



Beyond Immediate Release: FDM-Printed Pediatric 6-Mercaptopurine Chewable Tablets with Spontaneous *In Situ* Nanostructure Formation

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Abstract

Pediatric maintenance therapy for acute lymphoblastic leukemia requires prolonged daily administration of 6-mercaptopurine (6-MP), a drug characterized by a narrow therapeutic index and substantial interindividual variability, creating a need for flexible and patient-friendly dosage forms. This study aimed to develop pediatric chewable tablets 6-MP using hot-melt extrusion and fused deposition modeling (FDM) 3D printing. Preformulation studies and rheological characterization were performed to support formulation development. The influence of internal architecture on porosity, disintegration, mechanical properties, and chewability was investigated by varying infill density. Among the evaluated architectures, 30% infill provided the best balance between structural integrity, porosity, rapid disintegration, and softening after saliva exposure, ensuring adequate chewability. Tablets exhibited accurate drug content ($99.5 \pm 2.2\%$). Beyond their immediate-release behavior, complete drug release was achieved within 15 min, while colloidal nanostructures were spontaneously formed, associating approximately 11% of dissolved 6-MP, suggesting a hybrid release mechanism combining rapid drug availability with nano-mediated modulation. Dynamic light scattering and transmission electron microscopy confirmed these findings. Overall, the developed platform demonstrates the potential of FDM-based structural engineering to produce personalized pediatric medicines and reveals that thermally processed polymeric matrices may function as dynamic drug delivery systems rather than conventional immediate-release dosage forms.

Keywords 6-mercaptopurine · chewable tablets · fused deposition modeling · hot-melt extrusion · *in situ* nanostructures · pediatric formulation

Introduction

The development of age-appropriate pharmaceutical formulations remains a major challenge in pediatric pharmacotherapy. Children exhibit age-dependent physiological and metabolic characteristics that influence drug disposition and response, making simple extrapolation of adult dosing regimens inappropriate and often requiring individualized dose adjustment [1–4]. At the same time, sensory and

psychomotor factors strongly influence the acceptability of pharmaceutical dosage forms. Increased sensitivity to bitter taste, preference for sweet flavors, and difficulties swallowing conventional tablets, particularly among children younger than six years, may compromise drug administration and treatment adherence [1, 5–7]. Together, these challenges highlight the need for pediatric formulations that combine dose flexibility and accurate drug delivery with improved palatability, ease of administration, and patient acceptability.

These formulation-related challenges are particularly relevant in acute lymphoblastic leukemia (ALL), the most common childhood malignancy, which originates from the uncontrolled proliferation of immature lymphoid cells in the bone marrow [8, 9]. Although survival rates exceed 90% in high-income countries, relapse remains the leading cause of mortality and is strongly associated with poor adherence to oral maintenance therapy [8, 10]. Maintenance therapy

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relies on the long-term daily administration of 6-mercaptopurine (6-MP) in combination with weekly methotrexate for approximately two years [11–13]. Importantly, inadequate adherence to 6-MP has been associated with a 2.5- to 3.9-fold increase in relapse risk, and up to 59% of relapses have been attributed to poor treatment compliance [10, 14].

In addition to adherence-related challenges, 6-MP exhibits a narrow therapeutic index and marked interindividual variability arising from pharmacogenetic factors, particularly thiopurine S-methyltransferase and nudix hydrolase 15 polymorphisms [15, 16]. Consequently, the optimal dose is not fixed but adjusted according to hematological parameters, emphasizing the need for flexible pharmaceutical strategies capable of supporting individualized therapy and safe handling during preparation and administration [13, 17].

Despite these clinical requirements, currently available 6-MP dosage forms are limited to conventional fixed-dose tablets, which inadequately accommodate frequent dose adjustments [13, 15]. Tablet splitting remains common in clinical practice but is associated with mass variability, drug loss, and the risk of under- or overdosing [18, 19]. Moreover, as an antineoplastic agent classified as both a high-alert medication and a hazardous drug, 6-MP requires strict safety measures during handling and administration. Manipulation of this cytotoxic drug outside controlled environments may increase both occupational and household exposure risks [13, 20, 21]. In fact, 6-MP may generate drug residues and increase the risk of cutaneous exposure and contamination of caregivers, household surfaces, and other family members [22, 23].

In parallel, the lack of age-appropriate formulations and inadequate palatability may further impair adherence during prolonged therapy. Although chewable tablets offer improved acceptability, ease of administration, and superior stability compared with liquid formulations [24–27], no pediatric chewable formulation containing 6-MP is currently available. In addition, 6-MP has been reported as a Biopharmaceutics Classification System (BCS) class II drug, with low aqueous solubility representing a potential challenge for oral formulation development.

Recent advances in pharmaceutical manufacturing technologies have created new opportunities for personalized pediatric medicines. Hot-melt extrusion (HME) enables homogeneous incorporation of drugs into polymeric matrices and may contribute to taste masking, physicochemical stability, and the formation of amorphous solid dispersions [28–30]. When coupled with filament-based fused deposition modeling (FDM), HME also serves as a preparatory step to produce continuous drug-loaded filaments with controlled composition and suitable mechanical and rheological properties for reliable printer feeding and material deposition. This approach enables precise control of geometry, internal architecture, and dose, providing a robust platform

for digitally driven and reproducible dose individualization [31–33].

Therefore, an important unmet need persists at the interface between pediatric oncology and pharmaceutical technology: the lack of a dosage form capable of simultaneously combining dose flexibility, handling safety, pharmaceutical performance, and patient acceptability. In this context, the present study aimed to develop pediatric 3D-printed chewable tablets containing 6-MP to provide a personalized platform capable of improving adherence and supporting safer and more effective maintenance therapy in pediatric acute lymphoblastic leukemia. To support rational formulation design, preformulation studies and rheological characterization were performed, followed by evaluation of the influence of internal architecture on porosity, mechanical properties, disintegration, and chewability. Pharmaceutical performance was further investigated through drug content and dissolution studies, while the dynamic behavior of the hydrated matrix was explored by assessing the spontaneous formation of colloidal nanostructures and their potential impact on drug release.

Experimental

Materials

6-MP (batch MKCQ4491) and citric acid (batch MKBZZ7078V) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Commercial 6-MP 50 mg tablets (Purinethol®, batch 401773) were obtained from Excella GmbH & Co. KG (Feucht, Bavaria, Germany). Parateck® MXP (polyvinyl alcohol, PVA; batch F2304664422) and Parateck® ODT (batch F1977890) were supplied by Merck KGaA (Darmstadt, Hesse, Germany). Glycerol (batch 129208) and lactose (batch 102276) were obtained from Dinâmica (São Paulo, Brazil). Grape flavoring (batch 24111078) was purchased from Adicel (Belo Horizonte, Brazil).

Preformulation Studies

Hansen Solubility Parameters (HSP)

A theoretical screening of excipients was conducted to assess the potential miscibility between 6-MP and formulation components. HSP were employed as a predictive tool for estimating miscibility between materials [34].

The drug (6-MP) and the excipients PVA, glycerol, Parateck® ODT, flavoring agent, and xylitol were analyzed. Since Parateck® ODT and the grape flavoring are multicomponent commercial materials with proprietary compositions, their HSP values were estimated using the Hansen parameters of their major constituents, mannitol and maltodextrin, respectively.

Miscibility was investigated through the calculation of two sets of binary combinations: (i) 6-MP with each formulation component and (ii) PVA with each formulation component.

HSP analysis considers the total solubility parameter (δ_t), defined as the vector sum of the dispersive (δ_d), polar (δ_p), and hydrogen-bonding (δ_h) contributions. The parameters were obtained using HSPiP® software (version 5.4.08, Ipswich, United Kingdom). Theoretical miscibility was estimated based on the difference in total solubility parameter ($\Delta\delta_t$), calculated as the absolute difference between the δ_t of 6-MP and that of each excipient. $\Delta\delta_t$ values below 7 MPa^{1/2} were considered indicative of probable miscibility, according to literature [35].

Differential Scanning Calorimetry (DSC)

Drug–excipient interactions were further investigated by DSC. Binary physical mixtures were prepared at a 1:1 (w/w) ratio by homogenizing the drug with each excipient in a mortar and pestle for 5 min. The pure drug and individual excipients were also analyzed separately. Samples were analyzed using a DSC-60 instrument (Shimadzu, Kyoto, Japan) under an inert nitrogen atmosphere (50 mL min⁻¹) at a heating rate of 10°C min⁻¹.

Samples weighing 2–4 mg were placed in aluminum crimp pans (S201-52943, Shimadzu, Kyoto, Japan; Ø5.8 × 1.5 mm; nominal capacity 34 µL) and heated from 25 to 330°C. Comparative analysis of DSC curves allowed identification of shifts, reductions, or disappearance of the characteristic melting peak of the drug [36]. Such modifications are indicative of physicochemical interactions and contribute to the assessment of miscibility and potential amorphization of 6-MP within the system.

Thermogravimetric Analysis (TGA)

The physicochemical compatibility between the drug and excipients was further evaluated by TGA. Thermal degradation profiles of the individual components and their corresponding binary physical mixtures (1:1, w/w) were compared. In addition, to further assess potential processing-induced changes, TGA was performed on the final 3D-printed formulation and its corresponding physical mixture.

The analysis focused on determining the onset degradation temperature (T_{onset}) and identifying any changes in thermal degradation events relative to the isolated materials [35]. Components exhibiting degradation events near the processing temperatures used in hot-melt extrusion and 3D printing were considered unsuitable for formulation and excluded based on this thermal stability criterion.

Samples weighing 2–5 mg were placed in platinum crucibles and analyzed using a DTG-60H instrument (Shimadzu,

Kyoto, Japan). The assays were conducted under a nitrogen atmosphere (50 mL·min⁻¹) at a heating rate of 10°C·min⁻¹ over a temperature range of 25 to 500°C.

Preparation of Filaments

Filaments were produced by HME using a polymeric formulation developed for the incorporation of 6-MP. Initially, a placebo filament was prepared in which 6-MP was replaced with lactose. This placebo formulation served as a pilot filament to optimize processing parameters, particularly extrusion temperature and screw speed, thereby minimizing the risk of drug degradation during thermal processing.

After establishing suitable processing conditions, drug-loaded filaments were produced. The final formulation consisted of 10% (w/w) 6-MP; a blend of PVA and glycerol in a 70:30 (w/w) ratio, respectively, totaling 70% (w/w) of the formulation; Parteck® ODT (5% w/w); flavoring agent (5% w/w); xylitol (10% w/w); and colorant (0.1% w/w).

All components were pre-homogenized in a mortar and pestle for 5 min to ensure adequate dispersion prior to thermal processing [37]. The mixtures were then processed using a co-rotating conical twin-screw extruder (HAAKE MiniCTW, Thermo Scientific, Waltham, MA, USA) equipped with a 1.6 mm diameter die.

The extrusion system was coupled to an air-cooling filament puller and an in-line diameter monitoring device (FTR1, Filmaq3D, Curitiba, Brazil), allowing continuous measurement of filament diameter. Extrusion was performed at 135°C with a screw speed of 50 rpm. These parameters were defined based on preliminary placebo extrusion trials and the previously determined thermal stability of the drug.

Rheological Evaluation of Filaments

The rheological behavior of the filaments was investigated through oscillatory tests to characterize their viscoelastic response under the conditions employed during the 3D printing process [38]. Analyses were performed using a DHR-2 rheometer (TA Instruments, New Castle, DE, USA) equipped with a Peltier plate temperature control system and a parallel-plate geometry (40 mm diameter), with a fixed gap of 1 mm.

Measurements were conducted at 175°C, corresponding to the nozzle temperature employed during FDM printing, to reproduce the rheological behavior of the molten filament under processing conditions. Frequency sweep measurements were performed at 1% strain, previously verified to be within the linear viscoelastic region. Frequency sweep tests were performed over an angular frequency range of 0–650 rad·s⁻¹. The storage modulus (G') and loss modulus (G'') were determined during analysis, representing the elastic and viscous contributions of the molten material, respectively.

Digital Modeling and Printing Parameters

The modeling and printing of the tablets were performed with the aim of developing a dosage form with a playful design to enhance initial acceptance among pediatric patients, while ensuring adequate material deposition uniformity during the printing process [39].

The tablets were designed in a bear-shaped geometry using Tinkercad® (Autodesk® Inc., San Rafael, CA, USA) (Fig. 1). The 3D models were subsequently sliced using Creality Print software (version 4.3.7.6619, Shenzhen, China), where printing parameters were defined. The nozzle temperature was set at 175°C, and the build plate temperature was maintained at 60°C. A layer height of 0.2 mm was employed, and a gyroid infill pattern was selected. Printing speed was set at 60 mm·s⁻¹ for deposition movements and 150 mm·s⁻¹ for travel movements.

To investigate the effect of internal structure on tablet performance, five tablet variations were produced by varying the infill density from 20 to 40% in 5% increments (20, 25, 30, 35, and 40%). Fabrication was carried out using an FDM 3D printer (Creality CR-10 SE, Shenzhen, China) equipped with a 0.4 mm diameter nozzle.

Physical Characterization of Printed Tablets

Determination of Mass and Porosity

Ten tablets from each infill configuration were individually weighed in an analytical balance (AUY 220, Shimadzu, Kyoto, Japan) and used for porosity determination.

Tablet porosity was determined using an integrated methodological approach combining 3D modeling and gas pycnometry techniques. The total apparent volume (V_i) of each tablet was estimated from the .stl file generated during the digital modeling stage using Meshmixer software (Autodesk, version 3.5.474). In this procedure, the software calculates the geometric volume of the object based on its 3D mesh representation.

The effective volume (V_p) was measured by gas pycnometry using an Ultrapyc 5000 Micro instrument (Anton Paar, Ashland, VA, USA), employing high-purity nitrogen as the displacement gas. This technique determines the true volume occupied by the solid material, excluding void spaces accessible to the gas.

Porosity (VP%) was calculated from the difference between the total and effective volumes according to Eq. (1):

$$\text{Porosity (\%)} = \frac{(V_i - V_p) \times 100}{V_i} \quad (1)$$

Texture Analysis

Texture analysis was performed in triplicate to evaluate the force required to deform the 3D-printed tablets, simulating conditions comparable to those encountered during mastication. The test consisted of uniaxial compression of the tablets up to 50% of their original thickness, allowing determination of the mechanical resistance associated with chewability [40].

All tablet formulations produced with different infill densities (20, 25, 30, 35, and 40%) were evaluated. Each tablet

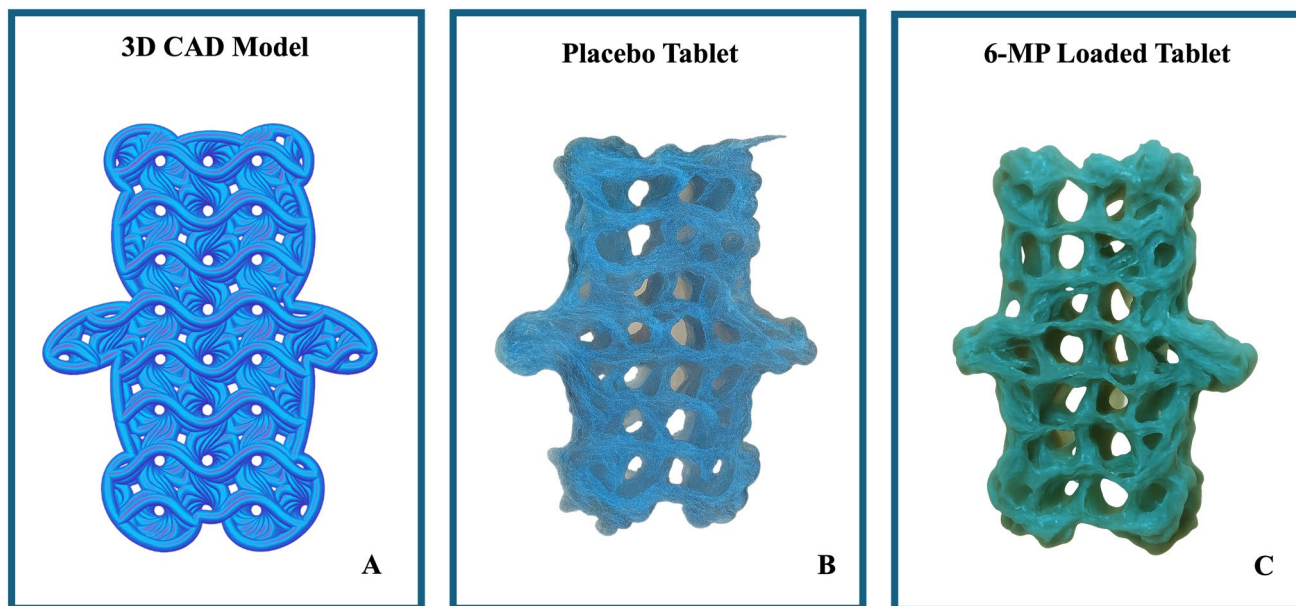


Fig. 1 Digital modeling and fabrication of chewable tablets by FDM 3D printing. **(A)** 3D-CAD model illustrating the predefined porous architecture and geometry. **(B)** Placebo tablet printed using optimized

parameters. **(C)** 6-MP-loaded tablet manufactured under selected printing conditions

was tested in two distinct orientations horizontal and lateral to simulate potential positioning scenarios during real-life mastication. As a reference material, the same test was performed on a commercially available gummy candy (Fini®) intended for children, used as a comparative texture model.

Analyses were conducted using a TAXT Plus texture analyzer (Stable Micro Systems, United Kingdom) equipped with a 35 mm diameter flat aluminum probe. The compression speed was set at 1 mm s^{-1} , with a maximum displacement corresponding to 50% of the tablet thickness. Each test had a total duration of 30 s.

Additionally, experiments were repeated with selected tablets previously moistened with 100 μL of artificial saliva (2.38 g Na_2HPO_4 , 0.19 g KH_2PO_4 , 8 g NaCl per liter) to simulate the oral environment during chewing [41]. The results enabled comparison of the mechanical behavior of dry and moistened tablets.

Morphological Analysis

Optical microscopy was employed to evaluate the structural integrity of the 3D-printed tablets and to identify potential surface imperfections arising from the manufacturing process. The analysis was performed using a stereomicroscope (SZT model, Laborana, São Paulo, Brazil) at $1\times$ magnification.

Disintegration Time

The disintegration test was performed using the apparatus and general procedure described in official pharmacopeial standards [42] as a comparative method to evaluate the effect of infill density. Six tablets were evaluated, with one tablet placed in each of the six tubes of the disintegration apparatus basket (Labor Estabille, São Paulo, Brazil). A disk was added to each tube as specified in the compendial method.

The test was conducted using purified water as the immersion medium, maintained at $(37 \pm 1)^\circ\text{C}$. The apparatus was operated for 10 min. At the end of the specified period, the basket movement was stopped, and the disintegration status of the tablets in each tube was visually assessed. A tablet was considered to have met the acceptance criterion when complete disintegration was observed, with no palpable solid residue remaining in the tube.

Evaluation of Pharmaceutical Performance

Drug Content

To evaluate dose distribution throughout the printed structure, the drug-loaded tablet was manually divided into ten approximately equal fractions. Each fraction was individually dispersed in distilled water and further diluted with methanol to obtain concentrations within the calibration range. The

samples were filtered through hydrophilic polytetrafluoroethylene membrane filters (0.45 μm pore size, 25 mm diameter) and analyzed by reverse-phase high-performance liquid chromatography (RP-HPLC) with UV detection at 325 nm, using an LC-20AT system (Shimadzu, Kyoto, Japan).

Chromatographic conditions included an injection volume of 20 μL and a C18 column (25 cm $\times$ 4.6 mm, 5 μm ; Phenomenex, Torrance, CA, USA) maintained at 25°C . The mobile phase consisted of acetonitrile and water (95:5, v/v), flowing at a rate of 1.0 mL min^{-1} . The analytical method was previously validated according to ICH Q2(R2) guidelines. The method demonstrated adequate selectivity, linearity over the concentration range of 0.5–20 $\mu\text{g mL}^{-1}$ ($r = 0.999$), accuracy and precision, with limits of detection and quantification of 0.13 and 0.39 $\mu\text{g mL}^{-1}$, respectively. Repeatability showed coefficients of variation below 2%, while intermediate precision was evaluated using different analysts and days [23].

Dissolution

The dissolution profiles of the optimized 3D-printed tablets and the commercially available 6-MP tablets (Purinethol®) were determined using a dissolution apparatus (Ethik model 299, Nova Etica, São Paulo, Brazil). The test was performed using 900 mL of 0.1 mol L^{-1} HCl as the dissolution medium. The temperature was maintained at $37 \pm 0.5^\circ\text{C}$, and Apparatus II (paddle method) was employed at a rotation speed of 100 rpm [43]. All experiments were performed in triplicate.

Aliquots of 5.0 mL were withdrawn at 1, 2, 5, 10, 15, 30, 45, and 60 min and immediately replaced with an equal volume of fresh dissolution medium maintained at the same temperature. The samples were filtered through qualitative filter paper. After filtration, the aliquots were appropriately diluted with methanol to enable quantification of total 6-MP by UV–Vis spectrophotometry using a UV-1800 spectrophotometer (Shimadzu, Kyoto, Japan).

All experiments were performed in triplicate for each formulation. Dissolution profiles were plotted using OriginPro 2019 software (OriginLab Corp., Northampton, MA, USA). The profiles were evaluated based on dissolution efficiency at 30 min (DE_{30}), and statistical differences between formulations were assessed using Student's *t*-test. The significance level (*p*) was set at 0.05. Data normality was evaluated using the Shapiro–Wilk test.

In Situ Nanostructure Investigation

The potential formation of nanostructures after tablet hydration was investigated using an adapted dissolution assay performed under more concentrated conditions than those employed in the conventional dissolution test. This approach was designed to increase the concentration of

dissolved polymer and drug in the medium, thereby favoring self-assembly phenomena and enabling subsequent characterization of the generated colloidal structures.

Drug-loaded printed tablets were placed in a beaker containing 20 mL of simulated saliva (pH 6.8) and maintained in a water bath at $37 \pm 3^\circ\text{C}$ under constant magnetic stirring (100 rpm). Aliquots of 3 mL were collected after 10, 20, and 30 min and immediately replaced with an equal volume of fresh medium.

The collected dispersions were characterized using a Zetasizer Nano ZS (Malvern Instruments, Malvern, UK). Hydrodynamic diameter, polydispersity index (PDI), and mean count rate were determined by dynamic light scattering (DLS), while zeta potential was obtained by electrophoretic mobility measurements [43].

The morphology of the structures formed after hydration was further investigated by transmission electron microscopy (TEM; JEM-1011, JEOL, Japan). After 30 min of dispersion, a 4 μL aliquot diluted 1:100 in simulated saliva (pH 6.8) was deposited onto a carbon-coated copper grid and allowed to dry overnight at room temperature. Subsequently, the sample was exposed to osmium tetroxide vapor for 5 min in a dark fume hood and examined by TEM.

The fraction of drug associated with the nanostructures was determined using an adapted centrifugal ultrafiltration method [44]. Briefly, 2 mL of the dispersion were transferred to a Vivaspın® 2 centrifugal filter unit (molecular weight cut-off 10,000 Da; Sartorius Lab Instruments GmbH & Co., Göttingen, Germany) and centrifuged at 4,000 rpm for 15 min using a Z306 centrifuge (Hermle Labortechnik GmbH, Wehingen, Germany). Under these conditions, free 6-MP permeated through the membrane, whereas colloidal structures and their associated drug fraction were retained in the upper compartment. The concentration of free 6-MP in the filtrate was quantified by UV–Vis spectrophotometry and used to calculate the encapsulation efficiency (EE%). Encapsulation efficiency was calculated according to Eq. (2):

$$EE\% = \frac{\text{Total amount 6MP} - \text{free 6MP}}{\text{Total amount 6MP}} \times 100 \quad (2)$$

where Total amount 6-MP represents the total drug concentration in the dispersion and Free 6-MP corresponds to the concentration measured in the ultrafiltrate.

Results and Discussion

Preformulation

HSP analysis was initially performed to estimate the theoretical miscibility between 6-MP and each component of the formulation. All excipients exhibited $\Delta\delta t$ values well below

7 $\text{MPa}^{1/2}$, a threshold commonly adopted in the literature as indicative of probable miscibility, suggesting a high degree of physicochemical affinity with 6-MP (Fig. 2, Table S1) [35, 43]. Notably, glycerol, xylitol, and mannitol (the major component of Parteck® ODT) presented $\Delta\delta t$ values below 1 $\text{MPa}^{1/2}$, suggesting a strong similarity in intermolecular cohesive forces and a pronounced tendency toward the formation of homogeneous molecular-level mixtures.

PVA, maltodextrin, and citric acid exhibited $\Delta\delta t$ values ranging from approximately 2 to 4 $\text{MPa}^{1/2}$, still substantially below the critical threshold, supporting theoretical miscibility despite their structural differences. The short distance in Hansen space suggests a reduction in the Gibbs free energy of mixing, favoring thermodynamic stability and minimizing the likelihood of phase separation or drug recrystallization.

Because PVA constitutes the predominant polymeric matrix of the formulation, the HSP analysis was further expanded to evaluate the theoretical miscibility between PVA and each formulation component (Fig. 2). This complementary analysis also showed $\Delta\delta t$ values below 7 $\text{MPa}^{1/2}$ for all evaluated pairs. Particularly low values were observed for the PVA–maltodextrin (0.6 $\text{MPa}^{1/2}$), PVA–citric acid (1.7 $\text{MPa}^{1/2}$), PVA–glycerol (4.0 $\text{MPa}^{1/2}$), PVA–xylitol (4.1 $\text{MPa}^{1/2}$), and PVA–mannitol (4.6 $\text{MPa}^{1/2}$) pairs, with all values remaining below the adopted miscibility threshold.

From a technological perspective, these findings are particularly relevant for systems intended for HME and FDM 3D printing. Proximity in Hansen space favors intermolecular interactions in the molten state, may contribute to reducing the molecular mobility of 6-MP, which may facilitate homogeneous drug incorporation into the polymeric matrix during thermal processing. Such behavior is critical for ensuring dose uniformity, physicochemical stability, and consistent biopharmaceutical performance in thermally processed systems [45].

However, although the HSP approach predicts thermodynamically favorable miscibility, strong intermolecular interactions may also alter the thermal behavior of the components, affecting events such as glass transition, melting, and degradation onset [46]. Considering that HME and FDM involve exposure to elevated temperatures, experimental evaluation of thermal compatibility represents an important complementary approach. Therefore, drug–excipient physical mixtures were subjected to thermal analysis to investigate potential modifications in characteristic thermal events and to confirm the feasibility of thermal processing for the proposed formulation.

The DSC thermal profile of pure 6-MP exhibited a discrete endothermic event at approximately 160°C (highlighted in Fig. 3), attributed to the loss of adsorbed moisture, followed by an endothermic melting event at approximately 319°C accompanied by decomposition [47, 48]. The high enthalpy associated with this event is consistent with

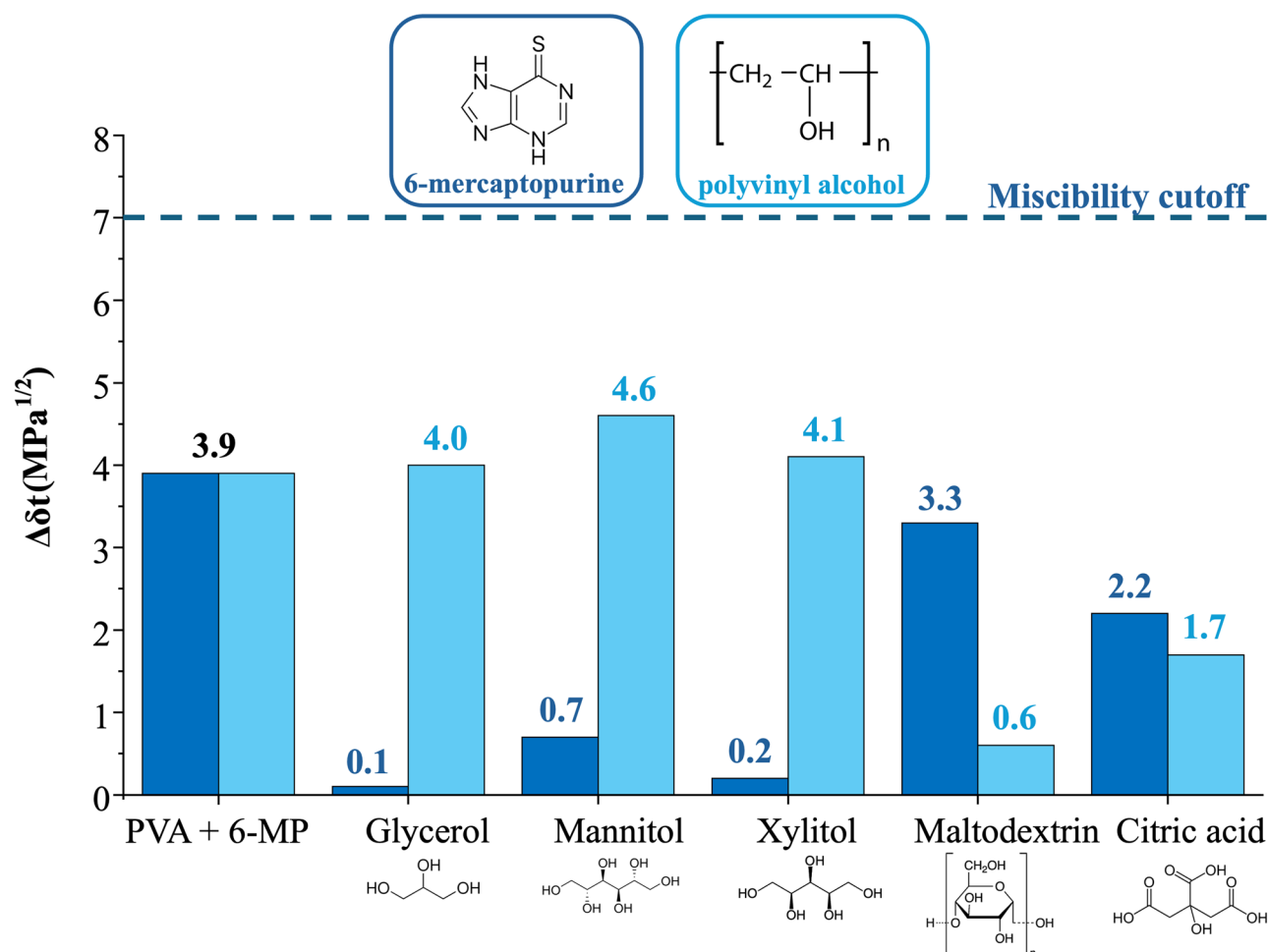


Fig. 2 Difference in Hansen total solubility parameter ($\Delta\delta t$) between 6-mercaptopurine (6-MP) and each formulation component (dark blue bars) and between polyvinyl alcohol (PVA) and each formulation component (light blue bars). The blue dashed line represents

the literature-reported miscibility cutoff (7 MPa^{1/2}), below which a higher probability of miscibility is expected. Calculations involving Parteck® ODT and grape flavoring were based on mannitol and maltodextrin as their major constituents, respectively

the predominantly crystalline nature of the drug prior to processing.

In the binary physical mixtures, the characteristic melting endotherm of 6-MP was markedly attenuated or, in some cases, no longer detectable. The reduction in melting enthalpy may indicate a decrease in the crystalline fraction of 6-MP and is commonly associated with partial dissolution of the drug into the molten excipient during heating. Such behavior suggests a strong thermodynamic affinity between the components and corroborates the theoretical screening results obtained through HSP analysis, which indicated low Hansen space distances ($\Delta\delta t$). Dissolution of the drug within the molten excipient phase is expected to reduce the crystalline fraction detectable by DSC and may promote the formation of a partially molecularly dispersed system under thermal conditions [34].

Specifically for mixtures containing Parteck® ODT (predominantly mannitol) and xylitol, the observed

melting-point depression is characteristic of partially miscible or eutectic systems, in which the presence of a second component disrupts the stability of the original crystalline lattice. Considering the previously determined low $\Delta\delta t$ values, this behavior further supports the hypothesis of favorable interactions between 6-MP and the polyols in the molten state, suggesting partial drug dissolution into the liquid phase prior to thermal degradation. This finding is particularly relevant for HME processing, as it suggests that incorporation of the active compound into the molten matrix may occur before degradative events become predominant.

For the glycerol mixture, a broad and poorly defined endothermic event was observed, consistent with progressive evaporation or partial volatilization, as expected for a low-molecular-weight plasticizer.

In contrast, anhydrous citric acid, when analyzed individually, exhibited an endothermic melting event followed

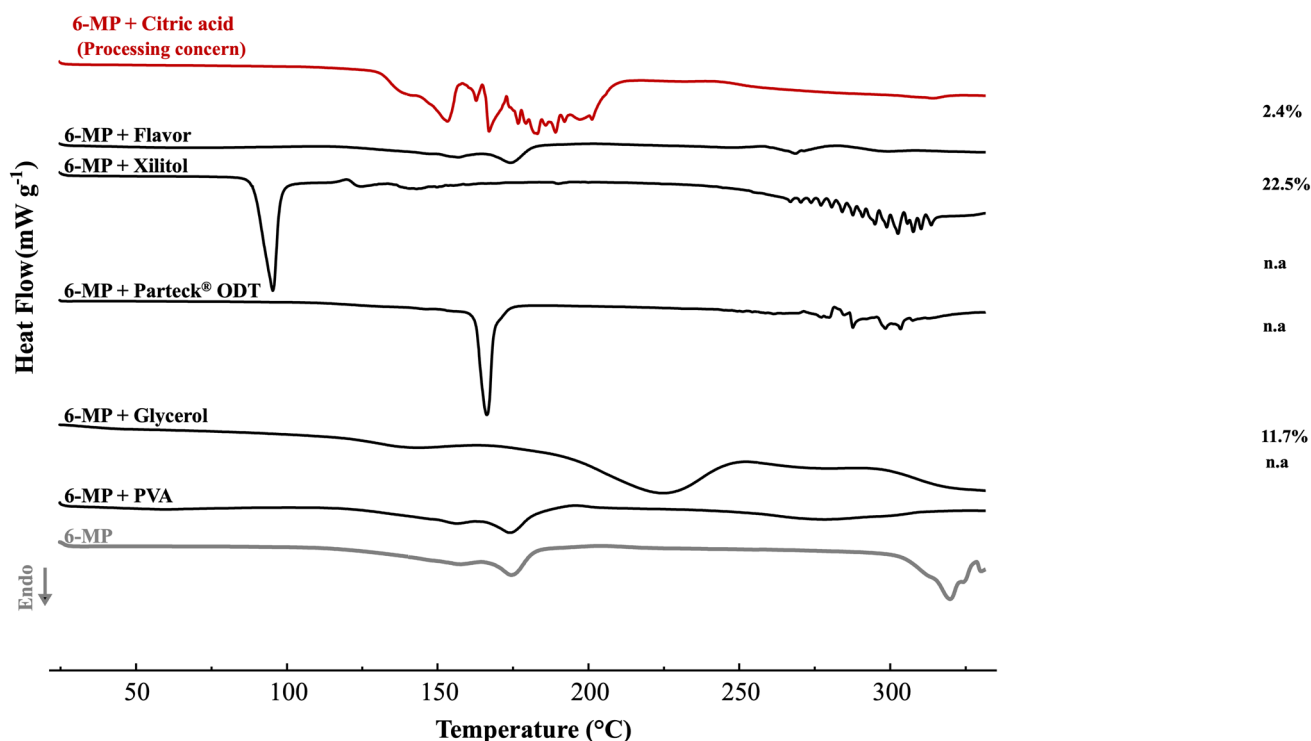


Fig. 3 Differential scanning calorimetry (DSC) curves of pure 6-mercaptopurine (6-MP) and its binary physical mixtures with the selected excipients (1:1, w/w). The inset shows an enlarged view of the 250–

330°C region, highlighting the characteristic melting endotherm of 6-MP ($T_m = 319^\circ\text{C}$) and its behavior in the corresponding physical mixtures

rapidly by thermal degradation, consistent with its known thermal instability upon transition to the molten state (Figure S1) [49]. In the binary mixture with 6-MP, an earlier onset and a greater multiplicity of endothermic events were observed at temperatures lower than those recorded for the pure components. This sequence of events may indicate modifications in the thermal degradation pathway, possibly resulting from acid–base interactions or molecular destabilization induced by the proximity of the components. Such behavior suggests a potential anticipation of degradation processes, a hypothesis further investigated by TGA.

Overall, the DSC results support the miscibility trend predicted by HSP analysis, as evidenced by the attenuation of the characteristic 6-MP melting endotherm, the apparent reduction in relative crystallinity, and the melting-point depression observed for crystalline excipients. However, they also suggest that thermodynamically favorable interactions may influence the thermal behavior of the system, particularly in the presence of citric acid and glycerol. Therefore, thermogravimetric analysis becomes essential to distinguish physical phenomena (melting, dissolution, and evaporation) from chemical events (degradation), enabling a more accurate determination of the safe thermal processing window for HME and FDM 3D printing.

Thermogravimetric analysis was conducted to define the safe thermal processing window for HME and 3D printing, since both techniques involve exposure to elevated temperatures and significant mechanical shear. The dashed lines in the TGA curves represent the operational temperatures employed during processing, allowing assessment of the proximity between the onset of thermal degradation of the materials and the actual processing conditions (Figure 4).

Most evaluated excipients exhibited T_{onset} values substantially higher than the extrusion and printing temperatures, indicating adequate thermal stability and compatibility with the proposed manufacturing process. Likewise, the binary physical mixture maintained degradation profiles comparable to those of the individual components (Figure S2), suggesting the absence of significant degradative interactions under the evaluated conditions.

In contrast, citric acid exhibited a degradation onset relatively close to the processing temperatures, and this behavior was markedly shifted to lower temperatures in the binary mixture with 6-MP. Specifically, the T_{onset} of the main mass-loss event occurred at approximately 170°C for anhydrous citric acid alone (Figure S2), whereas the citric acid/6-MP physical mixture exhibited an earlier onset at approximately 134°C , corresponding to a shift of approximately 36°C toward lower temperature. In addition, the physical

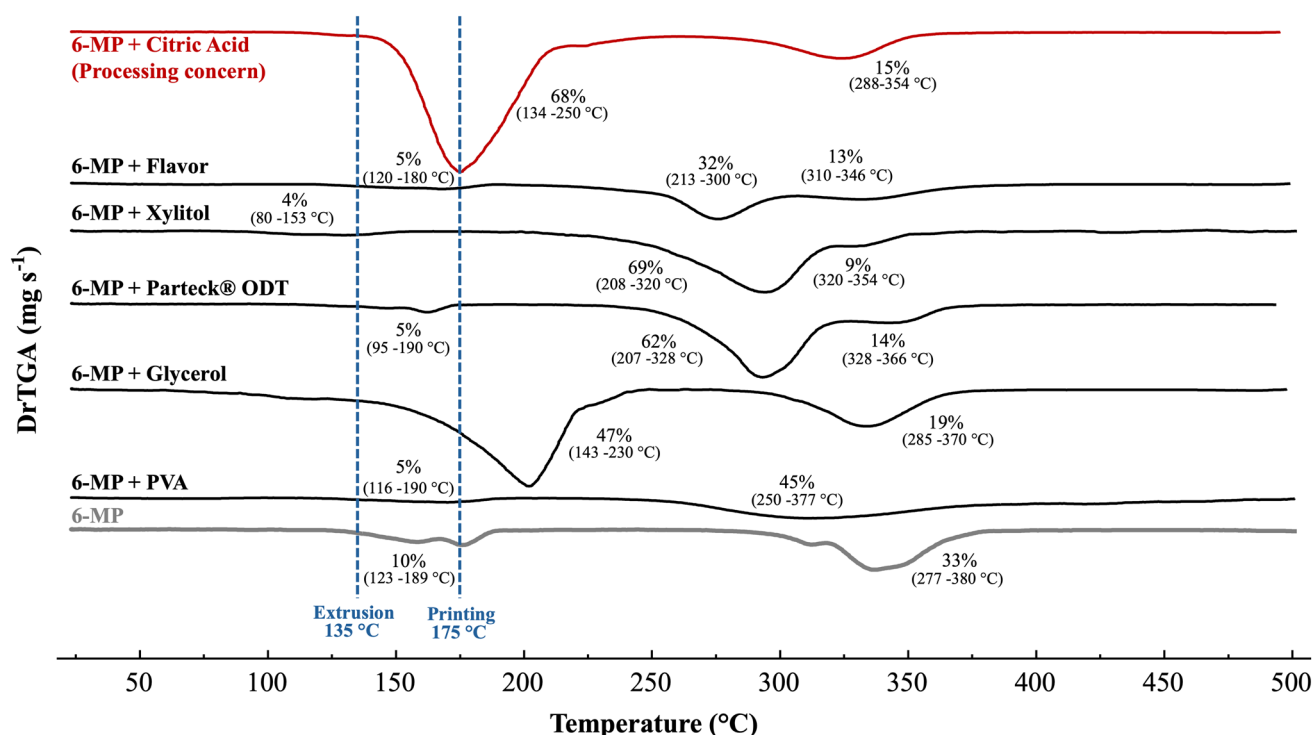


Fig. 4 Derivative thermogravimetric (DTG) curves of pure 6-mercaptopurine (6-MP) and its binary physical mixtures with the selected formulation excipients (1:1, w/w). The blue dashed vertical lines

indicate the processing temperatures used during hot-melt extrusion (135°C) and fused deposition modeling (175°C)

mixture showed approximately 68% mass loss between 130 and 220°C (Figure 4), which was greater than would be expected from the proportional contribution of citric acid alone to the 1:1 mixture of around 50%. These findings demonstrate that the presence of 6-MP altered the thermal degradation behavior of citric acid.

This behavior may be explained by a generalized base-catalyzed mechanism promoted by 6-MP. Basic nitrogen atoms within the purine ring system of 6-MP may interact with the carboxylic groups of citric acid, facilitating proton abstraction and the formation of citrate anions. The generation of carboxylate species increases electron density and reduces molecular stability, promoting decarboxylation reactions accompanied by CO₂ release. Consequently, premature fragmentation of citric acid may occur, leading to the formation of aconitic acid and anhydride derivatives, thereby accelerating thermal degradation [50].

From a technological standpoint, the proximity between T_{onset} and the processing temperature may represent a significant risk of excipient degradation, byproduct formation, and potential compromise of drug stability. For this reason, citric acid was excluded from the final formulation. Importantly, the exclusion of citric acid was not expected to compromise the functional performance of the formulation. Although organic acids are frequently incorporated into chewable dosage forms to enhance flavor perception and provide a

pleasant sour taste, the formulation already contained alternative sensory-modulating excipients, including xylitol and grape flavoring.

Glycerol, in turn, exhibited mass-loss onset at relatively low temperatures, consistent with progressive volatilization of the plasticizer. This behavior had already been suggested by the broad endothermic event observed in DSC and attributed to evaporation. The agreement between DSC and TGA findings confirms that this phenomenon is predominantly physical (volatilization) rather than indicative of initial chemical degradation. Nevertheless, this characteristic requires careful control of processing conditions, as plasticizer loss may alter melt rheology and negatively affect the quality and dimensional stability of the extruded filament.

Taken together, the TGA results underscore that prior assessment of thermal stability is critical for the rational development of formulations intended for HME and FDM 3D printing. The exclusion of citric acid highlights the strategic importance of preformulation studies in identifying potentially degradative interactions before processing, thereby supporting the selection of thermally suitable components for the final formulation. No glass-transition temperature could be reliably identified for the multicomponent formulation under the conventional DSC conditions employed in this study. Hence, the processing window was selected considering the thermal behavior of the formulation together with its experimental

processability during extrusion, while subsequent rheological characterization provided complementary information on the flow behavior relevant to FDM processing.

Filament Rheological Behavior

The loss modulus (G'') remained consistently higher than the storage modulus (G') across the entire angular frequency range evaluated, indicating that the molten filament exhibits predominantly viscous behavior at the printing temperature (175°C). The processing conditions were selected within the thermally acceptable range identified by DSC and TGA and subsequently refined through preliminary extrusion and printing trials to achieve continuous filament production and reproducible material deposition. Under these conditions, the energy dissipated through viscous flow exceeds the energy elastically stored, suggesting that the material can flow readily through the printing nozzle.

Both moduli increased with increasing angular frequency (ω), reflecting the typical frequency-dependent viscoelastic response of thermoplastic polymer melts (Fig. 5). The absence of a plateau region for either G' or G'' suggests that the polymer chains are in a rapid relaxation state. There is no evidence of a crosslinked network or sufficiently strong intermolecular interactions capable of inducing gel-like or solid-elastic behavior at this temperature.

At higher frequencies, which may be associated with the dynamic deformation conditions encountered during extrusion through the printer nozzle, the material maintained its viscous-dominant behavior. This characteristic facilitates continuous polymer extrusion without excessive elastic stress accumulation, which could otherwise lead to die swell phenomena or expansion upon exiting the nozzle.

Notably, no G'/G'' crossover was observed within the evaluated frequency range. Such a crossover would indicate a transition toward more elastic-dominant behavior at high shear rates. The persistent predominance of G'' suggests that the formulation maintains a stable viscous-dominant response in the molten state at the selected temperature, favoring homogeneous material deposition during printing [38].

The observed rheological profile is consistent with previous reports describing molten PVA-based formulations plasticized with glycerol, in which plasticizer incorporation increases chain mobility and promotes viscous-dominant behavior at processing temperatures. From a manufacturing perspective, viscous-dominant behavior is advantageous for FDM because it facilitates filament melting and flow through the nozzle while minimizing extrusion pressure and reducing the risk of nozzle clogging. Overall, the rheological results support the suitability of the selected formulation and processing temperature for FDM manufacturing, providing sufficient melt flowability while preserving controlled material deposition during printing.

Physical Characterization of Printed Tablets

The increase in tablet mass was highly proportional to infill density, with an approximately 74% increase between 20 and 40% infill (204 vs. 355 mg), demonstrating that digital control of internal architecture can be used as an effective strategy for mass and dose modulation without altering external geometry (Table I). The low standard deviations observed indicate high precision and reproducibility of printing, reflecting stable filament flow and consistent layer-by-layer material deposition.

Concomitantly, porosity exhibited an inversely proportional relationship with infill, decreasing from approximately 85% (20% infill) to 63% (40% infill). Porosity values obtained by gas pycnometry indicate that infill density is a critical parameter governing the internal density of the tablet and, consequently, influencing mechanical and performance-related properties. Importantly, even at the highest infill density, tablets exhibited porosity values above 60%, considerably higher than those typically observed in conventionally compressed tablets, which generally range from 5 to 25% porosity [51], highlighting the ability of FDM to generate highly porous architectures.

Optical microscopy revealed preservation of the intended geometric design across all formulations (Table I). A progressive increase in internal mesh density was observed with increasing infill, corroborating the quantitative porosity data. Tablets produced with lower infill densities (20–25%) exhibited greater spacing between deposited filaments and a higher volume of apparent voids, resulting in potentially less resistant structures. In contrast, tablets printed with 35% and 40% infill presented more compact architectures with reduced pore interconnectivity. Importantly, no structural collapse or significant defects were observed in systems with infill $\geq 30\%$, indicating more adequate interlayer cohesion and dimensional stability, an essential requirement for ensuring pharmaceutical uniformity and quality.

Disintegration time increased proportionally with infill density, ranging from 1.5 min (20%) to 5.4 min (40%) (Table I). This behavior is directly associated with the reduction in porosity and consequent decrease in matrix permeability to the aqueous medium. Highly porous structures facilitated rapid liquid penetration and accelerated disintegration, whereas denser systems delayed hydration and fragmentation. All formulations exhibited relatively rapid disintegration, although disintegration time increased progressively with increasing infill density.

The inverse relationship between porosity and disintegration time indicates that structural control through infill density directly translates into modulation of biopharmaceutical performance. In fact, the nearly four-fold increase in disintegration time observed between the 20% and 40% configurations (1.5 vs. 5.4 min) highlights the potential of

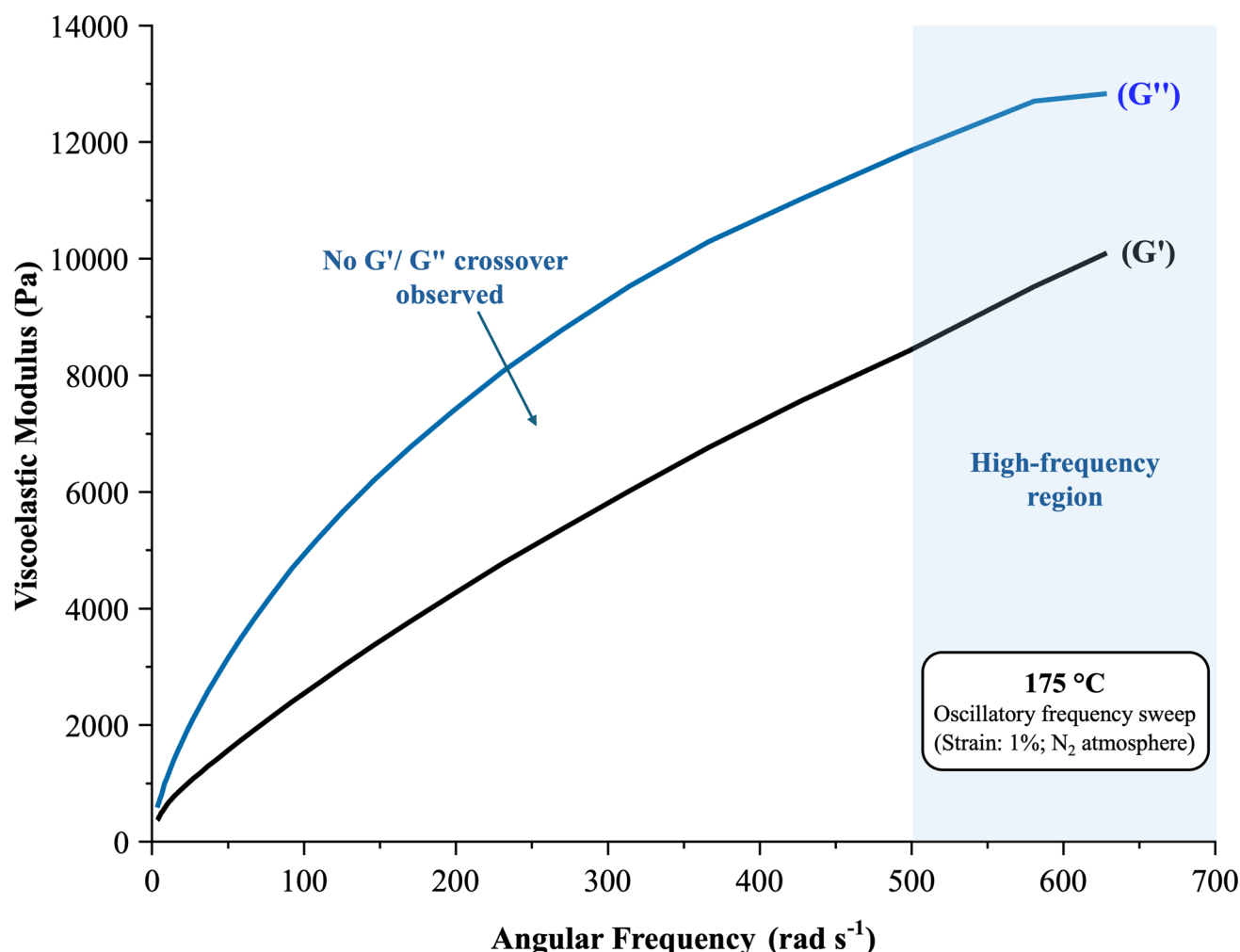


Fig. 5 Oscillatory rheological behavior of the placebo filament at printing temperature. Storage modulus (G') and loss modulus (G'') as a function of angular frequency, measured at the printing temperature

architectural design as a powerful tool to modulate tablet performance independently of formulation composition.

Texture analysis provided a functionally relevant assessment of the mechanical behavior of the chewable tablets, including the influence of printing orientation and hydration-induced softening, which are not captured by conventional breaking-force measurements alone. Under dry conditions, maximum compression force increased progressively with infill density in both horizontal and lateral orientations, confirming that denser architectures exhibit greater mechanical resistance (Fig. 6). In general, printed tablets displayed higher mechanical strength than the commercially available gummy candy used as reference (Fini®), indicating sufficient robustness to withstand storage, transport, and handling without deformation or fracture.

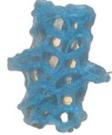
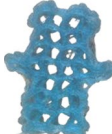
The influence of compression orientation revealed anisotropic mechanical behavior typical of FDM-manufactured structures, highlighting the importance of layer-by-layer

organization in defining mechanical response. In fact, inter-layer bonding is generally weaker than intralayer cohesion, generating direction-dependent mechanical properties [52].

When the 30% infill tablet was evaluated after moistening with artificial saliva, a marked reduction in the force required for deformation was observed, with values lower than those recorded for the Fini® reference (Fig. 6). This finding demonstrates that although structurally robust under dry conditions, the system undergoes rapid plasticization in a moist environment, becoming softer and more easily chewable due to rapid hydration and plasticization of the PVA-based matrix. Such behavior is quite desirable for pediatric application, as it ensures structural integrity until administration while enabling ease of mastication upon contact with saliva.

Overall, the integrated analysis demonstrates that infill density acts as a central design variable in the structural engineering of 3D-printed dosage forms, simultaneously

Table 1 Effect of Infill Density on Physical Properties of 3D-printed Tablets

Infill (%)	Optical microscopy	Mass (mg)	Porosity (%)	Disintegration (min)
20		204 ± 3.6	85.9 ± 1.7	1.5
25		245 ± 3.2	83.6 ± 0.6	2.2
30		280 ± 2.9	73.8 ± 1.1	3.2
35		320 ± 3.0	70.2 ± 4.4	4.6
40		355 ± 2.3	63.5 ± 0.9	5.4

modulating mass, structural density, porosity, mechanical resistance, and disintegration time.

Tablets with 20–25% infill exhibited very rapid disintegration and comparatively lower mechanical resistance, which may increase their susceptibility to mechanical damage during handling and transportation. Conversely, systems with 35–40% infill showed high mechanical strength but reduced porosity, prolonged disintegration time, and increased initial rigidity.

Among the evaluated architectures, the 30% infill configuration provided the most balanced combination of attributes, including controlled porosity (73.8%), rapid disintegration (3.2 min), preserved structural integrity, reproducible mass, mechanical resistance superior to the commercial reference under dry conditions, and a marked reduction in compression force after saliva exposure. Collectively, these findings highlight infill density as a critical quality attribute in FDM-manufactured chewable tablets, enabling simultaneous modulation of mechanical and biopharmaceutical performance without altering formulation composition. More broadly, they demonstrate the potential of architectural engineering as a strategy for the rational development of personalized pediatric dosage forms.

From a dose-personalization perspective, the predefined 6-MP concentration in the filament enables the amount of drug incorporated into each tablet to be controlled through the amount of material deposited during FDM printing.

Therefore, for future individualized manufacturing, maintaining the optimized internal architecture while adjusting tablet dimensions or programmed mass may represent a more appropriate strategy for dose tailoring.

Pharmaceutical Performance

The mean drug content of the 3D-printed tablets was $99.51 \pm 2.21\%$, demonstrating accurate drug incorporation and low variability in the final dosage form. Importantly, the quantitative HPLC assay was performed after completion of both HME and FDM processing. Therefore, the drug content close to the theoretical value indicates that no substantial loss of 6-MP was detected after the sequential thermal processing steps. This observation is consistent with the comparable thermogravimetric behavior observed before and after processing (Figure S3).

Both samples exhibited rapid dissolution profiles characteristic of immediate-release dosage forms, reaching more than 95% drug release within 15 min (Fig. 7). The commercial tablet demonstrated faster initial dissolution, with a greater fraction of drug released during the early sampling time points. Nevertheless, the 3D-printed tablet reached approximately 75% dissolution at 5 min and approached complete release ($\approx 100\%$) within 15 min.

DE_{30} was $83.6 \pm 0.9\%$ for the 3D chewable tablet and $90.3 \pm 0.6\%$ for the commercial tablet, with a statistically significant difference ($p < 0.001$). Despite the statistically

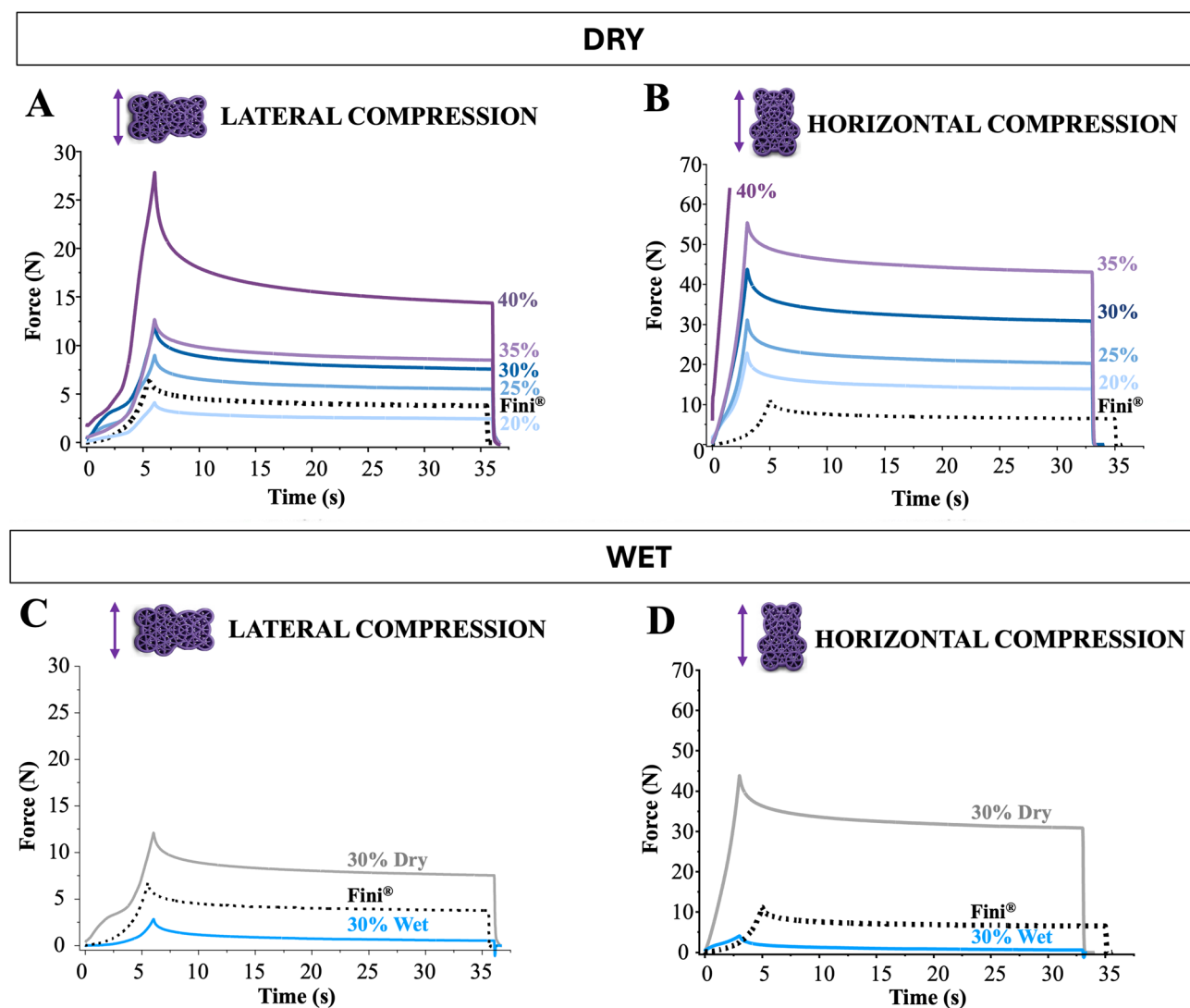


Fig. 6 Texture profile analysis of 3D-printed chewable tablets with different infill densities under lateral (A) and horizontal (B) compression in the dry state. Panels C and D compare the mechanical behavior of the optimized 30% infill tablet before and after exposure to

artificial saliva under lateral and horizontal compression, respectively. The commercial gummy candy (Fini®) was included as a reference material for chewability

significant difference in DE_{30} , both formulations achieved nearly complete drug release within 15 min, suggesting that the observed differences are unlikely to compromise the immediate-release performance of the dosage form. Importantly, the dissolution test was conducted using intact tablets, without simulation of prior mastication.

This consideration is particularly relevant, as chewable tablets are designed to undergo mechanical fragmentation in the oral cavity before swallowing. Mastication is expected to substantially increase the exposed surface area and reduce particle size, thereby further accelerating liquid penetration and drug dissolution. Therefore, the obtained results represent a conservative experimental scenario relative to real clinical use conditions.

The slightly slower release observed for the printed tablet may be associated with structural characteristics inherent to FDM manufacturing, including the layer-by-layer organization and tortuous diffusion pathways generated by the deposited strands. Such features may delay medium penetration and drug diffusion during the initial stages of dissolution despite the high overall porosity of the system.

Furthermore, the near-complete drug release over time confirms that neither the extrusion nor the printing processes compromised drug availability, corroborating the assay findings regarding the stability and integrity of 6-MP after thermal processing.

The rapid and complete dissolution profile is consistent with the high porosity and short disintegration time

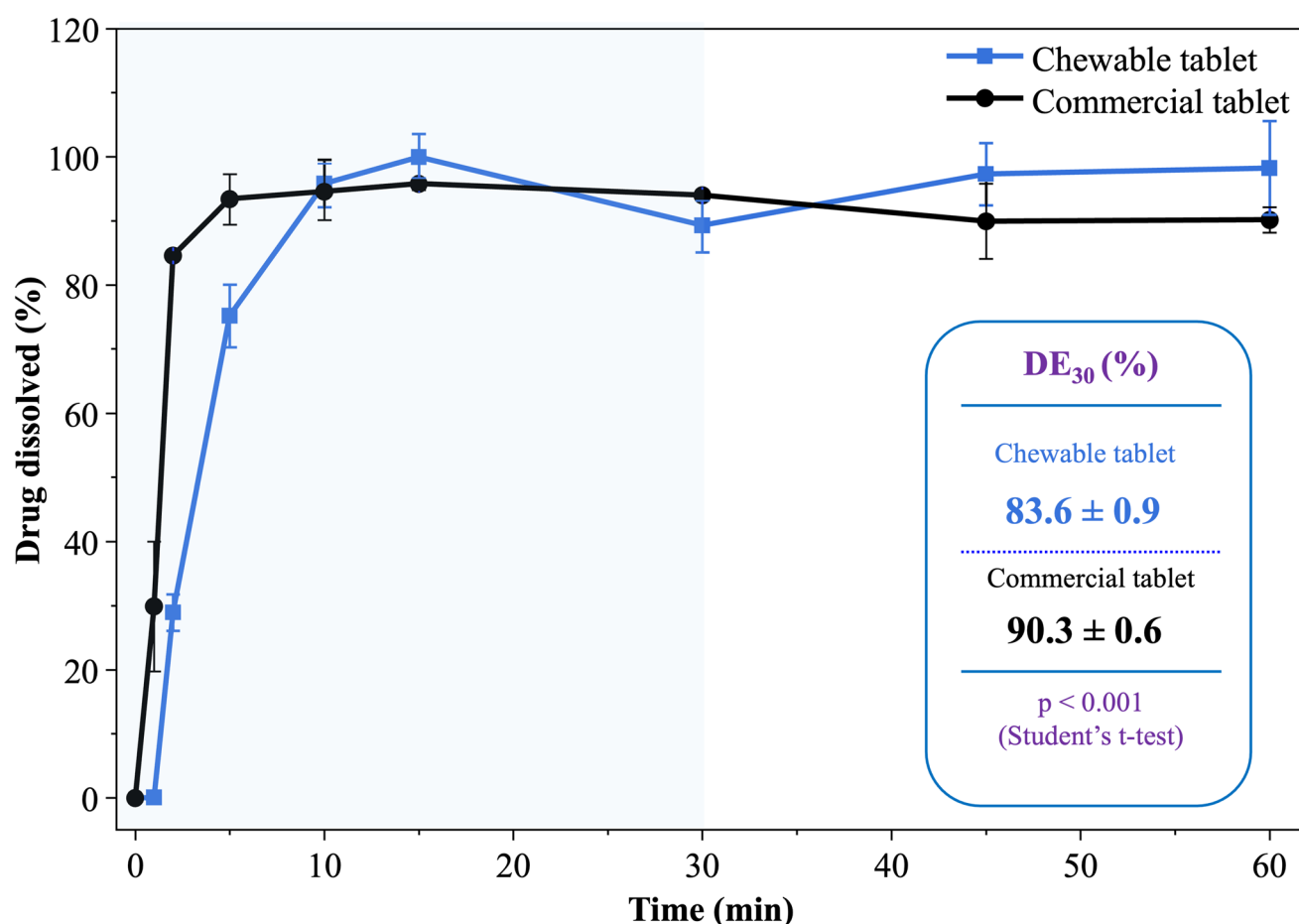


Fig. 7 Dissolution profiles of 6-mercaptopurine (6-MP) from the 3D-printed chewable tablet and the commercial tablet in 0.1 mol L⁻¹ HCl (37 ± 0.5°C, paddle apparatus, 100 rpm). The shaded region

highlights the first 30 min of the dissolution test, corresponding to the interval used for dissolution efficiency (DE₃₀) determination

previously observed for the selected 30% infill architecture, indicating that the structural design adopted was sufficient to ensure prompt medium penetration and efficient drug release.

Overall, the developed 3D-printed chewable tablet exhibited reproducible content uniformity and rapid dissolution behavior compatible with immediate-release dosage forms. Although the commercial product showed slightly faster initial release, the selected 30% infill architecture ensured nearly complete drug dissolution within 15 min, supporting the suitability of the FDM-manufactured system for pediatric oral administration.

In Situ Nanostructure Formation

Beyond controlling dose and mechanical performance, thermally processed polymeric systems may behave as dynamic drug delivery platforms rather than passive dosage forms. Upon hydration, polymer chains can undergo self-assembly phenomena and generate colloidal

nanostructures capable of influencing drug solubilization and release. Considering the high porosity and rapid hydration profile of the selected architecture, together with previous findings from our group using HME-based formulations [43], the hydrated matrix was further investigated to determine whether spontaneous nanoorganization occurred after tablet disintegration. Such an investigation provides additional insight into the mechanisms governing drug release and may reveal functionalities beyond those expected from conventional immediate-release systems.

DLS measurements revealed the presence of colloidal structures in the nanometric range throughout the evaluation period, suggesting spontaneous *in situ* nanoparticle formation after matrix hydration (Table II). Mean hydrodynamic diameters remained relatively constant over time, ranging from 329 ± 35 nm at 10 min to 350 ± 12 nm at 30 min, indicating reproducible generation of nanometric colloidal assemblies. The low coefficients of variation, particularly at 20 and 30 min, further support the temporal stability of the formed dispersions.

Table II Physicochemical Characterization and Encapsulation Efficiency of 6-MP-loaded Nanostructures Formed *in situ*

Time (min)	Count rate (kcps)	PdI	Zeta potential (mV)	Particle size (nm)	CV (%)
10	189.1 ± 2.1	0.76 ± 0.13	−11.8 ± 1.7	329.4 ± 34.6	10.5
20	134.0 ± 8.0	0.56 ± 0.06	−15.0 ± 1.0	370.0 ± 6.9	1.9
30	269.2 ± 5.8	0.44 ± 0.03	−14.3 ± 1.6	349.8 ± 11.8	3.4
Encapsulation parameters					
Total drug (µg/mL)		Free drug (µg/mL)		Encapsulation efficiency (%)	
5.27 ± 0.56		4.68 ± 0.14		11.16 ± 7.32	

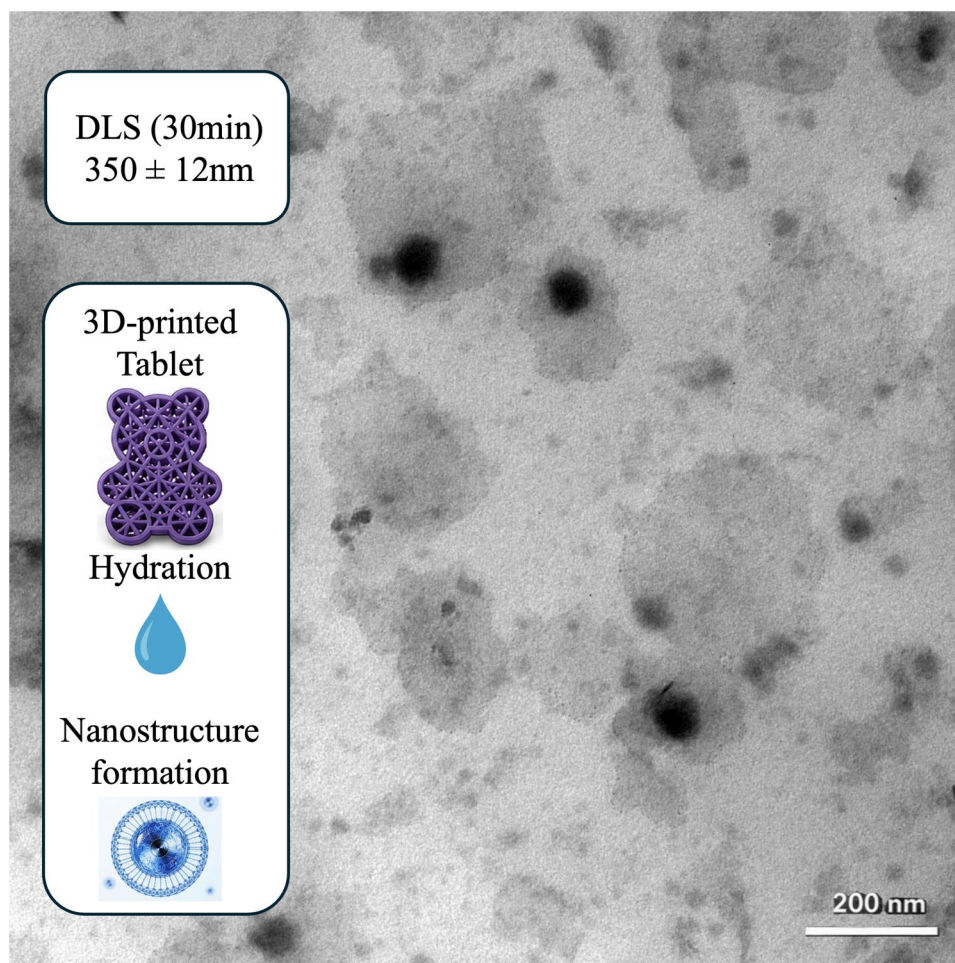
Data are presented as mean ± standard deviation ($n = 3$) coefficients of variation = CV

The progressive reduction in PdI from 0.76 to 0.44 suggests dynamic rearrangement of the colloidal assemblies, leading to a narrower size distribution over time. Zeta potential values remained moderately negative (−11.8 to −15.0 mV) under all evaluated conditions. Although values below ±30 mV are generally associated with limited electrostatic stabilization [53], steric mechanisms may also contribute to colloidal stability. In this regard, hydrated PVA chains adsorbed at the particle interface may provide steric barriers capable of preventing aggregation, even in the absence of strong electrostatic repulsion.

TEM analysis after 30 min of hydration provided morphological support for the presence of the nanoscale structures independently detected by DLS (Fig. 8), which revealed heterogeneous particles with nanometric dimensions.

The combined DLS and TEM results support the formation of nanoscale colloidal structures after hydration. EE% was approximately 11.2%, indicating that a small but measurable fraction of the dissolved drug became associated with the colloidal phase, whereas nearly 89% remained in the free fraction.

Fig. 8 Transmission electron microscopy (TEM) image of the colloidal dispersion obtained after 30 min of hydration of the 3D-printed 6-mercaptopurine (6-MP) chewable tablet in simulated saliva (pH 6.8). The schematic illustrates the proposed *in situ* nanostructure formation following tablet hydration, while the DLS box summarizes the mean particle size measured after 30 min of hydration



Although not predominant, this transient association may contribute to modulation of drug release. The slightly lower DE_{30} observed for the printed tablet relative to the commercial product may, at least partially, be explained by this additional organizational step. Unlike conventional tablets, where release is governed primarily by disintegration and dissolution, the printed system appears to introduce a dynamic colloidal phase in which a fraction of the drug becomes temporarily associated with polymeric assemblies [54]. Nevertheless, the predominance of free drug confirms that the formulation retains the characteristics of an immediate-release dosage form and does not behave as a classical controlled-release system.

From a biopharmaceutical perspective, this phenomenon may be particularly relevant for 6-MP, a drug characterized by low aqueous solubility and variable oral bioavailability. The spontaneous formation of colloidal structures may increase the apparent surface area available for dissolution, help maintain supersaturation, and potentially improve drug solubilization. Therefore, rather than acting as passive carriers, the polymeric components of the matrix appear to behave as dynamic structural elements capable of generating colloidal assemblies after hydration.

Jointly, these findings indicate that the developed dosage form exhibits hybrid behavior, combining the characteristics of an immediate-release chewable tablet with the ability to generate self-assembled nanostructures upon hydration. This phenomenon introduces an additional level of structural complexity to the system and highlights the potential of FDM-manufactured polymeric matrices as dynamic drug delivery platforms rather than passive dosage forms.

Conclusions

This study demonstrates the feasibility of producing pediatric 6-MP chewable tablets by FDM 3D printing with controlled architecture, accurate dosing, and immediate drug-release performance. In addition to conventional immediate-release behavior, hydration of the polymeric matrix promoted the spontaneous formation of colloidal nanostructures with partial drug association (~11%), suggesting a hybrid release mechanism combining rapid drug availability with transient nano-mediated modulation.

Infill density emerged as a critical design parameter, enabling simultaneous modulation of porosity, mechanical properties, disintegration, and chewability, with 30% infill providing the most balanced performance profile. The printed tablets exhibited high content uniformity and preserved drug integrity after thermal processing.

Overall, the developed platform highlights the potential of FDM-based structural engineering for personalized pediatric pharmacotherapy, particularly for drugs requiring individualized and frequently adjusted dosing, such as 6-MP. Because

the drug concentration in the filament is predefined, the dose can potentially be tailored by digitally controlling the amount of material deposited in each dosage unit. Such an approach could reduce tablet splitting and manual manipulation of hazardous antineoplastic medicines while providing an age-appropriate dosage form. However, translation to pharmacy- or clinical-based manufacturing will require validation of the relationship between digital design, tablet mass, and actual drug content. Furthermore, the findings suggest that thermally processed polymeric matrices may function as dynamic drug delivery systems capable of modulating drug release through structural design rather than acting solely as passive dosage forms. Ultimately, this platform provides a promising strategy for combining dose individualization with child-friendly drug administration, supporting the development of safer and more patient-centered pediatric pharmacotherapy.

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Data Availability Data will be made available on request.

Declarations

Declaration of Generative AI and AI-assisted Technologies in the Writing Process During the preparation of this work, the authors used ChatGPT 4 in order to review the English translation. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

Competing interests 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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References

- Golhen K, Buettcher M, Kost J, Huwyler J, Pfister M. Meeting challenges of pediatric drug delivery: the potential of orally fast disintegrating tablets for infants and children. *Pharmaceutics*. 2023. <https://doi.org/10.3390/pharmaceutics15041033>.
- Olayan HAH, Alenazi ASH, Alsalamman MMA, Alharbi MM, Albahri SMD, Alshariah MMS, et al. Pediatric nursing and pharmacology: safe drug administration for children. *Power Syst Technol*. 2024;48. <https://doi.org/10.52783/pst.1503>.
- Domingos JL, Medeiros-Souza P, Nogueira-Silveira CA, Lopes LC. Medicamentos em crianças. In: Brasil. Ministério da Saúde. Formulário Terapêutico Nacional 2010: Renome 2010. Brasília: Ministério da Saúde; 2010.
- Alqahtani MS, Kazi M, Alsenaidy MA, Ahmad MZ. Advances in oral drug delivery. *Front Pharmacol*. 2021;12:618411. <https://doi.org/10.3389/fphar.2021.618411>.
- Dersch-Mills D, Kaplan BJ. Giving oral medicines and supplements to children. *BMJ*. 2020. <https://doi.org/10.1136/bmj.m3550>.
- World Health Organization. Promoting safety of medicines for children. Geneva: World Health Organization; 2007.
- Kapoor DU, Garg R, Gaur M, Patel MB, Minglani VV, Prajapati BG, et al. Pediatric drug delivery challenges: Enhancing compliance through age-appropriate formulations and safety measures. *J Drug Deliv Sci Technol*. 2024;96:105720. <https://doi.org/10.1016/j.jddst.2024.105720>.
- Brown P, Inaba H, Annesley C, Beck J, Colace S, Dallas M, et al. Pediatric acute lymphoblastic leukemia, version 2.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2020;18:81–112. <https://doi.org/10.6004/jnccn.2020.0001>.
- Ding F, Deng L, Xiong J, Cheng Z, Xu J. Analysis of global trends in acute lymphoblastic leukemia in children aged 0–5 years from 1990 to 2021. *Front Pediatr*. 2025;13:1542649. <https://doi.org/10.3389/fped.2025.1542649>.
- Toksvang LN, Lee SHR, Yang JJ, Schmiegelow K. Maintenance therapy for acute lymphoblastic leukemia: basic science and clinical translations. *Leukemia*. 2022;36:1749–58. <https://doi.org/10.1038/s41375-022-01591-4>.
- Abhilasha S, Apoorva B. Effect of smart pill box on improving adherence to 6-mercaptopurine maintenance therapy in pediatric ALL. *Indian J Med Paediatr Oncol*. 2024;46:297–304. <https://doi.org/10.1055/s-0044-1790580>.
- Krishnan S, Mahadevan A, Mungle T, Gogoi MP, Saha V. Maintenance treatment in acute lymphoblastic leukemia: a clinical primer. *Indian J Pediatr*. 2024;91:47–58. <https://doi.org/10.1007/s12098-023-04687-6>.
- Larsen RH, Hjalgrim LL, Grell K, Kristensen K, Pedersen LG, Brünnér ED, et al. Pharmacokinetics of tablet and liquid formulations of oral 6-mercaptopurine in children with acute lymphoblastic leukemia. *Cancer Chemother Pharmacol*. 2020;86:25–32. <https://doi.org/10.1007/s00280-020-04097-x>.
- Bhatia S, Hageman L, Chen Y, Wong FL, McQuaid EL, Duncan C, et al. Effect of a daily text messaging and directly supervised therapy intervention on oral mercaptopurine adherence in children with acute lymphoblastic leukemia: a randomized clinical trial. *JAMA Netw Open*. 2020;3:e2014205. <https://doi.org/10.1001/jamanetworkopen.2020.14205>.
- Du S, Huang X, He X, Mao M, Chen M, Zhang R, et al. Association of NUDT15 gene polymorphism with adverse reaction, treatment efficacy, and dose of 6-mercaptopurine in patients with acute lymphoblastic leukemia: a systematic review and meta-analysis. *Haematologica*. 2024;109:1053–68. <https://doi.org/10.3324/haematol.2023.282761>.
- Schwarz UI, Woldanski-Travaglini M, Swanston V, Mikhail M, Cacciotti C, Cairney E, et al. Thiopurine methyltransferase intermediate metabolizer status and thiopurine-associated toxicity during maintenance therapy in childhood acute lymphoblastic leukemia. *Clin Pharmacol Ther*. 2023;113:1326–36. <https://doi.org/10.1002/cpt.2894>.
- Källström J, Niinimäki R, Fredlund J, Vogt H, Korhonen L, Castor A, et al. Effects of allopurinol on 6-mercaptopurine metabolism in unselected patients with pediatric acute lymphoblastic leukemia: a prospective phase II study. *Haematologica*. 2024;109:2846–53. <https://doi.org/10.3324/haematol.2023.284390>.
- Kemal LK, Abebe RB, Sendekie AK, Zeleke TK, Mehari EA, Mekonnen GA, et al. Rational prescribing and dispensing of oral dosage forms of medicines to children: an observational study. *BMJ Paediatr Open*. 2024;8:e002431. <https://doi.org/10.1136/bmjpo-2023-002431>.
- Bedogni GR, Lima AL, Gross IP, Gratieri T, Gelfuso GM, Lamas MC, et al. 3D printing as a solution for tablet splitting challenges dedicated to the Chagas disease treatment. *J Drug Deliv Sci Technol*. 2025;106:106745. <https://doi.org/10.1016/j.jddst.2025.106745>.
- Ovesen JL, Sammons D, Connor TH, MacKenzie BA, DeBord DG, Trout DB, et al. NIOSH list of hazardous drugs in health-care settings. National Institute for Occupational Safety and Health, DHHS (NIOSH); 2025.
- Silva LT, Modesto ACF, Costa FÂR, Costa JRS, Júnior JBP, Souza PM. Medicação sem danos como superar o Terceiro Desafio Global para a segurança do paciente. Universidade de Brasília; 2023.
- de Souza PM, Córdoba JCM, Magalhães IMQ. Cuidados da oncologia pediátrica. Universidade de Brasília; 2024.
- Oliveira GS, Lima AL, Gross IP, Sa-Barreto L, Medeiros-Souza P, Gratieri T, et al. Chromatographic method for determining 6-mercaptopurine in skin permeation assays for assessing cutaneous exposure risk. *ACS Omega*. 2025;10:32384–90. <https://doi.org/10.1021/acsomega.5c04686>.
- Barnett S, Bhatt A. A chewable pediatric preparation of ibuprofen is palatable and acceptable to children. *Paediatr Neonatal Pain*. 2020;2:2–6. <https://doi.org/10.1002/pne2.12013>.
- Januskaite P, Xu X, Ranmal SR, Gaisford S, Basit AW, Tuleu C, et al. I spy with my little eye: a paediatric visual preferences survey of 3D printed tablets. *Pharmaceutics*. 2020. <https://doi.org/10.3390/pharmaceutics12111100>.
- Michele TM, Knorr B, Vadas EB, Reiss TF. Safety of chewable tablets for children. *J Asthma*. 2002;39:391–403. <https://doi.org/10.1081/JAS-120004032>.
- Orubu S, Okwelogu C, Opanuga O, Tuleu C. A survey of caregivers of Nigerian children less than 6 years of age to determine the experience and perception of acceptability of oral solid dosage forms. *Int J Pharm*. 2018;536:582–9. <https://doi.org/10.1016/j.ijpharm.2017.10.047>.
- Almutairi M, Srinivasan P, Zhang P, Austin F, Butreddy A, Alharbi M, et al. Hot-melt extrusion coupled with pressurized

- carbon dioxide for enhanced processability of pharmaceutical polymers and drug delivery applications – an integrated review. *Int J Pharm.* 2022;629:122291. <https://doi.org/10.1016/j.ijpharm.2022.122291>.
29. Malaquias LFB, Schulte HL, Chaker JA, Karan K, Durig T, Marreto RN, et al. Hot melt extrudates formulated using design space: one simple process for both palatability and dissolution rate improvement. *J Pharm Sci.* 2018;107:286–96. <https://doi.org/10.1016/j.xphs.2017.08.014>.
 30. Marreto RN, Cardoso G, dos Santos Souza B, Martin-Pastor M, Cunha-Filho M, Taveira SF, et al. Hot melt-extrusion improves the properties of cyclodextrin-based poly(pseudo)rotaxanes for transdermal formulation. *Int J Pharm.* 2020;586:119510. <https://doi.org/10.1016/j.ijpharm.2020.119510>.
 31. Cailleaux S, Sanchez-Ballester NM, Gueche YA, Bataille B, Soulaire I. Fused deposition modeling (FDM), the new asset for the production of tailored medicines. *J Control Release.* 2021;330:821–41. <https://doi.org/10.1016/j.jconrel.2020.10.056>.
 32. Iqbal H, Fernandes Q, Idoudi S, Basineni R, Billa N. Status of polymer fused deposition modeling (FDM)-based three-dimensional printing (3DP) in the pharmaceutical industry. *Polymers.* 2024. <https://doi.org/10.3390/polym16030386>.
 33. Thakkar R, Pillai AR, Zhang J, Zhang Y, Kulkarni V, Maniruzzaman M. Novel on-demand 3-dimensional (3-D) printed tablets using fill density as an effective release-controlling tool. *Polymers (Basel).* 2020;12. <https://doi.org/10.3390/polym12091872>.
 34. Hansen CM. Hansen solubility parameters: a user's handbook. 2nd ed. Boca Raton, FL: CRC Press; 2007.
 35. Granados PA, Gross IP, Medeiros-Souza P, Sá-Barreto LL, Gelfuso GM, Gratieri T, et al. Application of theoretical solubility calculations and thermal and spectroscopic measurements to guide the processing of triamcinolone acetonide by hot-melt extrusion. *Pharmaceutics.* 2025;17. <https://doi.org/10.3390/pharmaceutics17050586>.
 36. Alves-Silva I, Sá-Barreto LCL, Lima EM, Cunha-Filho MSS. Pre-formulation studies of itraconazole associated with benzimidazole and pharmaceutical excipients. *Thermochim Acta.* 2014;575:29–33. <https://doi.org/10.1016/j.tca.2013.10.007>.
 37. Granados PA, Pinho LAG, Sa-Barreto LL, Gratieri T, Gelfuso GM, Cunha-Filho M. Application of hot-melt extrusion in the complexation of naringenin with cyclodextrin using hydrophilic polymers. *Adv Powder Technol.* 2022;33:103380. <https://doi.org/10.1016/j.apt.2021.11.032>.
 38. Lima AL, Pires FQ, Hilgert LA, Sa-Barreto LL, Gratieri T, Gelfuso GM, et al. Oscillatory shear rheology as an in-process control tool for 3D printing medicines production by fused deposition modeling. *J Manuf Process.* 2022;76:850–62. <https://doi.org/10.1016/j.jmapro.2022.03.001>.
 39. Scoutaris N, Ross SA, Douroumis D. 3D printed “Starmix” drug loaded dosage forms for paediatric applications. *Pharm Res.* 2018;35:34. <https://doi.org/10.1007/s11095-017-2284-2>.
 40. Zhang Y, Liu H, Wang J, Zhao F, Hu J, Liu Z, et al. A novel data-driven approach to assess the chewability and grittiness of the chewable tablets using a texture analysis. *Drug Dev Ind Pharm.* 2025;51:1203–17. <https://doi.org/10.1080/03639045.2025.2523547>.
 41. Kim Y, Oh IK, Kim H, Lee S. Artificial saliva-induced structural breakdown of rice flour gels under simulated chewing conditions. *Food Sci Biotechnol.* 2019;28:387–93. <https://doi.org/10.1007/s10068-018-0468-0>.
 42. USP. Disintegration <701>. In: USP–NF online. Rockville (MD): United States Pharmacopeial Convention; 2024. https://doi.org/10.31003/USPNF_M99460_04_01.
 43. Pires FQ, Gross IP, Sa-Barreto LL, Gratieri T, Gelfuso GM, Bao SN, et al. In-situ formation of nanoparticles from drug-loaded 3D polymeric matrices. *Eur J Pharm Sci.* 2023;188:106517. <https://doi.org/10.1016/j.ejps.2023.106517>.
 44. Holzem FL, Schaffland JP, Brandl M, Bauer-Brandl A, Stillhart C. Microdialysis and nanofiltration allow to distinguish molecularly dissolved from colloid-associated drug concentrations during biomimetic dissolution testing of supersaturating formulations. *Eur J Pharm Sci.* 2022;174:106166. <https://doi.org/10.1016/j.ejps.2022.106166>.
 45. Lima AL, Gross IP, de Sá-Barreto LL, Gratieri T, Gelfuso GM, Cunha-Filho M. Extrusion-based systems for topical and transdermal drug delivery. *Expert Opin Drug Deliv.* 2023;20:979–92. <https://doi.org/10.1080/17425247.2023.2241362>.
 46. Medarević D, Djuriš J, Barmapalexis P, Kachrimanis K, Ibrić S. Analytical and computational methods for the estimation of drug-polymer solubility and miscibility in solid dispersions development. *Pharmaceutics.* 2019. <https://doi.org/10.3390/pharmaceutics11080372>.
 47. Kersten KM, Matzger AJ. Improved pharmacokinetics of mercaptopurine afforded by a thermally robust hemihydrate. *Chem Commun (Camb).* 2016;52:5281–4. <https://doi.org/10.1039/c6cc00424e>.
 48. Niazi S. Thermodynamics of mercaptopurine dehydration. *J Pharm Sci.* 1978;67:488–91. <https://doi.org/10.1002/jps.2600670413>.
 49. Barbooti MM, Al-Sammerrai DA. Thermal decomposition of citric acid. *Thermochim Acta.* 1986;98:119–26. [https://doi.org/10.1016/0040-6031\(86\)87081-2](https://doi.org/10.1016/0040-6031(86)87081-2).
 50. Wyrzykowski D, Hebanowska E, Nowak-Wicz G, Makowski M, Chmurzyński L. Thermal behaviour of citric acid and isomeric aconitic acids. *J Therm Anal Calorim.* 2011;104:731–5. <https://doi.org/10.1007/s10973-010-1015-2>.
 51. Cunha-Filho M, Teixeira MT, Santos-Rosales V, Sa-Barreto LL, Marreto RN, Martin-Pastor M, et al. The subdivision behavior of polymeric tablets. *Int J Pharm.* 2019;568:118554. <https://doi.org/10.1016/j.ijpharm.2019.118554>.
 52. Sood AK, Ohdar RK, Mahapatra SS. Parametric appraisal of mechanical property of fused deposition modelling processed parts. *Mater Des.* 2010;31:287–95. <https://doi.org/10.1016/j.matdes.2009.06.016>.
 53. Rodriguez-Loya J, Lerma M, Gardea-Torresdey JL. Dynamic light scattering and its application to control nanoparticle aggregation in colloidal systems: a review. *Micromachines.* 2024. <https://doi.org/10.3390/mi15010024>.
 54. Beach MA, Nayanathara U, Gao Y, Zhang C, Xiong Y, Wang Y, et al. Polymeric nanoparticles for drug delivery. *Chem Rev.* 2024;124:5505–616. <https://doi.org/10.1021/acs.chemrev.3c00705>.

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