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Preparation of Orodispersible Films Using Semisolid Extrusion 3D Printing: A Versatile Manufacturing Approach

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Abstract

Orodispersible films (ODFs) emerged as a patient-friendly dosage form that is particularly suitable for pediatric therapy, where swallowing difficulties often interfere with adherence to therapy. In this study, the preparation of ODFs using semi-solid extrusion (SSE) 3D printing was investigated as an alternative to the conventional solvent casting method. Four hydrophilic polymers – hydroxypropyl cellulose (HPC), polyethylene glycol-polyvinyl alcohol graft copolymer (PVA-PEG), maltodextrin (MDX) and sodium alginate (SA) – were used either individually or in binary blends, with caffeine selected as the model active ingredient. Films were printed on an Ultimaker 2+ system and evaluated for uniformity, thickness, porosity, moisture content, mechanical strength, disintegration and drug release. Formulations containing only MDX or PVA-PEG exhibited poor printability due to leakage and spreading, while other systems showed reproducible film deposition and satisfactory dimensional stability. Binary blends generally resulted in increased film thickness. SA-based films showed the lowest porosity and moisture absorption, while HPC films exhibited favorable mechanical properties. The investigated samples achieved rapid disintegration and complete release of the caffeine. These results confirm the potential of SSE 3D printing as a versatile manufacturing platform for customizable ODFs that enable precise dosing and patient-centric design for pediatric drugs.

Key words: orodispersible films, semi-solid extrusion, 3D printing, pediatric dosage forms, personalized medicine

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Introduction

Orodispersible films (ODFs) are innovative dosage forms that rapidly disintegrate in the oral cavity, enabling easy swallowing of the resulting film fragments without the need for water, and thus offering an alternative approach to administration of solid oral dosage forms. The European Pharmacopoeia defines ODFs as “single- or multi-layered films of suitable materials, to be placed in the mouth where they disperse rapidly”, which points to their potential as patient-centric dosage forms (1, 2). ODFs are particularly valuable dosage forms in pediatric population, where swallowing difficulties and an aversion to conventional solid oral dosage forms often compromise adherence (3, 4). Given these specific needs, ensuring consistent quality, safety and performance of ODFs is crucial for their successful use in children. Despite these advantages, there is still a lack of standardized characterization methods and agreed ranges for critical quality attributes (CQAs) in this area, highlighting the need for more research into this field (4, 5).

Conventional manufacturing methods, such as solvent casting, are widely researched but can lead to problems such as solvent residue, bubble formation, non-uniformity, and they also require cutting large sheets into single films. These limitations can be especially problematic when developing low-dose, age-appropriate formulations (6). In contrast to traditional methods, 3D printing provides precise control over film design, enabling the preparation of customizable, multilayer, or individually dosed dosage forms. This adaptability facilitates the development of on-demand, patient-specific medicines, which is an especially valuable advancement for pediatric patients (4, 6). In this context, extrusion-based 3D printing is particularly promising as it allows fine control of size, shape, specific drug loading and flavor masking (3, 7).

Among extrusion technologies, semi-solid extrusion (SSE) 3D printing has emerged as particularly advantageous for ODF manufacturing. In SSE, drug-loaded gels or pastes are printed at or near ambient temperature, avoiding the thermal stress associated with filament-based methods and preserving the stability of thermosensitive active ingredients (8).

Recent studies have demonstrated the potential of SSE 3D printing as a versatile platform for the development of pediatric orodispersible films. As SSE allows flexible design of films, their size, thickness and drug content can be adapted to the variable dosing requirements of children at different ages (2, 6, 8). Personalization through 3D printing further supports the development towards child-centric therapy. Rather than relying on the limited available doses of conventional dosage forms, SSE can be used to prepare ODFs on demand, using safe excipients and adapting formulations to dietary restrictions or swallowing abilities (3, 7). This level of flexibility is particularly valuable in pediatrics, where patient needs are heterogeneous and adherence is often compromised by the lack of age-appropriate options (4). Beyond dose flexibility, this approach allows not only taste masking but also customization in shape, color and visual design, improving acceptability in the pediatric population (2, 7).

At the same time, important challenges remain. For pediatric medicines manufactured by SSE, clear identification of critical quality attributes and robust manufacturing parameters is essential to ensure consistency, safety and regulatory acceptance (4, 5). Addressing these aspects, together with the continued refinement of polymer combinations and the use of excipients, will be crucial to transitioning SSE-printed ODFs into clinical practice and establishing them as a reliable alternative to conventional pediatric formulations (8).

This study investigates the preparation of orodispersible films using 3D semi-solid extrusion as a versatile and pediatric-friendly manufacturing approach, focusing on the interplay of formulation factors to achieve rapid disintegration, reliable mechanical properties and precise dosing.

Materials and methods

Materials

Four different hydrophilic polymers were selected either as single film-forming agents or in binary blends to prepare 3D printed films: (i) hydroxypropyl cellulose (HPC, Klucel® GF, Ashland™, USA), (ii) polyethylene glycol–polyvinyl alcohol graft copolymer (PVA-PEG, Kollicoat® IR, BASF, Germany), (iii) maltodextrin (MDX, Glucidex IT6, Roquette, France), and (iv) sodium alginate (SA, Fisher Scientific, USA). Printing dispersions were prepared using anhydrous caffeine (CAF, Sigma-Aldrich Chemie GmbH, Germany) as a model drug. Simulated salivary fluid (SSF, pH 6.75) was prepared according to (9) and consisted of sodium chloride, potassium phosphate monobasic, disodium hydrogen phosphate, hydrochloric acid (all Sigma-Aldrich Chemie GmbH, Germany) and purified water (Ph. Eur.).

Methods

Preparation of orodispersible films by 3D Printing

Orodispersible films were prepared using a semi-solid extrusion technique with the Ultimaker 2+ 3D printer (Ultimaker, Netherlands). The 3D models were designed in the Tinkercad software (Autodesk, USA), saved in the .stl format and then processed in the Ultimaker Cura (Ultimaker, Netherlands). Two geometries were created: a cube-shaped and a bone-shaped model, the dimensions of which complied with the ISO 507-3 standard. Printing was carried out with a layer height of 0.5 mm and a total of six layers. The print head was programmed to follow a line-based infill pattern with an infill density of 100. The printer was set to deposit the first layer for all samples before continuing with subsequent layers. To ensure good adhesion to the print bed, the speed for the first layer was reduced to 5 mm/min, while the remaining layers were printed at 10 mm/s. The temperature of the printing plate was kept at 40 °C.

Both single polymer and binary polymer dispersions were prepared and their compositions are summarized in Table I (numerical values in the formulation compositions represent percentage concentrations). The selection and combination of

polymers were based on our previous studies and additional experimental data (data not shown), which demonstrated their suitability for semisolid extrusion 3D printing and the formation of mechanically stable, rapidly disintegrating films. The mixtures were formulated either as placebo films or as drug-loaded systems with caffeine as the model drug. Prior to use, the dispersions were allowed to settle for 24 hours to remove trapped air bubbles, and they were then transferred to syringes. Each syringe was then placed on the printer, connected to the appropriate nozzle, and the paste was extruded to print the films.

Table I Composition of prepared samples

Tabela I Sastav pripremljenih uzoraka

Sample	HPC	PVA-PEG	SA	MDX	CAF	Purified water (up to)	Absolute ethanol (up to)
S1	7.0	–	–	–	0/1	100.0	–
S2	–	7.0	–	–	0/1	100.0	–
S3	–	–	7.0	–	0/1	100.0	–
S5	7.0	5.0	–	–	0/1	–	100.0
S6	7.0	–	5.0	–	0/1	100.0	–
S7	7.0	–	–	5.0	0/1	100.0	–

Glycerol was added to the samples at a concentration of 1%

Uniformity testing

The uniformity of the films was evaluated based on their mass and thickness. Film thickness was measured at five positions (four corners and the center) using a micrometer (Insize 3203-25 A, Insize, China) with an accuracy of 10 μm. The mass of the films was determined by weighing each selected sample on an analytical balance. The results for film thickness and mass are reported as mean values (± SD) from ten replicate measurements.

Porosity testing

Film porosity was assessed by gravimetric analysis, based on the difference in film mass before and after 24 h immersion in liquid paraffin. The results are reported as mean values (± SD) from three replicate measurements.

Determination of moisture content

Moisture content of the samples was determined gravimetrically using a Mettler Toledo LJ 16 instrument (Mettler Toledo, Switzerland). Three samples were analyzed for each formulation and the results are expressed as mean values (± SD).

Mechanical characterization

Mechanical properties of the films were evaluated using a texture analyzer (EZ-X, Shimadzu Corporation, Japan). The test procedure followed the ISO 527-3 guidelines. Samples were printed into bone-shaped specimens and mounted in film holders – clamps. The clamps moved at a speed of 5 mm/min until the films ruptured, which was taken as the endpoint of the test. From the obtained stress–strain curves, tensile strength (TS), elongation at break (EB) and Young's modulus (YM) were calculated using equations (1–3). Each experiment was carried out on three specimens and the results are presented as mean values (± SD).

The mechanical parameters were calculated using the following equations:

$$TS\ (MPa) = F/A \qquad (1)$$

where F is the maximum force applied until rupture and A is the cross-sectional area of the specimen at the breaking point.

$$EB\ (\%) = 100 \times (\Delta L0)/L_0 \qquad (2)$$

where ΔL_0 represents the change in specimen length at break and L_0 is the original length of the sample.

$$YM = (\sigma 2 - \sigma 1)/(\varepsilon 2 - \varepsilon 1) \qquad (3)$$

where ($\sigma_2 - \sigma_1$) is the difference in applied stress corresponding to the strain values (ε_2 and ε_1) within the linear region of the stress–strain curve.

The viscoelastic properties of the investigated samples were evaluated based on complex modulus values determined using an oscillatory rheometer (Rheometer Rheolab MC 120, Paar Physica, Germany) equipped with a parallel plate system (MP50; plate diameter 12.5 mm; gap 50 μm). Samples were placed in special holders designed to prevent displacement during measurement.

Oscillatory tests were first conducted to identify the linear viscoelastic region (amplitude sweep). Once this region was established, all measurements were performed at a constant strain of 1% over a frequency range of 0.1–10.0 Hz in order to monitor changes in the storage and loss modulus.

The complex modulus (G*) was calculated according to the following equation:

$$|G*| = \sqrt{((G')\ 2 + (G'')\ 2)}$$

where G' is the storage (elastic) modulus and G'' is the loss (viscous) modulus.

Disintegration testing

The disintegration behavior of the films was evaluated using a conventional disintegration tester (Erweka ZT52, Erweka, Germany) with 500 mL of medium. Following the method described by Preis et al. (10), a film holder was employed, allowing one half of the film to be immersed in the medium while the other half remained dry. The immersed portion of the film was loaded with a 3 g weight to simulate the pressure applied

by the tongue during *in vivo* administration. The endpoint of the test was defined as the moment when the film ruptured and the magnet fell onto the device's wire mesh. Six films from each sample were tested and the results are reported as mean values (± SD).

Determination of incorporated drug content

The amount of incorporated caffeine, used as the model drug, was determined after six-layer deposition by the 3D printer. Films were dispersed in 10 mL of purified water and shaken on a laboratory shaker (KS 260 basic, IKA VR-Werke GmbH, Germany) at 250 rpm. The resulting dispersions were filtered through a 0.45 µm membrane filter (Millipore, UK), diluted appropriately and analyzed at 273 nm using a UV spectrophotometer (EvolutionTM 300, Thermo Scientific, USA). Determination of incorporated drug content was performed in triplicate and the results are expressed as mean values (± SD).

Drug release testing

The release rate of the caffeine from 3D-printed films was evaluated using a non-compendial method. Films were placed in wire holders and submerged in 50 mL of simulated salivary fluid (pH 6.75) maintained at 37 ± 0.5 °C in a thermostatically controlled shaking water bath (LSB Aqua Pro18, Grant, UK) agitated at 100 rpm. The samples were withdrawn at predetermined time intervals (1, 3, 5, 10, 15, 30, 45 and 60 min) and drug concentration was quantified spectrophotometrically at 273 nm using a UV/VIS spectrophotometer (EvolutionTM 300, Thermo Scientific, USA). For each formulation, the test was performed in triplicate and the results are expressed as mean values (± SD).

Results

Preparation of orodispersible films by 3D Printing

Formulations containing MDX as the film-forming polymer could not be used for 3D printing, as the prepared dispersion leaked from the 3D printer. Similarly, dispersions of PVA–PEG, with or without caffeine, were unsuitable for 3D printing due to nozzle leakage.

In contrast, all other formulations were uniformly and easily printed without any processing difficulties.

Uniformity

The film mass values ranged from 20.4 mg/cm² for HPC to 36.5 mg/cm² for HPC/SA films, while thickness values spanned from 137 µm for SA to 541 µm for HPC/MDX films. The greater thickness observed in films prepared from binary blends was likely due to higher polymer viscosity during extrusion, resulting in higher material deposition per layer. Importantly, the measured uniformity values confirmed that SSE printing produced reproducible films across all samples, a critical factor for dose precision in pediatric applications.

The scatter plot (Figure 1) illustrates the relationship between film thickness and mass. In general, thicker films tended to have a higher mass, but variations were observed depending on the polymer composition. For instance, HPC/MDX films achieved the highest thickness (> 500 μm) but did not correspond to the highest mass, which can be attributed to their higher porosity, as confirmed by the results presented in the following section. On the contrary, HPC/SA films exhibited the highest mass (36.5 mg/cm²) at intermediate thickness, suggesting denser packing and lower porosity. SA-based films were both the thinnest and densest, reflecting their non-porous nature. These differences emphasized how formulation composition can have an impact on the material deposition during SSE printing.

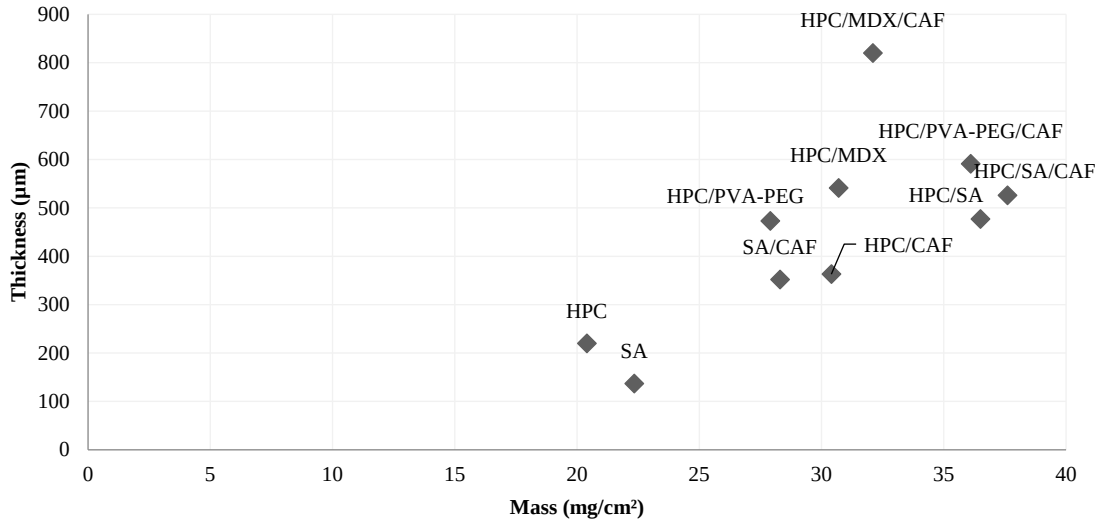

Figure 1. Correlation between 3D film thickness and mass
Slika 1. Prikaz korelacije između debljine i mase 3D filmova

Porosity

The porosity of the investigated 3D-printed ODFs (Figure 2) varied notably depending on the polymer composition. SA films exhibited the lowest porosity (≈ 0.5%), indicating a compact structure consistent with their rigid mechanical properties. On the contrary, films prepared with HPC/PVA-PEG blends exhibited the highest porosity (≈ 6.8%), while HPC/MDX films also showed increased values compared to single polymer films. These results suggest that blends containing cellulose derivatives and sugar-based excipients promote the formation of a more open microstructure (11).

Porosity is directly related to the ability of films to interact with the surrounding medium. Higher porosity facilitates fluid absorption and penetration into the matrix, which can possibly support rapid disintegration and faster drug release, important properties for pediatric administration. Conversely, very low porosity, as observed in

SA films, limits water access and results in slower dispersion, making them less suitable for fast-dispersing dosage forms (12).

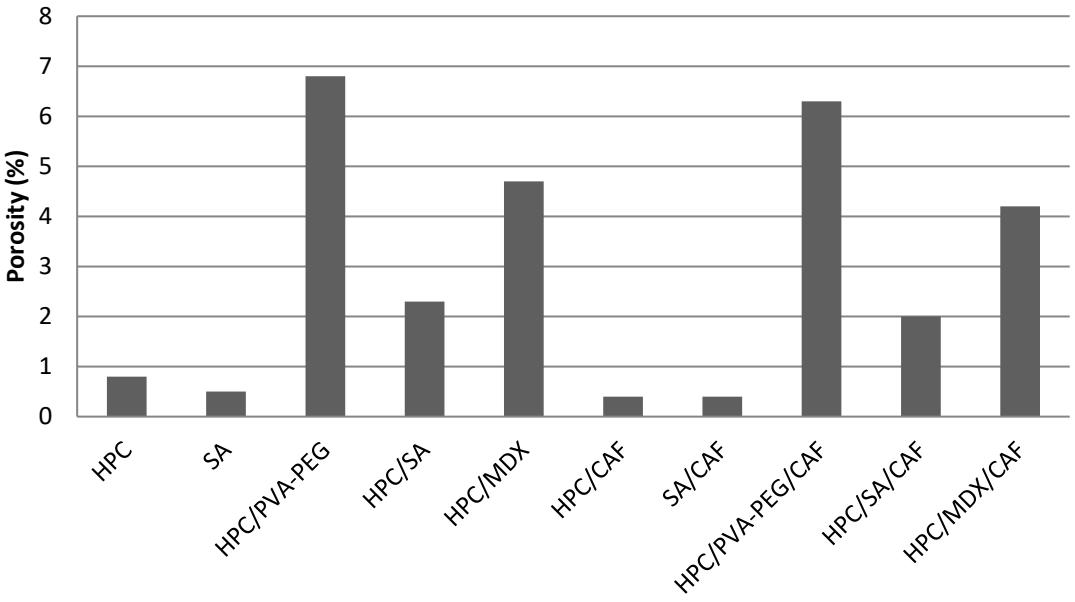

Figure 2. Porosity of the 3D printed films
Slika 2. Porozitet 3D štampanih filmova

Moisture Content

The moisture content of the 3D-printed ODFs (Figure 3) ranged from 2.2% to 6.2%, depending on the formulation. SA-based films contained the lowest amount of residual moisture (≈2.2%), which is consistent with their compact and rigid nature which restricts water retention. In contrast, films composed of HPC/PVA-PEG and HPC/MDX blends exhibited the highest values, reaching up to ≈ 6.2%. These elevated levels can be attributed to the strong hydrophilic character of cellulose derivatives and sugar-based excipients, which easily absorb and retain water (13).

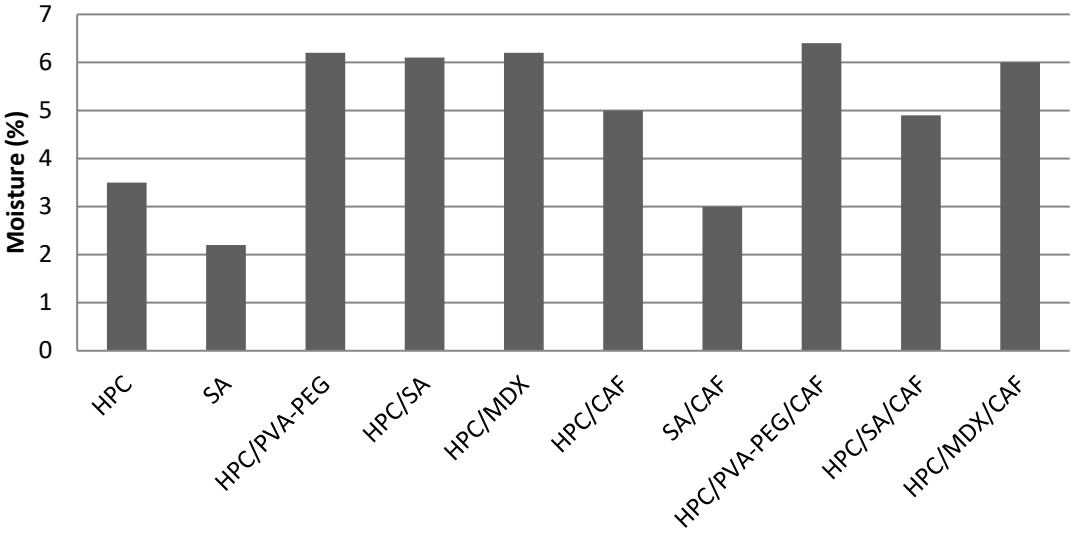

Figure 3. Moisture content of 3D printed films

Slika 3. Sadržaj vlage u 3D štampanim filmovima

Moisture content plays a crucial role in both the handling and performance of ODFs. On the one hand, sufficient moisture content can improve film flexibility, preventing brittleness and cracking during handling. On the other hand, excessive water retention can affect physical stability over time and potentially lead to microbial growth, tackiness or changes in mechanical properties. For pediatric formulations, maintaining a controlled but appropriate moisture content is particularly important to ensure that films remain flexible and acceptable to patients while maintaining their structural integrity throughout the shelf life. Overall, the results confirm that the choice of polymer and excipient composition strongly influences moisture content. Cellulose-based blends are more prone to moisture retention, while SA-based films remain comparatively dry and rigid. These differences provide opportunities to fine-tune ODF formulations depending on whether flexibility, rapid disintegration, or long-term stability is the primary concern.

Mechanical properties

Table II Mechanical characteristics of 3D printed films

Tabela II Mehaničke karakteristike 3D štampanih filmova

Sample	Tensile strength (MPa)	Elongation at break (%)	Young`s modulus (MPa)	Complex modulus (MPa)
HPC	3.46 ± 0.11	137.18 ± 3.27	18.5 ± 5.94	131.18 ± 10.17
SA	118.67 ± 11.12	2.61 ± 0.17	4722.47 ± 41.12	97.13 ± 6.15
HPC/PVA-PEG	2.75 ± 0.13	11.17 ± 1.23	116.23 ± 10.18	146.18 ± 12.71
HPC/SA	2.16 ± 0.57	58.11 ± 4.98	93.15 ± 7.85	219.24 ± 5.14
HPC/MDX	1.44 ± 0.03	4.62 ± 1.21	300.01 ± 20.14	298.15 ± 12.54
HPC/CAF	1.73 ± 0.15	108.47 ± 6.18	38.65 ± 2.15	136.59 ± 2.18
SA/CAF	24.82 ± 0.66	0.84 ± 0.01	2710.67 ± 35.17	278.16 ± 4.13
HPC/PVA-PEG/CAF	2.07 ± 0.53	3.85 ± 0.04	115.8 ± 5.84	290.15 ± 7.18
HPC/SA/CAF	1.73 ± 0.08	46.88 ± 1.45	95.83 ± 3.38	268.18 ± 2.17

The mechanical properties of the 3D-printed ODFs were notably affected by polymer composition (Table II). SA films exhibited remarkably high tensile strength (118.67 MPa) and stiffness (Young's modulus (≈ 4722 MPa), but these properties were accompanied by minimal flexibility, with elongation at break of only 2.61%. This inherent brittleness can be attributed to the formation of dense, rigid networks during the drying process, a phenomenon previously observed in SA-based film systems (15). In contrast, HPC films exhibited remarkable flexibility, with elongation values exceeding 130%, although with a reduced tensile strength of 3.46 MPa. Such flexibility is typical of cellulose ether-based films, which are known to absorb moisture and maintain flexibility even under mechanical stress (16).

Films prepared with HPC and PVA-PEG had moderate strength (2.75 MPa) with improved flexibility (11%), whereas films prepared with HPC/SA blends had more flexibility, with EB above 58%, while still maintaining higher strength than single blend HPC-based films. HPC/MDX films were characterized by higher stiffness, indicated by a YM of 300 MPa, and exhibited poor flexibility (< 5%), suggesting that sugar-based excipients promote a compact and fracture-prone microstructure. These findings highlight the relationship between polymer selection and mechanical properties. Films prepared from polymers that yield higher tensile strength often exhibit decreased flexibility and increased susceptibility to cracking, while more flexible samples generally demonstrate lower stiffness and reduced tensile resistance. Consequently, blending different polymers may offer advantages in achieving desired mechanical properties.

Moisture and porosity appeared to play key roles in affecting these mechanical properties. SA films, which retained the least moisture (≈ 2.2%) and had the lowest porosity (0.5%), were the strongest but also the most brittle. By contrast, HPC/PVA-PEG

and HPC/MDX films contained the highest moisture (≈ 6.2%) and exhibited porosities up to 6.8%, which corresponded with reduced tensile strength and lower stiffness. This is consistent with the plasticizing effect of water and the weakening influence of highly porous structures, which create stress concentrators and facilitate fracture under load (13). Notably, elongation at break did not follow the same trend and remained predominantly dictated by polymer selection: even at low moisture, HPC-based films had superior flexibility, while SA-based films remained brittle regardless of water content.

These findings underscore that, while the choice of polymer is the main factor influencing mechanical properties, both moisture content and porosity serve as modulators, adjusting the overall strength and stiffness of the films. By combining different polymers, desired properties can be achieved, with porosity and moisture content further tuning the properties. Such relationships are highly relevant in pediatric applications, where films must be mechanically stable for handling but also soft and comfortable in the oral cavity (14). Similar findings have been reported in recent studies of extrusion-printed ODFs, where mechanical robustness and flexibility were shown to be interdependent and strongly influenced by formulation design (13, 17).

The complex modulus (G*), obtained from oscillatory rheological testing, provides valuable information about the viscoelastic nature of the printed ODFs. Unlike tensile testing, which applies a continuous uniaxial load until fracture, G* measures the resistance of the material to small oscillatory deformations, capturing both elastic (storage modulus) and viscous (loss modulus) contributions. It therefore reflects the intrinsic rigidity of the polymeric network under dynamic conditions closer to those encountered during handling or oral administration (18).

In this study, the G* values varied considerably across formulations, with SA-based films showing the highest rigidity, while HPC-based and blended systems generally exhibited lower values. When analyzed against classical mechanical parameters, G* displayed moderate negative correlations with TS ($r = –0.42$) and EB ($r = –0.37$), as well as a weaker negative correlation with YM ($r = –0.24$). This finding indicates that G* describes different aspects of the film structure from uniaxial mechanical testing, pointing to a potential difference between small-strain viscoelastic behavior and large-strain tensile properties.

Such differences have been noted in recent studies. Elbl et al. (17) demonstrated that oscillatory rheological properties of ODFs often fail to predict tensile performance, as porosity, water content and microstructural inhomogeneity can disproportionately affect oscillatory response compared to tensile stress–strain testing. From a formulation perspective, G* remains an important complementary metric. High G* values, such as those observed for SA films, indicate rigid matrices that resist deformation under small stresses, correlating with their brittle character during tensile testing. Lower G* values, as seen in HPC-based systems, correspond to more flexible and viscoelastic films that are easier to handle and better tolerated in the oral cavity. Accordingly, integrating G* measurements with tensile strength and elongation data enables a more comprehensive characterization of film properties: tensile strength quantifies mechanical robustness,

elongation at break assesses flexibility and G* captures the microstructural viscoelasticity that may affect patient perception and mouthfeel.

Overall, while direct statistical correlations between G* and tensile parameters were weak in this dataset, the combined analysis highlights that oscillatory rheology offers insights beyond conventional mechanical testing. Incorporating such complementary methods will be critical for the rational design of ODFs tailored to pediatric needs, ensuring both mechanical robustness and a potentially favorable sensory performance.

Disintegration time

The disintegration times of the investigated 3D printed ODFs varied depending on the polymer composition and the presence of caffeine (Table III). The fastest disintegration was observed for the HPC/CAF films (20 s), where the incorporation of caffeine notably shortened disintegration time compared to HPC films (50 s). A similar trend was seen with SA/CAF films (53.7 s), although the effect was less pronounced. Films prepared solely with HPC exhibited moderate disintegration (50 s), while SA-based films disintegrated much more slowly (180 s), which is consistent with the dense and rigid network formed by SA.

Table III Disintegration time of 3D printed films

Tabela III Raspadljivost 3D štampanih filmova

Sample	Disintegration time (s)
HPC	50.0 ± 0.9
SA	180.0 ± 10.0
HPC/PVA-PEG	87.7 ± 4.0
HPC/SA	145.7 ± 2.1
HPC/MDX	137.7 ± 9.3
HPC/CAF	20.0 ± 0.4
SA/CAF	53.7 ± 5.5
HPC/PVA-PEG/CAF	141.0 ± 3.5
HPC/SA/CAF	212.7 ± 1.2

Binary polymer mixtures further affected disintegration behavior. HPC/PVA-PEG (87.7 s), HPC/SA (145.7 s) and HPC/MDX (137.7 s) films showed prolonged disintegration compared to HPC alone. This can be attributed to the increased film thickness and formation of tighter polymeric networks introduced by the additional components (19).

The films prepared from polymer blends containing caffeine, specifically HPC/MDX/CAF (299.7 s) and HPC/SA/CAF (212.7 s), exhibited the slowest disintegration. These formulations resulted in thick films with high mechanical strength and reduced porosity, which limited water penetration and led to prolonged disintegration.

Overall, the results demonstrate that, while HPC films have rapid disintegration, the addition of other polymers (SA, MDX, PVA-PEG) tends to prolong disintegration due to structural changes and increased thickness. The incorporation of caffeine into the polymer matrix modulates disintegration depending on the formulation. Caffeine accelerated disintegration in the single-polymer HPC matrix, likely by increasing hydrophilicity and creating microchannels; however, in blended matrices (e.g., HPC/SA, HPC/MDX, HPC/PVA-PEG) caffeine coincided with higher solids deposition (thicker films) and tighter networks, which prolonged disintegration. These observations are highly relevant for tailoring ODF formulations to pediatric applications, where films must be mechanically stable for handling but also suitably fast-dissolving to ensure patient compliance.

Drug release

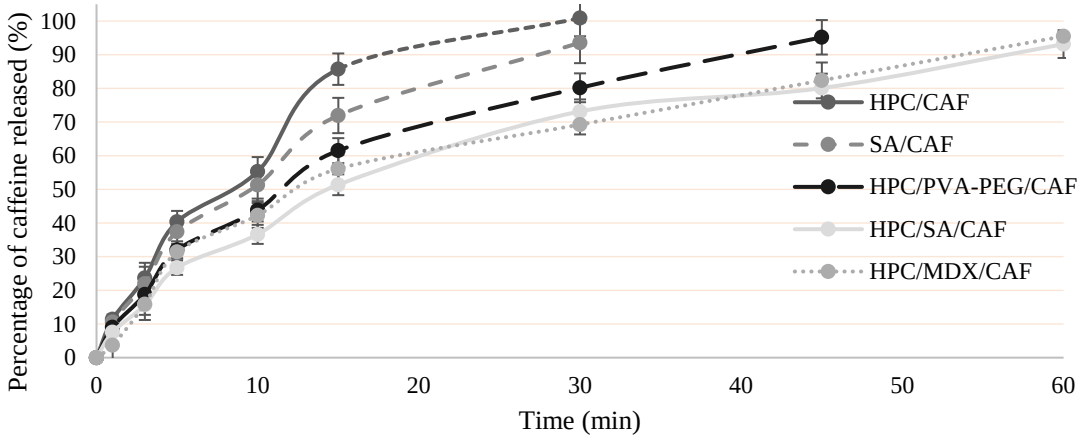

Figure 4. Drug release profiles from 3D printed films
Slika 4. Brzina oslobađanja kofeina iz 3D štampanih filmova

In the examined films, active substance release was primarily driven by rapid hydration and erosion of the film surface, enabling swift penetration of the dissolution medium and diffusion of caffeine (Figure 4). The fastest release was observed for HPC/CAF films (15 min), confirming that HPC-based films, due to their hydrophilic and flexible nature, allow rapid water uptake, matrix softening and swift diffusion of the incorporated drug. This makes HPC-based films particularly suitable for applications requiring quick drug availability. In contrast, SA/CAF films required 30 min to release 80% caffeine, indicating a slower dissolution profile. SA forms denser, more rigid films that resist rapid water penetration, thereby delaying disintegration and diffusion.

Formulations containing polymer blends showed slower release kinetics. The HPC/PVA-PEG/CAF films released 80% caffeine in 45 min, suggesting that the addition

of PVA-PEG increased structural interconnection and reduced the rate of hydration and erosion. Similarly, HPC/SA/CAF and HPC/MDX/CAF films reached 80% release only after 60 min, the longest time observed. These results demonstrate that the inclusion of SA or MDX creates tighter polymeric networks and thicker matrices, which limit water diffusion and prolong drug release. The results confirmed that formulation design is a key modulator of drug release performance, with the potential to fine-tune ODFs for either fast-release pediatric applications or for more controlled release scenarios where prolonged dissolution may be advantageous (20).

Conclusion

This study demonstrated the feasibility of preparing orodispersible films (ODFs) using semi-solid extrusion (SSE) 3D printing as a versatile and patient-centric manufacturing method. The approach enabled the fabrication of films with uniform mass and thickness, while formulation choices strongly influenced porosity, moisture content, mechanical performance, disintegration and drug release. Hydroxypropyl cellulose (HPC) led to flexible films with rapid disintegration and release, whereas sodium alginate (SA) resulted in dense and brittle matrices with delayed dissolution. Binary blends such as HPC/PVA-PEG, HPC/SA and HPC/MDX further modulated performance by increasing film thickness and altering porosity, thereby prolonging disintegration and drug release. The incorporation of caffeine showed dual effects, in some cases accelerating film breakup and in others reinforcing rigidity, depending on the polymer matrix.

Taken together, the findings highlight that SSE printing enables fine control over ODF properties through polymer and excipient selection. By balancing mechanical properties with rapid disintegration and tailored release profiles, this technology has a strong potential for developing age-appropriate pediatric medicines. Future work should focus on scaling up the process, standardizing characterization methods and evaluating *in vivo* performance to facilitate translation into clinical practice.

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Declaration of competing 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.

Author contributions

E.T., J.P.: Conceptualization, Methodology, Investigation, Formal analysis, Data interpretation, Data curation, Writing – original draft preparation, Visualization; I.P.: Methodology, Formal analysis, Investigation, Data Interpretation, Writing – original draft preparation; J.P.: Writing – review and editing, Supervision, Data Interpretation. All authors have read and agreed to the published version of the manuscript.

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Izrada oralno-disperzibilnih filmova metodom 3D štampanja ekstruzijom polučvrstog materijala: fleksibilan pristup izradi farmaceutskih oblika

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Kratak sadržaj

Oralno-disperzibilni filmovi (ODF) predstavljaju farmaceutski oblik posebno pogodan za primenu kod pedijatrijskih pacijenata gde poteškoće pri gutanju često utiču na adherencu. U ovom radu je ispitana mogućnost izrade ODF korišćenjem 3D štampanja metodom ekstruzije polučvrstog materijala (SSE) kao alternativne metode konvencionalnom izlivanja disperzija. Korišćena su četiri hidrofilna polimera – hidroksipropilceluloza (HPC), polietilenglikol-polivinil alkohol graft kopolimer (PVA-PEG), maltodekstrin (MDX) i natrijum-alginat (SA) – pojedinačno ili u binarnim mešavinama, a kofein je izabran kao model aktivna supstanca. Filmovi su štampani korišćenjem 3D štampača Ultimaker 2+ i procenjivana je njihova uniformnost, debljina, porozitet, sadržaj vlage, mehaničke karakteritistike, raspadljivost i brzina oslobađanja kofeina iz filmova. Formulacije koje sadrže samo MDX ili PVA-PEG nisu bile pogodne za štampanje usled curenja disperzije iz mlaznica, dok su druge formulacije štampane nanošenjenjem uniformnih slojeva i imale su zadovoljavajuću strukturnu stabilnost. Binarne mešavine su generalno dovele do povećanja debljine filma. Filmovi izrađani sa SA imali su niske vrednosti poroziteta i sadržaja vlage, dok su HPC filmovi pokazali povoljne mehaničke karakteristike. Ispitani uzorci su se brzo raspadali i imali potpuno oslobađanje kofeina. Dobijeni rezultati potvrđuju potencijal SSE 3D štampe kao fleksibilne metode za izradu ODF koji omogućavaju precizno doziranje i dizajn usmeren na pojedinačnog pacijenta, posebno za pedijatrijske lekove.

Ključne reči: oralno-disperzibilni filmovi, ekstruzija polučvrstog materijala, 3D štampanje, pedijatrijski farmaceutski oblici, personalizovana terapija