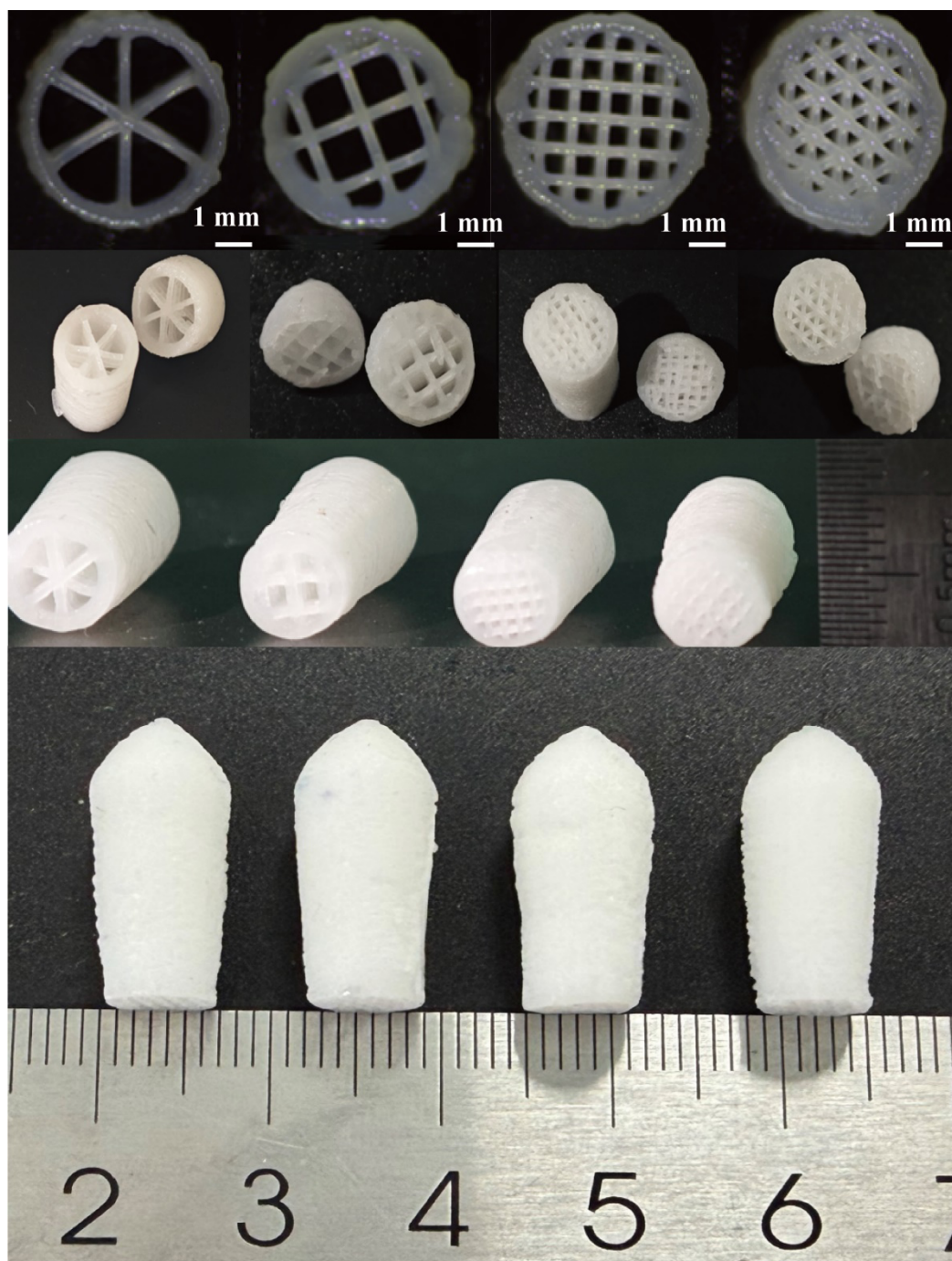


Figure 3. Shape fidelity and internal architecture of vertically printed β -sitosterol-loaded suppositories

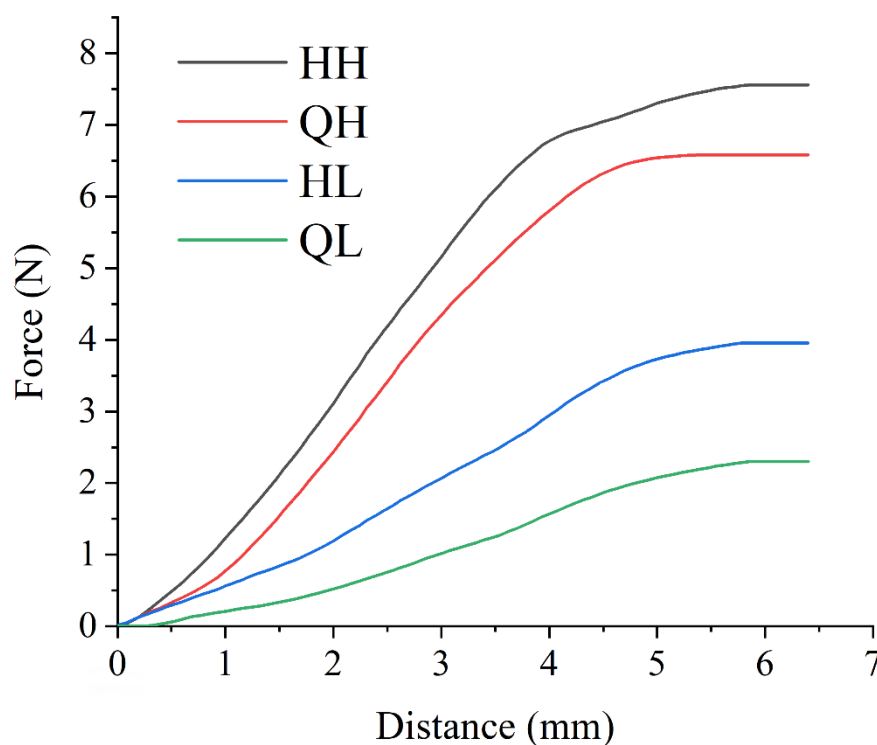
indentation force followed the order of HH > QH > HL > QL, indicating that both infill geometry and nominal infill density contributed to mechanical performance. The HH structure exhibited the highest maximum indentation force (7.5 N), suggesting greater resistance to local deformation. In contrast, the QL structure showed

the lowest maximum indentation force (2.3 N), which may be attributed to its larger pore spacing and reduced internal supporting framework. These findings suggest that denser and more continuous lattice structures may improve load transfer within the printed suppository, thereby enhancing mechanical robustness. Because the

Table 2. Weight, β -sitosterol content, and base diameter of three-dimensionally printed β -sitosterol-loaded suppositories with different internal architectures

Formulation	Weight (mg)	Drug content (mg)	Base diameter (mm)
HH	447 $\pm$ 2.72	10.42 $\pm$ 0.45	8.07 $\pm$ 0.19
HL	410 $\pm$ 5.75	9.86 $\pm$ 0.18	7.98 $\pm$ 0.08
QH	396 $\pm$ 16.47	8.27 $\pm$ 0.10	8.03 $\pm$ 0.15
QL	340 $\pm$ 14.02	7.78 $\pm$ 0.34	7.99 $\pm$ 0.11

Abbreviations: HH: High-density hexagonal; HL: Low-density hexagonal; QH: High-density quadrilateral; QL: Low-density quadrilateral.

**Figure 4.** Force-displacement curves obtained from indentation testing of β -sitosterol-loaded suppositories with different internal architectures
Abbreviations: HH: High-density hexagonal; HL: Low-density hexagonal; QH: High-density quadrilateral; QL: Low-density quadrilateral.

compression test was performed under displacement-controlled conditions, the mechanical behavior was evaluated using force-displacement curves, which more directly reflect deformation resistance under the present test conditions than force-time profiles. Furthermore, this localized indentation test was used to compare the structural integrity and handling robustness of different printed architectures rather than to directly simulate the mechanical environment encountered during rectal administration.

Scanning electron microscopy was further used to examine the microstructural features of the printed

suppositories (Figure 5). The samples exhibited well-defined layered deposition patterns, relatively uniform filament arrangement, and continuous interlayer interfaces. No obvious cracks, delamination, or structural collapse were observed, indicating satisfactory printing fidelity and interlayer adhesion under the selected formulation and vertical SSE printing conditions. A relatively smooth lipid-rich surface was observed, although dedicated friction or lubrication studies would be required to determine whether this feature improves administration-related performance. Together with the weight, β -sitosterol content, and dimensional data, these mechanical and morphological results demonstrate that the selected formulation-process

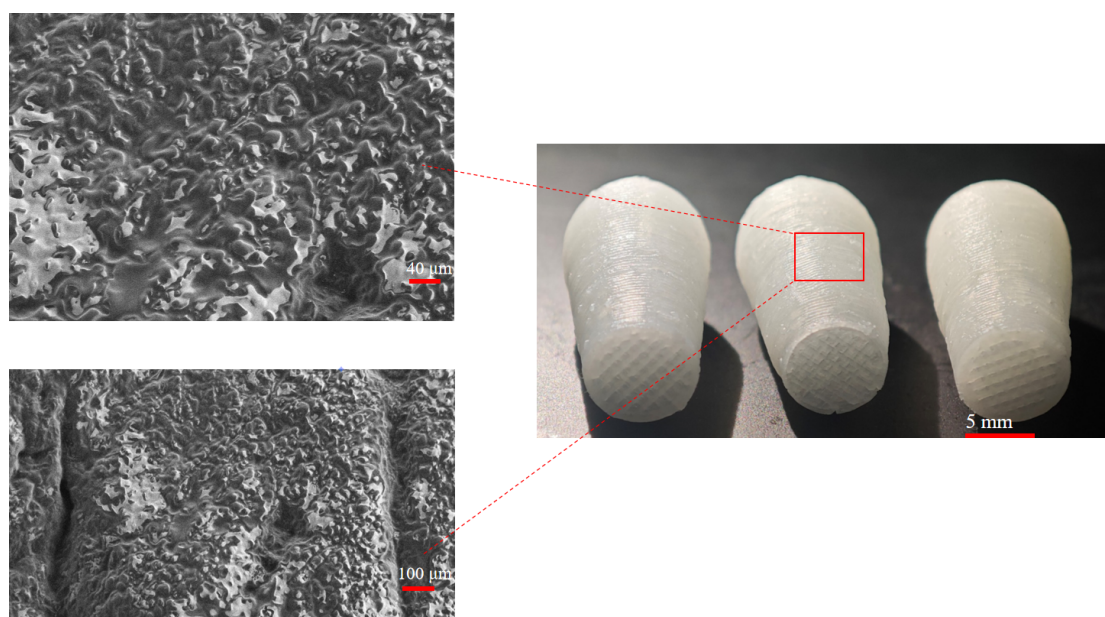


Figure 5. Scanning electron microscopic images showing the surface morphology and layered microstructure of 3D-printed β -sitosterol-loaded suppositories. Scale bars: 40 μm , 100 μm ; magnifications: 200 $\times$, 100 $\times$.

combination enabled the reproducible fabrication of β -sitosterol-loaded suppositories with architecture-dependent mass, β -sitosterol dose, and mechanical properties, providing a reliable basis for subsequent evaluation of structurally modulated *in vitro* release.

3.4. Drug–matrix compatibility and physical state of β -sitosterol

In addition to macroscopic structural design, the physicochemical state of β -sitosterol within the lipid matrix is critical to formulation performance. Therefore, FTIR, DSC, and X-ray diffraction (XRD) analyses were performed to evaluate potential drug–excipient interactions and the physical state of β -sitosterol in the printed suppositories. The FTIR spectra of β -sitosterol, the excipients, the physical mixture, and the 3D-printed suppositories showed similar characteristic absorption bands without new peaks or evident peak shifts (Figure 6A). This result suggests that β -sitosterol maintained its chemical integrity during formulation preparation and SSE 3D printing, with no evident chemical interactions between the drug and the lipid matrix. DSC analysis was used to examine the thermal behavior of the formulation components and printed suppositories (Figure 6B). Gelucire[®] 44/14, coconut oil, stearic acid, and mannitol exhibited their characteristic endothermic peaks, indicating that the main thermal features of the excipient matrix were retained. Pure β -sitosterol exhibited a melting peak at approximately 135 °C–145 °C; however, this peak

was not clearly observed in either the physical mixture or the printed suppositories. This may be attributed to the earlier melting of the lipid excipients during heating, which may promote β -sitosterol solubilization in the molten lipid phase and thereby mask its crystalline melting transition. XRD analysis further supported a reduction in β -sitosterol crystallinity in the printed formulation (Figure 6C). Pure β -sitosterol showed multiple sharp diffraction peaks, whereas these characteristic peaks were markedly weakened in the 3D-printed suppositories. These results suggest that β -sitosterol was at least partially solubilized or dispersed and existed in a less crystalline state within the lipid matrix. Collectively, the FTIR, DSC, and XRD results indicate good compatibility between β -sitosterol and the lipid excipients, as well as a marked reduction in drug crystallinity after incorporation into the SSE 3D-printed suppositories. Such a less crystalline state may improve apparent solubility and facilitate the self-emulsification and aqueous dispersion of β -sitosterol, thereby providing a favorable physicochemical basis for subsequent drug release.

3.5. Self-emulsification behavior and colloidal characteristics of three-dimensionally printed β -sitosterol suppositories

To evaluate the self-emulsifying performance of the 3D-printed suppositories, liquefaction time, self-emulsification time, droplet size, ζ -potential, and PDI were determined (Table 3). Because all four printed suppositories

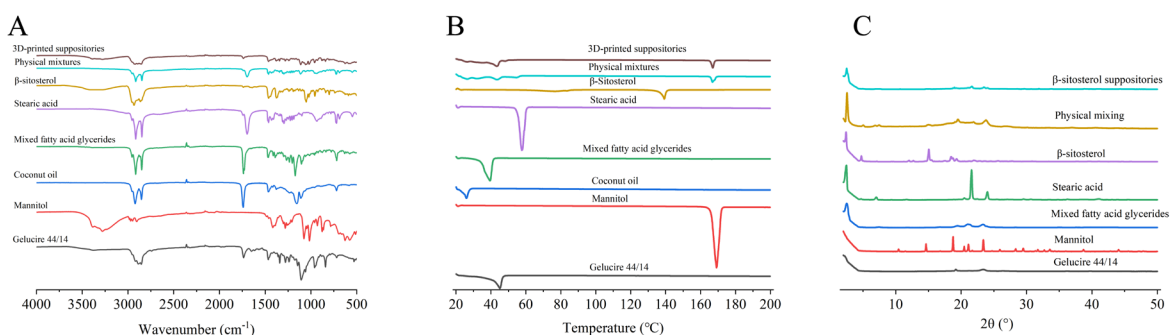


Figure 6. Drug–matrix compatibility and solid-state characterization of β -sitosterol in 3D-printed lipid suppositories. (A) FTIR spectra of β -sitosterol, the excipients, the physical mixture, and the 3D-printed suppositories. (B) DSC thermograms showing the thermal behavior of the formulation components and printed suppositories. (C) XRD patterns showing the crystalline characteristics of β -sitosterol before and after incorporation into the lipid matrix. Abbreviations: 3D: Three-dimensional; DSC: Differential scanning calorimetry; FTIR: Fourier transform infrared spectroscopy; XRD: X-ray diffraction.

shared the same Gelucire® 44/14-based formulation and differed only in their internal architecture, liquefaction and self-emulsification times were evaluated for all four architectures. In contrast, droplet size, ζ -potential, PDI, and TEM morphology were determined using a representative printed formulation after complete self-emulsification, as these colloidal properties were mainly governed by formulation composition rather than printed internal architecture. The liquefaction time varied among the four printed architectures, ranging from 18.27 ± 1.35 min for QL to 24.27 ± 1.15 min for QH. Similarly, the self-emulsification time ranged from 4.33 ± 0.20 min for QL to 8.54 ± 0.23 min for HH. Compared to the high-density structures, the low-density architectures exhibited shorter liquefaction and self-emulsification times. This may be attributed to their larger pore volume and enhanced aqueous medium penetration, which accelerated matrix softening and lipid dispersion. The representative self-emulsified dispersion exhibited an average droplet size of 370.67 ± 39.09 nm, indicating the formation of a submicron dispersion. The PDI was 0.27 ± 0.04 , indicating a relatively narrow particle size distribution and good dispersion homogeneity.³⁶ The ζ -potential was 40.31 ± 5.06 mV, suggesting that the dispersed droplets possessed a positively charged surface and sufficient electrostatic repulsion to reduce particle aggregation. Such a high absolute ζ -potential is generally considered favorable for maintaining colloidal stability.³⁷ Overall, these results demonstrate that the Gelucire® 44/14-based lipid matrix possessed favorable self-emulsifying characteristics, while the different internal architectures mainly influenced the liquefaction and self-emulsification processes rather than the intrinsic colloidal properties of the resulting self-emulsified dispersion.³⁸

Transmission electron microscopic observations further confirmed the formation of self-emulsified droplets after hydration (Figure 7A and 7B). Representative

TEM micrographs from different fields of view and magnifications showed that the droplets exhibited a predominantly spherical or quasi-spherical morphology with well-defined boundaries and were uniformly dispersed, with no obvious aggregation or coalescence. Although slight variations in droplet size were observed, most droplets were 250–450 nm in diameter, consistent with the average droplet size determined using DLS (370.67 ± 39.09 nm). The slightly smaller particle size observed in TEM is expected because DLS measures the hydrodynamic diameter, including the surfactant layer and hydration shell surrounding the droplets, whereas TEM is performed on dried samples and therefore reflects the physical droplet diameter. These findings indicate that SSE 3D printing preserved the self-emulsifying properties of the lipid formulation, enabling the printed suppositories to readily form uniformly dispersed lipid droplets upon hydration, which may enhance the aqueous dispersion of β -sitosterol and facilitate contact with the rectal mucosa after administration.³⁹

Table 3. Liquefaction and self-emulsification times of three-dimensionally printed β -sitosterol suppositories with different internal architectures

Formulation	Liquefaction time (min)	Self-emulsification time (min)
HH	23.15 ± 1.57	8.54 ± 0.23
HL	19.35 ± 1.33	4.54 ± 0.17
QH	24.27 ± 1.15	7.38 ± 0.15
QL	18.27 ± 1.35	4.33 ± 0.20

Abbreviations: HH: High-density hexagonal; HL: Low-density hexagonal; QH: High-density quadrilateral; QL: Low-density quadrilateral.

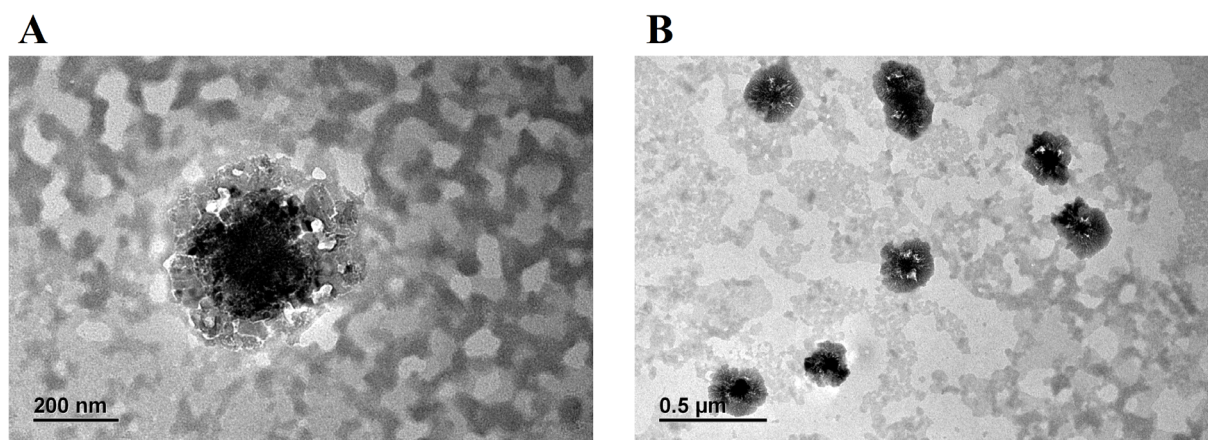


Figure 7. Representative transmission electron microscopic micrographs of the self-emulsified droplets observed at different magnifications. (A) Representative individual droplet with a quasi-spherical morphology. Scale bar: 200 nm; magnification: 140,000 $\times$. (B) Uniformly dispersed droplets. Scale bar: 0.5 μ m; magnification: 50,000 $\times$.

3.6. *In vitro* release behavior and kinetic analysis

As discussed above, the printed suppositories readily formed a submicron emulsion-like dispersion upon contact with the aqueous medium, providing a favorable basis for β -sitosterol dispersion. However, the overall drug release behavior was determined not only by the self-emulsifying lipid matrix but also by the internal architecture of the printed formulation. In particular, the infill geometry and nominal infill density influenced pore connectivity, medium penetration, matrix relaxation, and diffusion resistance, thereby modulating β -sitosterol release from the lipid matrix. The QL structure showed the highest cumulative release, reaching $97.19\% \pm 2.63\%$ at 45 min (Figure 8). The HL structure also exhibited rapid drug release, reaching $91.09\% \pm 5.19\%$ at 45 min. In contrast, the high-density structures showed slower release profiles. The more compact internal architecture reduced pore space and increased the complexity of medium penetration pathways, thereby delaying matrix softening, lipid dispersion, and drug diffusion. At 120 min, the cumulative release was $86.97\% \pm 2.27\%$ for the HH structure and $81.67\% \pm 2.99\%$ for the QH structure. These results indicate that internal infill geometry and density jointly modulated early-stage β -sitosterol release under the same matrix composition.

To compare the release behavior among different internal architectures, the release profiles were fitted using zero-order, first-order, and Higuchi kinetic models (Table A1). For the zero-order model, QH exhibited the highest correlation coefficient ($R^2 = 0.9761$), followed by HH ($R^2 = 0.9705$), whereas QL and HL showed relatively

poorer fits ($R^2 = 0.8136$ and 0.6713 , respectively). In the first-order model, QL showed the best fit ($R^2 = 0.9745$), followed by HH ($R^2 = 0.9626$) and QH ($R^2 = 0.9575$), while HL exhibited the lowest correlation ($R^2 = 0.7576$). For the Higuchi model, QL again exhibited the highest correlation coefficient ($R^2 = 0.9539$), whereas HH, QH, and HL showed lower values ($R^2 = 0.8676$, 0.8276 , and 0.7679 , respectively). These results indicate that the release kinetics differed among the four internal architectures. The observed differences are likely associated with the combined effects of internal geometry and infill density. At the same nominal low infill density, QL showed better agreement with both the first-order and Higuchi models than HL, indicating that the quadrilateral architecture produced a release profile more closely described by these kinetic models.^{40,41} This difference may be related to variations in the internal transport pathways created by the two geometric patterns, which could influence release medium penetration and drug diffusion within the lipid matrix. Similarly, increasing the infill density shifted the release behavior of the quadrilateral architecture from better agreement with the first-order and Higuchi models for QL toward the zero-order model for QH ($R^2 = 0.9761$), suggesting a slower and more sustained release pattern. Overall, these findings demonstrate that both internal geometry and infill density modulate the release behavior of 3D-printed lipid-based suppositories. Nevertheless, only four representative structural configurations were evaluated in this study, and further investigation using additional architectures is warranted.

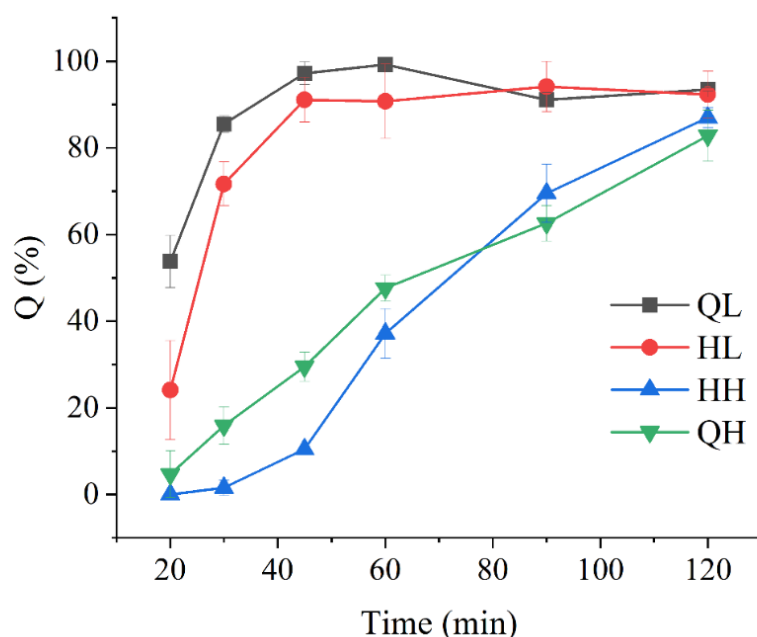


Figure 8. *In vitro* release profiles of β -sitosterol-loaded suppositories with different internal architectures ($n = 3$)
Abbreviations: HH: High-density hexagonal; HL: Low-density hexagonal; QH: High-density quadrilateral; QL: Low-density quadrilateral.

4. Conclusion

In this study, β -sitosterol-loaded self-emulsifying lipid suppositories were fabricated using SSE 3D printing. The Gelucire[®] 44/14-based lipid matrix exhibited suitable rheological behavior for extrusion printing and temperature-responsive softening near the physiological rectal temperature. By adopting a vertical printing strategy, β -sitosterol-loaded suppositories with satisfactory shape fidelity and reproducible internal architectures were obtained. The printed formulations also showed favorable self-emulsifying behavior, forming a submicron dispersion upon contact with an aqueous medium, thereby facilitating the aqueous dispersion of the poorly water-soluble drug. Under the same matrix composition and identical external geometry, changing the internal infill geometry and nominal infill density altered the mass, experimentally determined β -sitosterol content, localized mechanical response, and *in vitro* release behavior of the printed suppositories. Low-density architectures promoted faster medium penetration and earlier β -sitosterol release, whereas high-density architectures resulted in slower release profiles, likely due to increased structural resistance and greater diffusion path complexity. These findings demonstrate that internal architecture can serve as a practical design variable for modulating early-stage *in vitro* β -sitosterol release from self-emulsifying lipid suppositories, providing an additional structural design strategy beyond conventional

composition-based approaches. Overall, this work supports the feasibility of combining SSE 3D printing with self-emulsifying lipid systems for structure-modulated rectal dosage forms. Although further studies on rectal retention, mucosal distribution, pharmacokinetics, and pharmacodynamic efficacy in colitis models are required, the present study establishes a useful formulation basis for the further development of structurally tunable 3D-printed suppositories for poorly water-soluble natural compounds.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Writing–original draft: Xin Li

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

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

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Appendix

Table A1. Kinetic model fitting of β -sitosterol release from three-dimensionally printed suppositories with different internal architectures

Model	HH	QL	HL	QH
Zero-order	$R^2 = 0.9705$	$R^2 = 0.8136$	$R^2 = 0.6713$	$R^2 = 0.9761$
First-order	$R^2 = 0.9626$	$R^2 = 0.9745$	$R^2 = 0.7576$	$R^2 = 0.9575$
Higuchi	$R^2 = 0.8676$	$R^2 = 0.9539$	$R^2 = 0.7679$	$R^2 = 0.8276$

Abbreviations: HH: High-density hexagonal; HL: Low-density hexagonal; QH: High-density quadrilateral; QL: Low-density quadrilateral.