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Innovations in pediatric dosage forms via 3D printing: Chewing lozenges as an example

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Abstract

Three-dimensional (3D) printing offers a versatile platform for producing personalized, age-appropriate dosage forms that address the specific therapeutic and administration needs of the pediatric population. Among several oral dosage forms that can be prepared by 3D printing, chewing lozenges offer numerous advantages, especially for the pediatric population. This study illustrates a formulation development and selection of process parameters for 3D-printed chewing lozenges containing propranolol hydrochloride as a model drug, with potential application in the pediatric population. It also highlights the advantages of 3D printing using the semi-solid material extrusion method.

Gelatin and sodium alginate were used as carriers for 3D printing. Immersion time in the calcium chloride solution (t_{im}) and lozenges shape were varied, while the following tests were performed: the assessment of organoleptic properties, mass and thickness variations, melting and disintegration time, drug content and dissolution rate.

Initially, the key 3D printing parameters for lozenge production were identified, and then the appropriate formulation was selected. Subsequent testing demonstrated that the shape of lozenges, along with variations in t_{im}, influenced the pharmaceutical-technological characteristics. A formulation based on the combination of gelatin and sodium alginate in 1:3 ratio, immersed for 60 seconds in a calcium chloride solution, was found to be suitable for 3D printing of chewable lozenges.

Key words: 3D printing, chewing lozenges, propranolol hydrochloride, sodium alginate, gelatin

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Introduction

The pediatric population carries numerous specificities, starting from the frequent difficulty in swallowing medicines, allergic reactions, as well as certain psychological aspects of treatment. For all these reasons, the formulation of medicines for pediatric use requires a flexible dosing strategy, pharmaceutical dosage forms adapted to children, and excipients suitable for pediatric patients (1, 2). Taking these aspects into consideration, it can be concluded that the development of pediatric drug formulations is a challenging and complex process.

Prescribing medicines approved for adults to children is commonplace, although they have neither been tested nor adapted for the pediatric population. Such medicines are therefore used off-label and are potentially inappropriate for children in terms of dose, dosage form, and the excipients used (3, 4). Although the number of newly approved drugs and indications for pediatric use has increased, it is still insufficient for the needs. In practice, it is often necessary either to adapt an existing medicine before giving it to a child or for the pharmacist to prepare an extemporaneous formulation (e.g., a liquid dosage form). This approach, in addition to making accurate dosing more difficult, can lead to reduced efficacy, increased adverse reactions, and drug wastage (1, 5). Furthermore, the taste of a medicine must be considered, since an unpleasant taste can cause fear and refusal to take the medicine, which in turn leads to reduced compliance (6).

Issues related to pediatric drug dosing and pediatric dosage forms have been recognized by leading regulatory authorities, and addressed in specific guidelines. In particular, Guideline on pharmaceutical development of medicines for paediatric use (7) and Reflection paper: formulations of choice for the paediatric population (8) provide recommendations on the selection of formulations intended for pediatric populations. These guidelines provide general suggestions regarding the choice of dosage forms, based on the acceptability scoring system in children. However, it should be noted that these recommendations are based on data obtained from relatively small pediatric sample sizes, implying the necessity for additional studies.

Given the above, there is a clear need in the pediatric population for appropriate doses, dosage forms, and formulations. Due to their flexibility, 3D-printed medicines are a promising solution in pediatric patient treatment (9, 10). 3D-printed medicines are revolutionizing the pharmaceutical market as a potential tool for achieving personalized treatments tailored to the specific needs of each patient, taking into account their age, weight, comorbidities, and pharmacokinetic characteristics (10).

Among various 3D printing techniques, semi-solid extrusion (SSE) was selected in this study to prepare chewable lozenges with propranolol hydrochloride, as a novel pediatric-friendly medicine.

Opportunities for 3D printing of pediatric medicines

The advantages of 3D printing as a manufacturing method for medicines lie in its flexibility regarding dose adjustment and increased individualization of therapy. When it

comes to children, the need for flexibility is particularly significant, making 3D printing of medicines a potential manufacturing pathway of choice for patient-centric treatments. For some children, preferences in taste, color, or shape can significantly influence treatment success (9). With conventional drug manufacturing procedures, it is impossible to meet individual preferences of all patients, but nowadays, 3D printing offers versatile solutions to address this challenge. Furthermore, a medical doctor or pharmacist, in collaboration with the patient's parents or the patients themselves, could obtain information about preferred colors or shapes of the medicine, which could then be used to prepare an appropriate pharmaceutical product. Another advantage of 3D printing is the possibility of combining two or more active substances in the same pharmaceutical product, thereby facilitating pharmacotherapy, as the child needs to take only one 3D-printed medicine instead of several conventional drug products (9). Moreover, the possibility of combining immediate and modified release of the active substance(s) in the same dosage form or pharmaceutical product enables less frequent administration (11). This is particularly important from a psychological perspective, as some children feel discriminated against by their surroundings when they have to take medicine in the presence of peers. Another potential problem is that responsibility for taking the medicine may be transferred to the child without parental supervision, depriving parents of control and insight into whether and when the necessary treatment has been administered. This could be prevented by less frequent dosing, in the morning and evening when parents can supervise medicine intake.

For the production of flexible dosage forms in terms of dose, geometry, drug release rate, and composition, various 3D printing techniques can be used. 3D printing technologies can be classified into six groups: photopolymerization-based printing, powder-based printing, extrusion-based printing, binder jetting, material jetting, and lamination-based printing. The most commonly used 3D printing technologies in the development of pharmaceutical solid oral dosage forms are fused deposition modeling (FDM), SSE, direct powder extrusion (DPE), selective laser sintering (SLS), and stereolithography (SLA) (12).

FDM technology uses previously prepared filaments containing the active substance(s), which are extruded through a heated nozzle. The print head moves along the x-y axis to deposit the extrudate, which solidifies at room temperature. Numerous advantages of combining hot melt extrusion (HME) with FDM 3D printing have been described in the literature. For example, the production of amorphous solid dispersions can improve the solubility of poorly soluble drugs. Another advantage of this technique is the possibility of using multiple nozzles to produce combination medicines. This printing technique is also cost-effective. However, it has certain drawbacks, such as unsuitability for thermosensitive drugs (12). An example from the literature describes mini-tablets containing propranolol hydrochloride and caffeine – two substances used in the pediatric population, which were successfully prepared using this method (13). Furthermore, 3D-printed mini-waffle shapes containing hydrocortisone have been

manufactured using this method, with their characteristic appearance enhancing acceptability in children (14).

DPE technology involves placing a powder mixture containing the drug into a powder reservoir, which can be processed through a nozzle for direct powder extrusion to print solid dosage forms containing the target drug doses. The reservoir feeds into a heated single-screw extruder in the print head, producing a fused extrudate. Advantages of this technique include the ability to produce formulations with immediate and extended drug release, as well as to improve the solubility of poorly soluble drugs. A disadvantage of this technique is its unsuitability for thermosensitive drugs (12). A literature example describes mini-tablets manufactured by this technique containing budesonide, a drug used in the treatment of eosinophilic colitis in pediatric patients (15).

The SSE method involves extruding an initial semi-solid material containing a drug through a heated syringe-based tool. This technique relies on the layer-by-layer deposition of a gel or paste to create a 3D product. Advantages include the ability to produce various types of formulations with different drug release profiles. Drawbacks include low resolution and capacity, as well as limitations in production speed. Another disadvantage is the necessity for the drug to be formulated in a semi-solid form (12). This method has been successfully employed to prepare soft tablets of various shapes (heart, moon, dog), containing isoniazid, which is used in pediatric tuberculosis treatment (16). Another example of a pediatric medicine prepared by this method is Lego™-like chewable bricks made of edible soft material (gelatin-based matrix) containing a combination of paracetamol and ibuprofen as model substances (17). Medicinal gummies containing ranitidine hydrochloride have also been printed in various shapes (heart, circle, bear) using semi-solid extrusion (18).

SLA is a printing technique where a photopolymerizable resin is exposed to high-energy light, such as UV light, to induce the polymerization and solidification of the material. This technique requires the development of drug-loaded, photo-curable resins, which consequently limits the selection of pharmaceutical polymers that can be used. Additional drawbacks include potential excipients toxicity concerns and limitations for thermosensitive and photosensitive drugs. On the other hand, this technique offers high resolution, enabling the production of complex geometries, which makes it widely used for experimental 3D printing of extended-release formulations (12).

SLS uses a laser to draw a specific pattern onto a powder layer, leading to partial or complete melting of powder particles. Once the layer is formed, a roller spreads a new layer of powder over the previous one. This process is repeated layer by layer to produce a 3D object. Due to its operating principle, this technology may be unsuitable for photosensitive and thermosensitive drugs, and requires precise control over powder flow properties. Another drawback is the need for post-processing. However, SLS offers a high capacity for producing highly porous, fast-dissolving dosage forms with high resolution, which is a significant advantage (12).

Due to their characteristics, extrusion-based technologies such as FDM, SSE, and DPE would be more suitable for on-demand printing at points of dispensing, such as hospitals and pharmacies, rather than the other techniques described. Considering this, the SSE method was used in this study for 3D printing of chewable lozenges containing propranolol hydrochloride as a common pediatric drug.

Chewable lozenges as a pediatric-friendly dosage form

Chewable lozenges are a relatively novel oral dosage form that, with further research and the introduction of appropriate pharmacopoeial regulations, could become much more prevalent in the market in the future. These preparations are intended for chewing and retention in the oral cavity before swallowing, so they can exert both local and systemic effects. They can be used in various populations but are particularly interesting for pediatric patients, who often encounter difficulties in medicine administration, especially in terms of swallowing. Unlike conventional solid dosage forms, chewable lozenges are suitable for individuals with swallowing difficulties, they do not require water for administration, and can be produced in various shapes, colors, and flavors to increase adherence in pediatric patients (19, 20). In the pediatric population, liquid dosage forms such as syrups and solutions are most commonly used, but their use is associated with certain challenges such as inaccurate measuring and dosing, product instability during storage, difficulty in masking the taste of the active substance, and children's aversion to taking medicines (21, 22). Therefore, a much better option for children of different ages would be to use medicines whose texture and mode of administration resemble an attractive children's treat, such as gummies.

Conventional lozenges are usually prepared by casting, which involves manually pouring the formulation into molds, making the process less automated and flexible. In contrast, 3D printing supports automated, small-scale, and personalized production, with greater control over shape and reproducibility.

Comprehensive reviews that summarize the excipients suitable for 3D printing by SSE, discussing their types, functional characteristics, and practical applications, are already available (23, 24). In addition, literature reports include a study on children's perception of the taste and texture of round, yellow 3D-printed oral dosage forms. Chewable lozenges produced by extrusion were considered the most acceptable for administration. Researchers emphasized the connection between color and perceived taste in children, expecting yellow to indicate a lemon/orange flavor. Children commented that they considered medicines with a smooth surface easier to swallow than those with a rough texture (25).

Tailoring propranolol therapy to pediatric patient needs

Cardiovascular disorders are among the most common health problems in children, whose treatment requires daily use of medicines (26, 27). Therefore, it is essential to design a suitable, child-friendly dosage forms for this versatile group of patients who

often refuse to cooperate when it comes to medicine administration, making pharmaceutical care and treatment more difficult for both parents and clinicians.

One of the drugs often used for pediatric cardiovascular diseases is propranolol (in the form of hydrochloride salt). In pediatric practice, propranolol hydrochloride is administered orally or intravenously in doses that vary according to the indication and patient's age (28). In Serbia, only one propranolol-containing medicinal product is marketed – a 40 mg tablet, which limits dose flexibility (29). According to DailyMed and EMC database records, the global market offers a broader range of propranolol-containing medicinal products (30, 31). These include various dosage forms in different strengths and concentrations, but most commonly modified-release tablets and capsules (10–160 mg). This poses challenges in pediatric care, where age, weight, and clinical condition require individualized dosing. The tablet form is unsuitable for many children, particularly those with swallowing difficulties, and splitting tablets compromises dosing accuracy, especially for small pediatric doses, potentially affecting safety and efficacy.

In this context, 3D printing offers a way to produce propranolol dosage forms precisely tailored to the individual needs of pediatric patients, enabling accurate dose adjustment and improving administration safety. Chewable lozenges, in particular, combine a child-friendly appearance and texture with ease of use, supporting better treatment adherence and therapeutic outcomes.

It is worth noting that propranolol hydrochloride is highly soluble in water (32), so the limited amount of available physiological fluids to dissolve the drug after the administration of a chewable lozenge (when the medicine is not taken with water) will not present a limitation for drug absorption. Saliva is an aqueous fluid, in which, during chewing and release of the active substance, the dissolution and absorption process could begin. This may also allow improved drug bioavailability and reduced drug dosing in comparison to conventional oral dosage forms, considering that propranolol undergoes first pass metabolism in the liver (33).

Experimental part

Materials

The following substances were used for the preparation of chewable lozenges: propranolol hydrochloride (Ph. Eur. quality; provided by Galenika a.d., Serbia), sodium alginate (Fisher Scientific, UK), gelatin (Sigma-Aldrich Co., USA), glycerol, 85% (Fisher Scientific, USA), calcium chloride (provided by Zdravlje Leskovac, Serbia), and purified water (in-house).

Methods

In the first phase of the study, the possibility of 3D printing of semi-solid mixtures with various compositions was tested, with the goal of selecting the most suitable "carrier" for the active pharmaceutical ingredient. The selected formulations were 3D

printed using the SSE method, and subjected to appropriate pharmaceutical-technological testing procedures.

Formulation development and 3D printing process

Based on information from available literature, gelatin and/or alginate (sodium salt) were selected as polymers for the preparation of chewable lozenges (34, 35), with the addition of glycerol as a humectant and purified water as the vehicle. The qualitative and quantitative composition of the tested formulations in terms of excipients is shown in Table I.

Table I Composition of drug-free (placebo) formulations

Tabela I Sastav placebo formulacija (bez aktivne supstance)

Formulation	Gelatin (g)	Sodium Alginate (g)	Glycerol, 85% (g)	Purified Water (g)
F1	-	1.5	9	19.5
F2	1.5	-	9	19.5
F3	0.75	0.75	9	19.5
F4	0.375	1.125	9	19.5

In the preliminary phase, the possibility of 3D printing and organoleptic properties of drug-free (placebo) formulations, made with the addition of one of the selected polymers, as well as their mixtures in different proportions, were tested.

To ensure appropriate printing quality and reproducibility (uniformity of the printed lozenges), certain parameters of the 3D printing device had to be adjusted and controlled. During the preliminary experiments, the most significant parameters that should be controlled during printing were identified.

After selecting the optimal formulation and printing parameters, the immersion time of the printed forms in a 0.1 M calcium chloride aqueous solution (30, 60, or 120 s) was varied, as well as the shape of the lozenges (cube dimensions 1×1×1.5 cm and cylinder Ø1.5 cm). The predefined geometry of the lozenges and their arrangement during printing are shown in Figure 1.

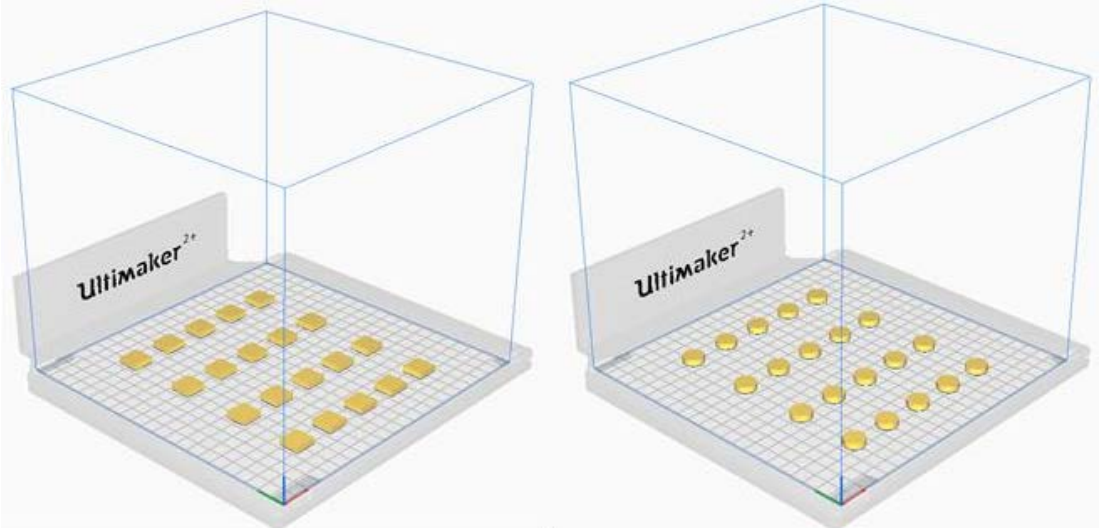

Figure 1. Geometric representation of the product in a predefined format for 3D printing (cube – left; cylinder – right)
Slika 1. Geometrijski prikaz izgleda preparata u unapred definisanom formatu za 3D štampu (kvadar – levo; cilindar – desno)

Preparations of lozenges

The mixture for 3D printing was prepared by transferring the previously measured active and excipient substances into a chemical beaker and continuously mixing them for 1 hour on a magnetic stirrer (IKA® RH basic 2, Germany), with heating to 40 °C. The active substance content in the mixture was 2.7%, which corresponds to the theoretical value of about 10 mg of propranolol hydrochloride per lozenge. This value aligns with the recommended dosing of the substance in the treatment of arrhythmia and hypertension in children with an average weight of around 20 kg (36).

The warm mass was transferred into a syringe, which was part of the 3D printer, and allowed to cool before printing. 3D printing was performed using the extrusion technique of a semi-solid material with the Ultimaker2+ device (Ultimaker B.V., Netherlands). Printing files were prepared using Ultimaker Cura 5.5.0 software (Ultimaker, Netherlands). The selected printing parameters are shown in Table II.

Table II The selected printing parameters
Tabela II Odabrani parametri štampe

Parameter	**Value**
Layer height	1 mm
Top/bottom pattern (Pattern for the first and subsequent layers)	Lines
Wall speed (Printing speed for the “wall” and first layer)	8 mm/s
Infill speed (Printing speed of other layers)	10 mm/s
Infill (printing) density	100%

Lozenges testing

The prepared lozenges were subjected to the following tests: organoleptic evaluation, variation in mass and thickness, melting time of the lozenges, determination of drug content and drug dissolution rate. Given that propranolol hydrochloride is highly soluble in water, regardless of pH value, and considering that saliva (the biological fluid in contact with lozenges) is an aqueous solution, purified water was used as the medium in the tests (37).

Organoleptic properties

The appearance, color, texture, stickiness under the fingers, and the color and appearance of the edges of each lozenge sample were observed.

Variation in lozenges thickness

The variation in thickness was tested with 20 lozenges from each printed batch, where the thickness of each lozenge was determined using a digital caliper (Vogel, Germany) and expressed in mm. From the obtained values, the average value (AV) and standard deviation (SD) were calculated.

Variation in lozenges mass

This test was performed by measuring the individual mass of 20 lozenges from each printed batch on a technical scale with an accuracy to three decimal places. The results were expressed as AV and SD.

Melting time of lozenges (melting test)

The melting time of the lozenges was tested in a water bath with a shaker (Grant LSB 18, United Kingdom) set at 37 ± 0.5 °C and 75 rpm, by measuring the time required for complete lozenge dissolution or disintegration (min). The test was carried out in chemical beakers, each filled with 150 mL of purified water, which simulates the volume of saliva produced over 30 minutes. The test was performed in duplicate, and the results were expressed as AV and SD.

Determination of propranolol hydrochloride content in lozenges

The determination of propranolol hydrochloride content in the lozenges was performed by placing one lozenge in a standard vessel with approximately 150 mL of purified water and mixing in an ultrasonic bath (Bandelin, Sonorex RK 102H, Germany) for 30 minutes at 70 °C. After that, the vessel was topped up to the 200 mL mark, the sample was filtered through a membrane filter (0.45 μm), and the propranolol hydrochloride content was determined spectrophotometrically (Evolution 300 UV-Vis spectrophotometer, Thermo Fisher Scientific, USA) at the wavelength of maximum absorption (290 nm). The test was carried out in duplicate. The results were expressed as AV and SD.

Disintegration of lozenges and drug dissolution rate

Propranolol hydrochloride dissolution rate from the prepared lozenges was tested in chemical beakers on a magnetic stirrer with controlled temperature at 37 ± 0.5 °C and a star-shaped magnet rotating at 150 rpm (to simulate the mechanical effect of the tongue). The test was conducted with 100 mL of medium (purified water). Samples of 4 mL were taken at predefined time intervals, with replenishment of the heated medium after each sampling. The samples were then filtered through a membrane filter (0.45 µm), and the dissolved propranolol hydrochloride content was determined spectrophotometrically at the wavelength of maximum absorption (290 nm). Simultaneously, the disintegration of the lozenge samples under the described conditions was monitored. The tests were performed in duplicate for each sample. The results were expressed as AV and SD.

The obtained dissolution profiles of the active substance were compared by calculating the similarity factor (f_2), according to the following equation:

$$f_2 = 50\, log\left\{\left[1 + \frac{1}{n}\sum_{i=1}^{n}(R_i - T_i)^2\right]^{-0.5} \bullet 100\right\}$$

where symbols have the following meaning: R, T – the percentage of dissolved substance from the comparing products (marked as R and T) after time t, n – the number of samplings. Values of f_2 between 50 and 100 indicate that there is a similarity between the compared drug dissolution profiles.

Results and discussion

Adjustment of 3D printing parameters

To ensure appropriate printing quality and uniformity of the lozenges, it is necessary to adjust and control certain parameters of the 3D printing device. Preliminary tests showed that the most significant parameters to be controlled during printing are: needle distance adjustment, bed leveling (before and during printing), needle movement speed, bed temperature, and the direction of needle movement during printing. Additionally, it was shown that the final appearance and mechanical properties of the finished products depend on the number of layers, number of lozenges, and the shape of lozenges.

At the start of the printing process, it is crucial to set the bed distance in relation to the needle to ensure precise printing. There are three screws on the bed that are used to adjust its height and alignment in all areas relative to the needle. During the printing process, it is important to set the minimum possible distance between the needle and the bed so that the mixture is evenly extruded onto the bed. It is best to tighten the screws as much as possible and then adjust the needle, since, during the printing of semi-solid

preparations, there is a need to loosen the screws during printing to reduce the distance between the bed and the needle. As the layers dry and their initial thickness decreases, the needle needs to be brought closer to the bed to reach the layer that is already deposited. It is important that the needle can reach the previous layer across the entire surface to prevent uneven application of the mixture and the formation of gaps. This issue is less significant when printing a smaller number of lozenges simultaneously, as the layers do not dry out in time. However, when printing more than 5 samples, it is necessary to monitor and adjust the screws at the beginning of printing each layer.

The optimal needle movement speed on the Ultimaker2+ device is expressed as a percentage (100%). It was shown that the needle movement/printing speed for the first layer should be slightly lower than for subsequent layers (8 mm/s) to precisely draw the edges and form a solid base for the subsequent layers, while the printing speed for the following layers should be set to somewhat higher value (10 mm/s). During operation, the speed should not be increased beyond 100% as this leads to skipping of the needle and the formation of gaps when applying the mixture onto the bed.

Preliminary experiments showed that the bed temperature (glass plate) should be set to around 25 °C. In case of higher temperature, the material melts during application to the bed, causing the mixture to spread and preventing the subsequent layer from being applied and adhering to the previous one. In such cases, the edges do not retain their initial shape, and lozenges with an uneven appearance are formed.

It was shown that the optimal number of layers for producing the desired lozenges is five. When 10 layers are printed, lozenges with an unstable shape are formed. Also, due to a higher likelihood of uneven material application during printing with a larger number of layers, these lozenges have a more irregular visual appearance. On the other hand, using fewer than five layers leads to the formation of products that resemble films rather than chewable lozenges.

The direction of needle movement affects the alignment of the printed lozenges with the predefined shape. When the cylindrical shape is printed with a ‘zig-zag’ movement of the needle, the shape does not fully resemble a circle when viewed from all sides. However, circular movements of the needle maintain the appearance of the cylinder perfectly. Furthermore, the needle movement should be adjusted differently when printing each layer, which is set when preparing the 3D printing file. Changing the direction of needle movement for each layer allows the material to be applied in different directions, and since the needle is very close to the previous layer (even slightly submerged in the deposited mass), the distribution of the material and its slight accumulation in the corners will not always occur on the same side, ensuring uniformity in all parts of the lozenge.

Selection of the optimal formulation

To select the appropriate “carrier” for the active substance, the feasibility of 3D printing and the organoleptic properties of printed formulations F1-F4 containing different types and amounts of polymers (Table I) were tested first. The results are described in

Table III, and visual appearance of the prepared lozenges is shown in Figure 2. Based on the comparative examination of the printed products and the observations during printing, F4 was chosen as the optimal placebo formulation for chewable lozenges.

Table III Organoleptic properties of the tested formulations and performance during printing

Tabela III Organoleptičke osobine ispitivanih formulacija i ponašanje prilikom štampanja

Formulation	Description
F1	The mixture was highly viscous, cloudy, and yellowish during mixing. After cooling, there was no trapped air, the mixture easily extruded from the needle, and precise shapes were formed. The printed products (resembling films) were elastic, homogeneously colored, thin, and smooth to the touch but brittle and too hard (for chewable lozenges).
F2	During preparation, the mixture was liquid, low-viscosity, clear, and pale yellow. After cooling, it became very viscous, difficult to extrude from the syringe, and unevenly applied from the needle to the bed. It did not adhere sufficiently to the bed, preventing the formation of proper lozenge shapes.
F3	The produced mixture was cloudy, pale yellow. After cooling, a little trapped air remained in the syringe, causing the cooled mixture to extrude unevenly and intermittently. During printing, irregularly shaped layers were deposited, which shifted during the transition of the needle to the next layer. The final appearance of the lozenges was irregular, resembling clusters.
F4	This formulation extruded easily from the needle and adhered well to the bed. During printing, there were no “skips” or gaps between the deposited material, and the subsequent layers adhered to the previous ones without irregular shapes forming. The produced lozenges were light yellow, homogeneous in appearance, with clear edges. They were soft, elastic, and slightly sticky to the touch after cooling.

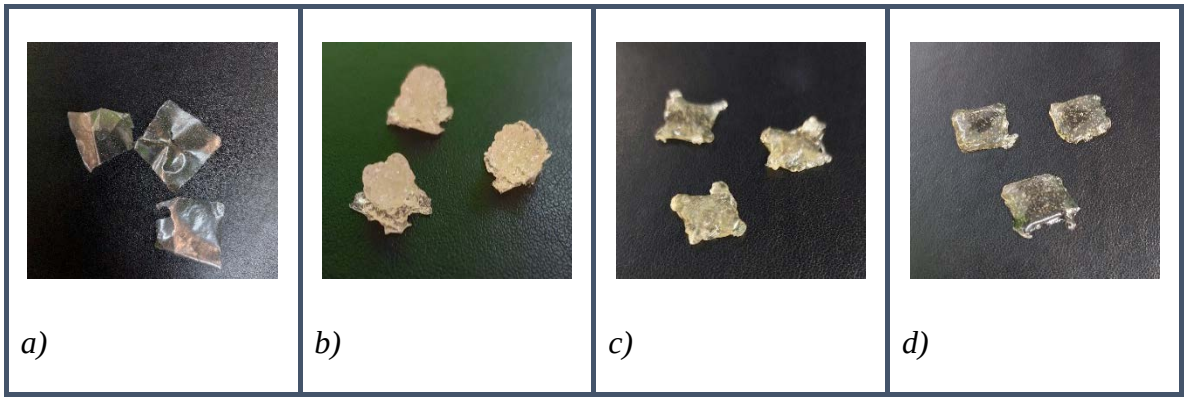

Figure 2. Appearance of the tested formulations: a) F1; b) F2; c) F3; d) F4
Slika 2. Izgled ispitivanih formulacija a) F1; b) F2; c) F3; d) F4

Based on the composition of the selected "carrier" formulation (F4), a mixture containing 2.7% of the active substance was prepared and used for printing the lozenges. Due to the stickiness and softness of the printed F4 formulation (Table III), the printed product was subsequently immersed in a 0.1 M aqueous solution of calcium chloride. This process crosslinks the polymers, increasing the strength and reducing the stickiness of the lozenges (38).

To assess the effect of immersion time in the calcium chloride solution (and the degree of polymer crosslinking), the immersion time was varied: 30, 60, or 120 seconds. Additionally, to evaluate the effect of the lozenge's shape on its characteristics, the lozenges were printed in a square and cylindrical form. The prepared products were labeled as K_{30}, K_{60}, K_{120}, C_{30}, C_{60}, and C_{120}, where K stands for square, C stands for cylinder, and the added numbers indicate the immersion time in the calcium chloride solution.

Characteristics of 3D-printed chewable lozenges

Organoleptic properties

The appearance of the prepared lozenges is shown in Figure 3. The square-shaped lozenges have more pronounced corners compared to the center, making them thicker at the ends than in the middle (Figure 3a–c). This happens because during printing the needle pulls the mass from the center to the corners, where it lingers, and the subsequent layers bond to these parts more easily. The cylindrically shaped lozenges, after printing, have visually uniform edges and thickness, with a slightly concave bulge (Figure 3d–f). The organoleptic properties of the produced lozenges are described in Table IV.

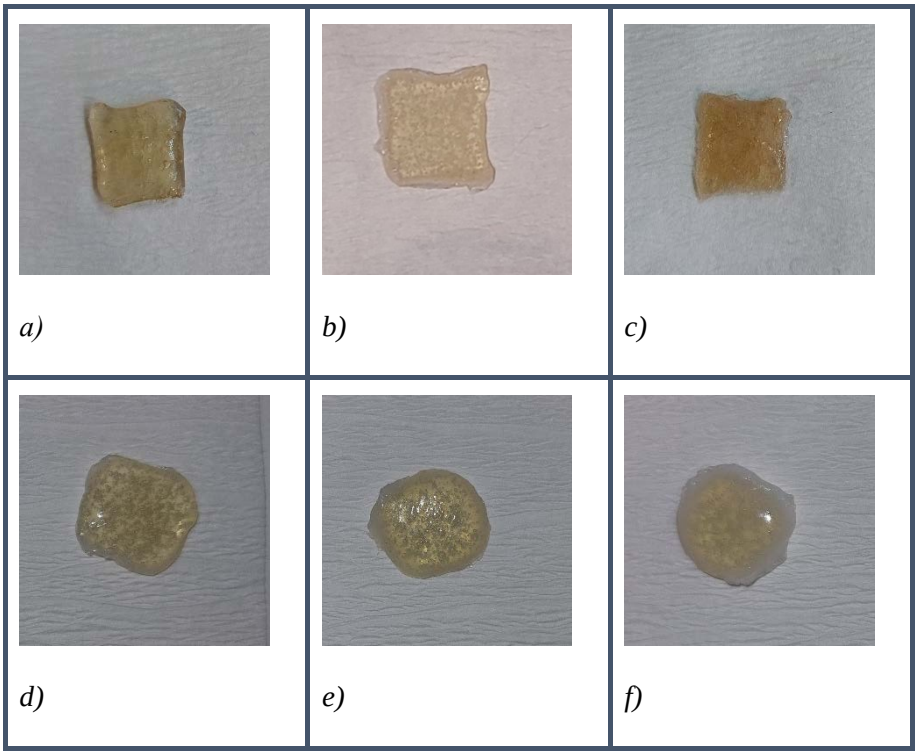

Figure 3. **The appearance of 3D printed lozenges with propranolol hydrochloride after immersion in the calcium chloride solution: a) S_{30}; b) S_{60}; c) S_{120}; d) C_{30}; e) C_{60}; f) C_{120}**

Slika 3. **Izgled 3D štampanih lozengi sa propranolol-hidrohloridom nakon potapanja u rastvor kalcijum-hlorida: a) S_{30}; b) S_{60}; c) S_{120}; d) C_{30}; e) C_{60}; f) C_{120}**

Table IV Organoleptic properties of the lozenges in relation to the immersion time in calcium chloride solution

Tabela IV Organoleptičke osobine lozengi u odnosu na dužinu potapanja u rastvor kalcijum-hlorida

30 s	**60 s**	**120 s**
Slightly sticky to the touch	Not sticky to the touch	Not sticky to the touch
Shape retained after immersion and drying	Shape retained after immersion and drying	Shape retained after immersion and drying
Defined edges, minimally altered by swelling	Edges slightly bent from swelling, white in color	White edges, wider “border” of whitish color (from trapped air)
No signs of delamination/layer separation	Some samples show signs of delamination	Certain level of delamination observed in majority of samples
Yellow color	Yellow with thin white border	Yellow with thicker white border

Variability in lozenges mass and thickness

Table V presents AV and SD values of mass variability for the square and cylindrical lozenges in relation to their immersion time in the calcium chloride solution. For chewable lozenges, the European pharmacopoeia (Ph. Eur.) does not specify allowable percentage deviations, but similar regulations are given for tablets (with an allowable deviation of 5% for tablets weighing over 250 mg) (39). The mass of cylindrical lozenges immersed in calcium chloride for 60 s and 120 s varied within the 95–105% range compared to the AV, which aligned with Ph. Eur. requirements. The other tested lozenges (K_{30}, K_{60}, K_{120}, C_{30}) contained one sample (out of 20) outside the acceptable range, so they did not meet the pharmacopoeial standards. For square-shaped lozenges, extended immersion time in the calcium chloride solution led to an increase in the average mass of the product, while this was not evident for cylindrical lozenges.

The thickness of chewable lozenges of both shapes increased with longer immersion time in the calcium chloride solution (Table V). This is attributed to the swelling that occurs when a lozenge is immersed in the aqueous solution; the longer the immersion time, the greater the amount of liquid the product absorbs.

Table V Variability in lozenge's mass and thickness in relation to their shape and immersion time in calcium chloride solution

Tabela V Variranje mase i debljine lozengi u zavisnosti od njihovog oblika i dužine potapanja u rastvor kalcijum-hlorida

Mass (*g*)	**S_{30} *(n=20)***	**S_{60} *(n=20)***	**S_{120} *(n=20)***	**C_{30} *(n=20)***	**C_{60} *(n=20)***	**C_{120} *(n=20)***
AV	0.3990	0.4090	0.4410	0.3240	0.323	0.325
SD	0.0172	0.0157	0.0126	0.0260	0.0090	0.0120
Thickness (*mm*)	**S_{30} *(n=20)***	**S_{60} *(n=20)***	**S_{120} *(n=20)***	**C_{30} *(n=20)***	**C_{60} *(n=20)***	**C_{120} *(n=20)***
AV	2.0840	2.1350	2.6410	2.3280	2.6770	2.8370
SD	0.0900	0.0620	0.1244	0.0380	0.0930	0.0450

n – number of replicates

Drug content in lozenges

The obtained results referring to propranolol hydrochloride content in the tested lozenges are shown in Table VI. The experimentally determined content was found to be considerably higher than the theoretical value. This can be explained by the fact that the lozenges dry out while standing in the air, and as water evaporates, the concentration of the active substance increases. Additionally, the lozenges of a square shape contain a

higher amount of the active substance compared to the cylindrical ones, which corresponds to the results indicating a higher average mass of these preparations.

Table VI Propranolol hydrochloride content in the tested lozenges

Tabela VI Sadržaj propranolol-hidrohlorida u ispitivanim lozengama

	AV *(mg)*	**SD**
S_{30} *(n=2)*	17.24	0.53
S_{60} *(n=2)*	17.75	0.21
S_{120} *(n=2)*	14.73	0.38
C_{30} *(n=2)*	24.35	0.09
C_{60} *(n=2)*	20.71	1.90
C_{120} *(n=2)*	15.51	0.31

n – number of replicates

Drug dissolution rate

Figure 4 presents propranolol hydrochloride dissolution profiles from the tested lozenges. Table VII shows the calculated similarity factors between drug dissolution profiles from lozenges of different shapes, subjected to different immersion times in calcium chloride solution. It was shown that for 60 and 120 seconds immersion time, the profiles can be considered similar for both square- and cylindrically shaped lozenges, as the f_2 value is higher than 50, while the other profiles differ from each other.

For the square-shaped samples (Figure 4a), drug dissolution rate decreases with the increase in immersion time of the lozenges in the calcium chloride solution. The samples immersed for 30 seconds showed the highest percentage of the dissolved substance, which occurred due to the minimal effect of calcium chloride on polymer crosslinking, allowing the active substance to be released from lozenges more easily. As the immersion time increased, the degree of crosslinking increased, resulting in a decreased rate of drug dissolution, which looks proportional for the samples S_{60} and S_{120}.

In the figure displaying profiles for the cylindrical lozenges (Figure 4b), no clear trend is observed, and after 30 minutes, similar values for the percentage of drug dissolved are obtained regardless of the lozenges immersion time in the calcium chloride solution. These results can be attributed to the spontaneous delamination of cylindrically shaped samples immersed for 120 seconds in the calcium chloride solution, which occurs within the first minutes of the test and increases the surface area available for drug dissolution. The spontaneous delamination observed in these samples can be attributed to the layer-by-layer nature of the applied 3D printing technique, which likely facilitates water penetration between the layers rather than through the layers themselves. Future imaging studies could

provide valuable insights into this phenomenon. In the case of cylindrically shaped samples immersed for 60 seconds in the calcium chloride solution, after 15 minutes the samples began to break down, and in this case too, due to the larger surface area for dissolution, an unexpected increase in the percentage of drug dissolved was observed.

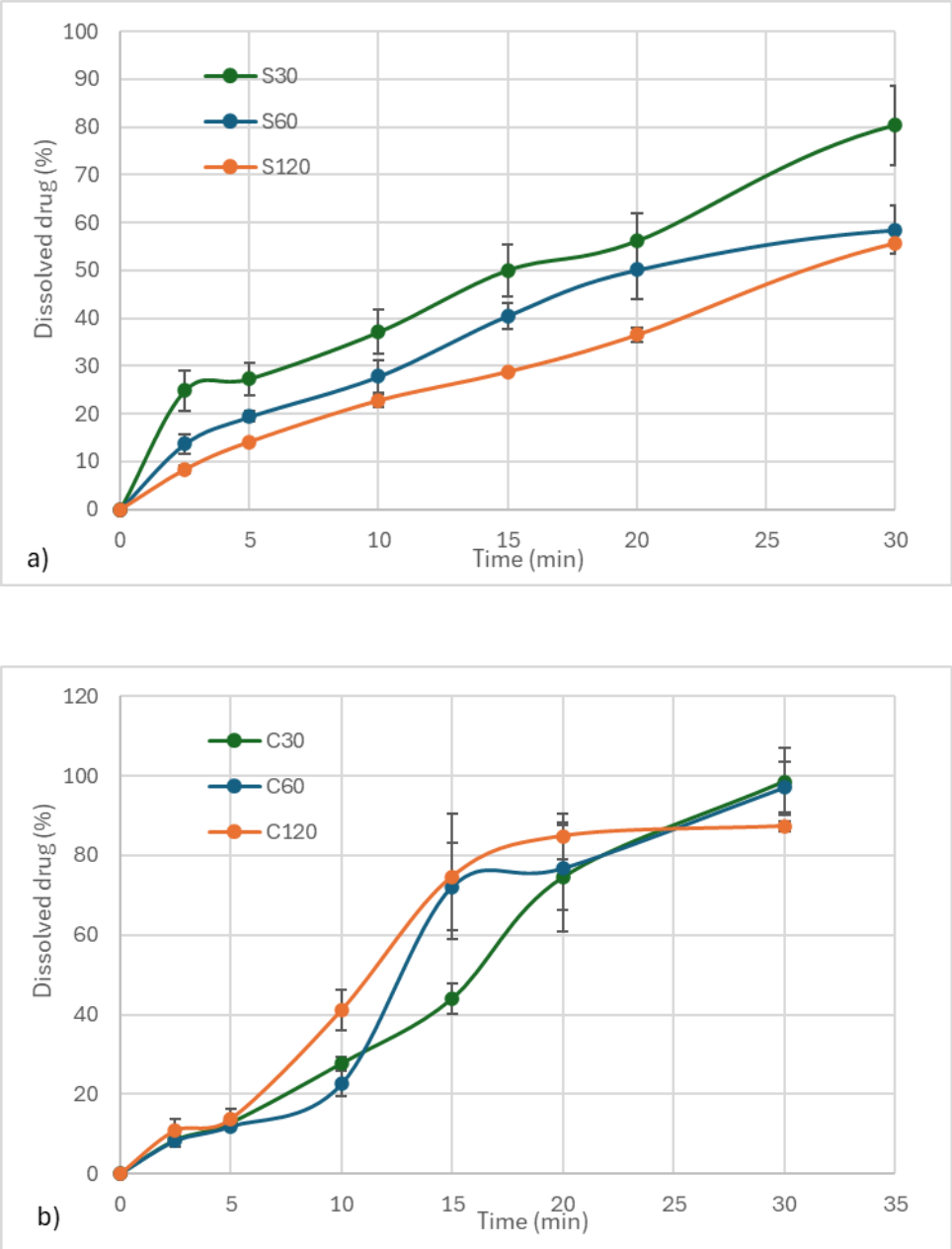

Figure 4. **Percentage of dissolved drug over time from: a) square shaped lozenges; b) cylindrically shaped lozenges (AV and SD for two replicates)**

Slika 4. **Procenat rastvorene lekovite supstance tokom vremena iz: a) lozengi oblika kvadra; b) lozengi oblika cilindra (srednja vrednost i standardna devijacija za dva uzorka)**

Table VII Similarity factor (f_2) between drug dissolution profiles from different lozenges

Tabela VII Faktor sličnosti (f_2) između profila brzine rastvaranja lekovite supstance iz različitih lozengi

Compared products	f_2 **value**
S_{30} and S_{60}	45.84
S_{30} and S_{120}	36.46
S_{60} and S_{120}	53.97
C_{30} and C_{60}	46.43
C_{30} and C_{120}	41.10
C_{60} and C_{120}	51.41

Melting time and disintegration of lozenges

The Ph. Eur. does not provide specific guidelines or requirements for testing the disintegration and melting times of chewing lozenges. Therefore, the lozenges melting time was tested according to the monograph for suppositories (39), while the disintegration time was monitored during dissolution testing. The tests were conducted only on cylindrically shaped lozenges, as preliminary observations indicated that disintegration and melting times are not dependent on the lozenges shape.

Table VIII compares the obtained values, showing that the average disintegration time aligns with the average melting time for different samples. It was noted that the disintegration time was approximately half of the melting time, which can be explained by differences in the hydrodynamics during the test (the magnetic stirring exposes the sample to greater hydrodynamic stress).

Table VIII Average melting and disintegration time of lozenges

Tabela VIII Srednje vreme topljenja i raspadanja lozengi

	Disintegration Time (min)	**Melting Time (min)**
C_{30} *(n=2)*	30	60
C_{60} *(n=2)*	20	45
C_{120} *(n=2)*	30	60

n – number of replicates

Conclusion

Pharmacotherapy of pediatric patients is associated with a range of specific challenges arising from the patient's physiological, developmental, and psychological characteristics. The need for an individualized approach is particularly evident when it comes to drug dosing, choice of dosage form, and tailoring organoleptic properties of a

medicine. Conventional dosage forms/formulations, widely available on the market, are usually not designed in line with a patient- or population-centric approach, which is why, in practice, commercial products are often modified or extemporaneous formulations are prepared. Such approaches can result in problems with dosing accuracy, stability, and the acceptability of medicines.

Recent technological advancements, particularly the development of 3D printing, have opened new possibilities for manufacturing personalized medicines that fully meet the needs of individual patients. This technology enables precise dose control, customization of the product's shape according to the child's age and preferences, the combination of multiple active substances, as well as the adjustment of drug release profile. Among the various available 3D printing techniques, the extrusion-based ones, especially SSE, seems to be the most suitable for use in hospital and pharmacy settings. SSE technique can be used to prepare dosage forms with a variety of geometries and organoleptic properties, which is particularly important for improving compliance in the pediatric population. However, practical considerations remain essential, including considerations regarding scalability of 3D printing process, its integration into hospital pharmacy and industrial workflows. Also, regulatory requirements must be addressed to ensure the quality and/or approval of 3D printed medicines. In addition, the introduction of specific pharmacopeial standards for chewable lozenges will be beneficial to ensure the consistent quality of these products. From the current point of view, producing small batches of 3D printed medicines tailored to individual patients in hospital pharmacies seems feasible, while industrial-scale manufacturing still faces many challenges.

The conducted research demonstrated that a formulation based on the combination of gelatin and sodium alginate in 1:3 ratio can be successfully used for 3D printing of chewing lozenges for the pediatric population, with the appropriate control of printing parameters.

The testing results for propranolol chloride-loaded lozenges of different shapes and varying immersion times in the calcium chloride solution revealed that variations in these parameters affect the pharmaceutical-technological and organoleptic properties of the product. Among the samples tested, the best characteristics were observed for cylindrical lozenges immersed for 60 seconds in the 0.1M aqueous calcium chloride solution.

Although the sample size tested in this study is relatively small, the obtained results demonstrate clear trends, and may serve as a basis for future studies orientated toward the development of child-friendly dosage forms, suitable for personalized treatment of specific pediatric patient groups. The selected chewing lozenges formulation has appropriate pharmaceutical-technological characteristics, and is suitable for personalized drug dosing. Moreover, the selected dosage forms imply easier swallowing, which may contribute to better therapeutic success and reduced children's aversion to oral medication.

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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

MI: Investigation, Formal analysis, Writing – original draft preparation; MP: Investigation, Formal analysis, Writing – original draft preparation; JĐ: Conceptualization, Writing – review and editing; SC: Conceptualization, Writing – review and editing, Supervision

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Inovacije u 3D štampanim farmaceutskim oblicima lekova za pedijatrijsku populaciju: Primer lozengi za žvakanje

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Kratak sadržaj

Trodimenzionalna (3D) štampa pruža široku platformu za proizvodnju personalizovanih farmaceutskih oblika prilagođenih uzrastu, koji odgovaraju specifičnim terapijskim potrebama pedijatrijske populacije. Među različitim oralnim farmaceutskim oblicima koji se mogu pripremiti pomoću 3D štampe, lozenge za žvakanje nude brojne prednosti, naročito za pedijatrijske pacijente. Ovaj rad prikazuje razvoj formulacije i izbor procesnih parametara za 3D-štampane lozenge za žvakanje koje sadrže propranolol-hidrohlorid kao model supstancu, sa potencijalnom primenom u pedijatrijskoj populaciji. Takođe, ističu se prednosti 3D štampe korišćenjem metode ekstruzije polučvrstog materijala.

Želatina i natrijum-alginat korišćeni su kao nosači za 3D štampu. Varirani su vreme uranjanja u rastvor kalcijum-hlorida (t_{im}) i oblik lozengi, pri čemu su sprovedena sledeća ispitivanja: procena organoleptičkih svojstava, variranje mase i debljine, vreme topljenja i raspadljivost lozengi, sadržaj i brzina rastvaranja propranolol-hidrohlorida.

U početnoj fazi identifikovani su ključni parametri 3D štampe za izradu lozengi, a zatim je odabrana odgovarajuća formulacija. Dalja ispitivanja su pokazala da oblik lozengi, u kombinaciji sa varijacijama u vremenu uranjanja, utiče na farmaceutsko-tehnološke karakteristike izrađenih preparata. Formulacija zasnovana na kombinaciji želatine i natrijum-alginata u odnosu 1:3, uronjena 60 sekundi u rastvor kalcijum-hlorida, pokazala se pogodnom za 3D štampu lozengi za žvakanje.

Ključne reči: 3D štampa, lozenge za žvakanje, propranolol-hidrohlorid, natrijum-alginat, želatina