



3D-printed chewable gummy tablets: A new tool for oral amoxicillin administration in paediatric population

Anna Imbriano^{a,1}, Costanza Fratini^{b,1}, Giulia Bondi^c, Ilenia D'Abbrunzo^d, Serena Bertoni^c, Mattia Tiboni^b, Angela Abruzzo^c, Dritan Hasa^d, Cinzia Pagano^{a,*}, Luca Casettari^b

^a Department of Pharmaceutical Sciences, University of Perugia, via del liceo 1 - 06123 Perugia, Italy

^b Department of Biomolecular Sciences, School of Pharmacy, University of Urbino Carlo Bo, Via Ca le Suore 2 - 61029 Urbino (PU), Italy

^c Department of Pharmacy and Biotechnology (FaBiT), Alma Mater Studiorum - University of Bologna, Via S. Donato 19/2-40127, Bologna, Italy

^d Department of Chemical and Pharmaceutical Sciences, University of Trieste, Piazzale Europa, 1 - 34127 Trieste, Italy

ARTICLE INFO

Keywords:

Amoxicillin
Starch
Gummy tablet
Paediatric formulations
3D printing
Personalized medicine

ABSTRACT

Amoxicillin is one of the most prescribed antibiotics in the paediatric population. Currently available formulations (i.e., suspensions and tablets) suffer from limited acceptability often responsible for the therapeutic failure. In the present study it is proposed an innovative formulation for amoxicillin oral administration that could meet acceptability requirements of the paediatric population. Chewable gummy tablets were produced by the Pressure-Assisted Microsyringe 3D printing technology. As “ink” it was used a gel obtained by the co-formulation of corn starch with acacia honey. The optimized formulation, having a final dose of 200 mg per unit, resulted visually appealing. Good accuracy between the computer-aided design and final 3D-printed product was evident as well. The fabricated gummy tablets (1.07 ± 0.05 g) showed acceptable mechanical properties such as hardness (150.52 ± 5.67 N), and gumminess (68.13 ± 6.51 N) when exposed to simulated salivary fluid. Moreover, the 3D-printed gummy tablets determined the almost complete release of the drug in the gastric environment within 2 h and assured its permeation through the PermeaPad® membranes. The obtained results suggest that 3D printing is a versatile and scalable technology useful in the pharmaceutical industry to fabricate customized chewable formulations as a suitable alternative to conventional formulations for amoxicillin administration in the paediatric population.

1. Introduction

Amoxicillin (AMOX) is a broad-spectrum beta lactam antibiotic widely prescribed in the paediatric population. AMOX-containing formulations available on the market are tablets, capsules and suspensions. However, these dosage forms are characterized by relevant limitations (Juárez-Hernández et al., 2022; Rampedi et al., 2024). Specifically, solid formulations, like capsules and tablets, are difficult for children to swallow and are generally more suitable for those aged 6 and older. On the other hand, liquid dosage forms, like suspensions, generally used for infants and preschool children (< 6 years), suffer from instability, dosing errors and limited acceptability. AMOX is a bitter drug thus, especially the liquid formulations available on the market are projected in order to mask the bad taste (Moreira and Sarraguça, 2020). The most common approach used is represented by the addition of sweeteners and

flavouring agents (Malkawi et al., 2022). However, this strategy does not always guarantee an adequate taste masking resulting often in unpleasant formulations (Holás et al., 2005). Other taste masking approaches are represented by i) drug complexation with carriers (e.g., cyclodextrins) (Wüpper et al., 2021; Lopalco et al., 2022), ii) pro-drugs or salt preparation (Malkawi et al., 2022); iii) isolation of the bitter compound by formulating it in coated dosage forms such as micro-particulates, tablets (Qin et al., 2019).

The low acceptability of a formulation, especially in the paediatric population, is one of the main reasons for the therapeutic treatment interruption (Mennella et al., 2013; Ranmal and Tuleu, 2013; Challener et al., 2023). As patient acceptability has a considerable impact on the therapeutic treatment success, a solution could be represented by the development of child-friendly formulations.

In this context, chewable dosage forms (gummies) represent a very

* Corresponding author.

E-mail address: cinzia.pagano@unipg.it (C. Pagano).

¹ These authors contributed equally to this work.

promising tool for drug administration in the paediatric population (Khan et al., 2022). In fact, these formulations, compared to the traditional solid ones (tablets, capsules): i) are soft and flexible, thus can be easily chewed, ii) are appealing and possess good organoleptic properties (taste, smell) thus easily acceptable by paediatric patients; iii) do not require water for administration iv) do not require specific storage conditions; v) are easy to transport (Rodríguez-Pombo et al., 2022; Vlachou et al., 2023; Adeleke et al., 2024). The conventional manufacturing methods to produce gummies are wet or dry granulation and direct compression (Rodríguez-Pombo et al., 2022). These processes are often complex, time-consuming, and do not allow an easy personalization in terms of size and dose. Instead, 3D printing (3DP) represents an innovative, versatile and scalable manufacturing technique useful for the development of batches of customizable gummies especially for paediatric use (Tegegne et al., 2024). 3DP can be performed using different techniques but semisolid extrusion (SSE) is recently gaining a lot of interest due to an easy and less time-consuming preparation of a semisolid “ink” (usually a gel or a paste) that is filled into the syringe of the printer (Seoane-Viaño et al., 2021; Bernatoniene et al., 2025). Additionally, this technique allows to employ a wider range of materials such as natural excipients and thermosensitive drugs. 3DP has been successfully employed for the formulation of many drugs intended for paediatric use such as hypoglycemic (Santamaria et al., 2024), anti-inflammatory and antacid agents (Bialek et al., 2025). The use of SSE technique in the formulation of 3DP gummies based on antibiotic agents has not been deeply investigated. In literature in fact, they can be found just few papers dealing with the development of gummies for paediatric use based on antimicrobial agents as isoniazid (Kean and Adeleke, 2023; Murugan et al., 2024) and ciprofloxacin (McCloskey et al., 2023) but not papers dealing with 3DP gummy tablets based on AMOX can be found.

The aim of this study was to design, develop, and characterize gummies useful for children aged 6 years old and above, as an alternative to conventional formulations used for AMOX oral administration. In order to meet this objective, 3DP SSE technique was employed for the gummies' fabrication. This technique is advantageous because of its scalability, sustainability as well as versatility. In fact, the same semisolid “ink” can be used to produce formulations of different shapes as well as doses, allowing an easy customization of the therapy.

In the development of medicinal products, especially those intended for paediatric patients, it is very important to select appropriate and child safe excipients (Salunke et al., 2012; Salunke et al., 2013). Hence, within this study suitable excipients using natural sources, namely corn starch (CS) and acacia honey were firstly identified. CS was employed as the polymeric component of the formulation. It is classified as generally recognized as safe (G.R.A.S.) and for this reason largely employed in the pharmaceutical industry. Furthermore, acacia honey was employed as a flavouring and sweetening agent (Osuna et al., 2022; Valverde et al., 2022). In literature there are few examples of chewable tablets, based on CS, realized for AMOX oral administration in paediatric patients using different production techniques than 3DP. For instance, Synaridou et al., produced chewable tablets by direct compression using maize starch, magnesium stearate and crospovidone; a combination of aspartame and milk chocolate was used to improve the taste (Synaridou et al., 2021). Within our study, the use of natural ingredients such as starch and honey make the formulation a greener and potentially healthier alternative to synthetic excipients.

Then, bear-shaped gummy tablets were developed by exploiting the SSE 3DP technique, specifically the Pressure-Assisted Microsyringe (PAM) method and characterized in terms of physical-chemical and functional properties. The bear-shaped design makes the tablets more appealing to children, further improving compliance and acceptance of the treatment. To the best of our knowledge, the formulation detailed in this work represents a novelty as it has not yet been applied to produce paediatric gummies for antibiotics oral administration.

2. Materials and methods

2.1. Materials

Corn starch (“Maize starch” European Pharmacopoeia –Ph. Eur. 11th Ed.) and amoxicillin trihydrate were purchased from A.C.E.F. s.p.a. (Fiorenzuola d'Arda, Italy). Glycerol E422 food additive-vegetable origin was a gift of Spiga Nord Spa (Carasco, Italy). Organic (certified according to Regulation CE 848/2018) acacia honey produced by hives on the farm ‘La raia’, was bought at NaturaSi (Corciano, Perugia, Italy). The honey microbiological quality complies with the limits reported in the Ph. Eur. 11th Ed. par. 5.1.4. “Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use”. In fact, the limits for non-aqueous preparations for oral use are: 10^3 CFU/mL TAMC (total aerobic microbial count) and 10^2 CFU/g TYMC (total combined yeast/moulds counts). For the honey the microbial characteristics reported in the producer datasheet are: mesophilic microbial load ≤ 1.000 CFU/mL; moulds ≤ 50 CFU/g; yeasts: ≤ 50 CFU/g; Sulphite-reducing Clostridia: absent. Ultrapure water was obtained by reverse osmosis in a MilliQ Millipore system (Roma, Italy). All other products and reagents were of analytical grade.

2.2. Gel preparation

Five starch-based gels (Table 1) were prepared after proper optimization (Pérez Gutiérrez et al., 2023) of the “starch glycerolate” recipe reported in the Italian Pharmacopoeia (Farmacopea Ufficiale Italiana FU XII Ed.). Starch-gel was prepared following the procedure described both by Perotti et al. and Valencia et al. properly modified (Perotti et al., 2013; Valencia et al., 2018). Glycerol (Gly) and/or honey were dissolved in bidistilled water contextually under magnetic stirring (500 rpm) for 5 min at room temperature (R.T.). Then, CS was dispersed and the suspension left under magnetic stirring (600 rpm) for 5 min at 80 °C to induce starch gelation. In addition, the preparation procedure of the gel was carried out in a closed jar to prevent water evaporation. The obtained gel was kept under magnetic stirring (200 rpm), at R.T., until complete cooling.

2.3. Sensory analysis

Drug free gummies were prepared by casting method to obtain prototypes useful to perform a selection of the most suitable composition by sensory assay. The gels were casted in silicon molds and maintained under CaCl_2 for 72 h to promote the formulation drying. As the portion of formulation in contact with the mold remained almost moist, after 72 h the gummy tablets were removed and kept for further 24 h under CaCl_2 in order to reach a uniform drying. The sensory analysis was a preliminary study and thus, in order to reduce the exposure of the paediatric population to unnecessary studies (Regulation EC 1901/2006) this experiment was done on adult volunteers. These were selected according to the following criteria: absence of allergies and/or intolerances to the ingredients used. Participants (7 males and 13 females) were properly instructed before the assay in order to perform the sensory analysis correctly. In particular:

Table 1
Gels compositions.

	Water % w/w	Corn starch (CS) % w/w	Glycerol (Gly) % w/w	Honey % w/w
GB0	60	10	30	–
GH1	60	10	–	30
GH2	60	10	15	15
GH3	60	10	6	24
GH4	60	10	24	6

1. do not take food for at least half an hour before the assay;
2. drink a glass of water between evaluations;
3. express their evaluation after each tasting without interacting with other participants.

Each participant was asked to express their opinion by using the questionnaire reported in Fig. S1 (Supplementary material). The evaluation is about: taste, intensity of taste and flavour, olfactory intensity and chewability.

2.4. Rheological properties

The rheological properties of the gel significantly affect its printability, and are, therefore, important parameters to determine (Herrada-Manchón et al., 2023). Rheological analysis was performed using a MCR 302e rheometer (Anton Paar, Austria) provided with a plate-plate geometry (PP, 25 mm Ø, gap 1 mm), at a controlled temperature of 25 °C. The operating parameters were set as follows. *Flow curve*: shear rate from 0.01 to 10³ s⁻¹, logarithmic ramp. Shear stress and viscosity were recorded to determine the flow behaviour of the material during the extrusion stage. *3ITT Osc-Rot-Osc recovery test*: procedure is shown in Table 2 and consists of two subsequent cycles. The percentage of recovery was used to define the thixotropic behaviour of the gels. *Amplitude sweep*: oscillating strain set from 0.01 to 100 %, logarithmic ramp with a fixed angular frequency at 10 rad/s. Trends of storage (G') and loss (G'') modulus were recorded and used to determine the linear viscoelastic region (LVR), the yield and flow point (loss of linearity and crossover point, respectively). *Frequency sweep*: oscillating strain fixed at 0.1 % (considering the LVR) and the angular frequency range set from 300 to 0.03 rad/s, logarithmic ramp. All the analyses were performed in triplicate.

2.5. Gummy tablets 3D printing: computer-aided design and operating parameters

The most suitable composition selected in the sensory analysis was then used to prepare the AMOX loaded gummy tablets by 3DP. The gel was prepared according to the procedure described in section 2.2. AMOX (10 % w/w) was incorporated in the cooled gel by mechanical stirring (2000 rpm for 2 min, ArgoLab AM20-D, Giorgio Bormac, Italy). The selected design (Fig. 1A) was obtained using a free Computer-aided Design (CAD) software (Tinkercad®, Autodesk Inc, USA). A 3 mL syringe equipped with a plastic nozzle 22G (0.4 mm) was filled with the pre-formulated gel and loaded into the 3D printer (BioX, Cellink, Sweden). Infill was set at 80 % with a rectilinear design, pressure around 60–80 kPa and printing speed kept between 7 and 10 mm/s. After preparation the 3DP gummy tablets were dried under CaCl₂ environment. The best drying was evaluated at different time points (24, 48, 72 h) through a Tensile Profile Analysis (Texture Analyzer, TA. XT plus, Stable Micro Systems, UK) to reduce excess moisture maintaining desirable mechanical properties. The TPA test procedures are described in section 2.6.7. After drying, each gummy tablet was stored individually in packages under vacuum.

Table 2

Setting parameters for the 3ITT-Osc-Rot-Osc recovery test.

Step	Oscillating strain and angular frequency	Shear rate	Time interval
1	0.1 %, 10 rad/s	/	120 s
2	/	10–100 s ⁻¹	60 s
3	0.1 %, 10 rad/s	/	120 s
4	/	10–100 s ⁻¹	60 s
5	0.1 %, 10 rad/s	/	120 s

2.6. Gummies characterization

2.6.1. Weight uniformity

The assay was performed, according to the Ph. Eur. 11th Ed., “Uniformity of mass of single-dose preparations” on 20 units of each batch produced. The weight was measured by a calibrated analytical balance (VWR®, Avantor, USA). Results were expressed as mean weight value ± SD.

2.6.2. Drug content

AMOX content was determined by dispersing the gummies, previously minced by a scalpel, in 250 mL of pure water and stirred at 600 rpm for 24 h. Thereafter, the suspension was centrifuged at 4,000 rpm for 10 min and then the supernatant was analysed. AMOX quantification was performed by UV–Vis spectrophotometry using a spectrophotometer Agilent 8453 (Agilent Technologies, Germany) by a calibration curve in water ($\lambda_{\text{max}} = 228.0 \text{ nm}$; $r^2 = 0.99$). The procedure was carried out in triplicate, and the percentage of AMOX average content was calculated.

2.6.3. Drug content uniformity assay

The assay was performed, according to the Ph. Eur. 11th Ed., “Uniformity of content of single-dose preparations” on 10 units randomly taken from each batch produced. AMOX amount was measured by UV–Vis spectrophotometry as described in par. 2.6.2.

2.6.4. Fourier-Transform Infrared Spectroscopy (FTIR)

The raw materials and AMOX-loaded and unloaded 3DP gummies were analyzed by FTIR (ATR-FTIR, Spectrum Two, Perkin Elmer, USA) to evaluate any possible interaction within the materials and the drug. Transmittance (%) was recorded in the wavelength interval of 4000–400 cm⁻¹. Samples underwent 64 scans using a resolution of 4 cm⁻¹. To evaluate the homogeneous distribution of AMOX, the dosage form was divided into smaller pieces and three of them randomly analyzed. Air was used as the background for each analysis.

2.6.5. Differential scanning calorimetry (DSC)

The thermal profile of the pure drug, excipients and the 3DP gummy tablet was investigated through DSC (DSC 6000, Perkin Elmer, USA). Specifically, approximately 5 mg of sample were placed in an aluminium pan and heated up from 25 °C to 200 °C at 5 °C/min. Nitrogen flow rate was kept at 30 mL/min. Analyses were carried out in triplicate.

2.6.6. Powder X-ray diffraction (PXRD) analysis

The 3DP gummies (both freshly made and aged for six months in a vacuum package) were sectioned into several slices to allow analysis via PXRD. For each gummy, 5 sections were prepared (Fig. S2, Supplementary material) and individually placed on the “zero background” silicon sample holder. PXRD measurements were carried on a Bruker D2 Phaser benchtop diffractometer (Bruker, Mannheim, Germany), using Cu-K α radiation ($\lambda = 1.5418 \text{ Å}$) with a 300 W low-power X-ray generator (30 kV at 10 mA). All the measurements were conducted in the 2 θ range of 5–35° with a step size of 0.02° and a scan speed of 0.6°/s.

2.6.7. Texture analysis

A TPA was carried out on the 3DP gummies to assess the mechanical properties. The test was run using a Texture Analyzer, TA. XT plus, (Stable Micro Systems, UK) equipped with a loading cell of 50 Kg and a compression probe (P/20 Ta.Tx, 20 mm diameter). A two-cycle compression was performed. The strain and trigger force were set at 60 % and 5 kg, respectively and test speed set at 1 mm/s. 5 s were waited before the second cycle took place. Parameters such as hardness (N), elasticity (%), cohesivity, adhesivity (N*s), and chewability (kN) were calculated using Eq. 1–3. Analyses were carried out in triplicate.

$$\text{Hardness(N)} = F_1 \quad (1)$$

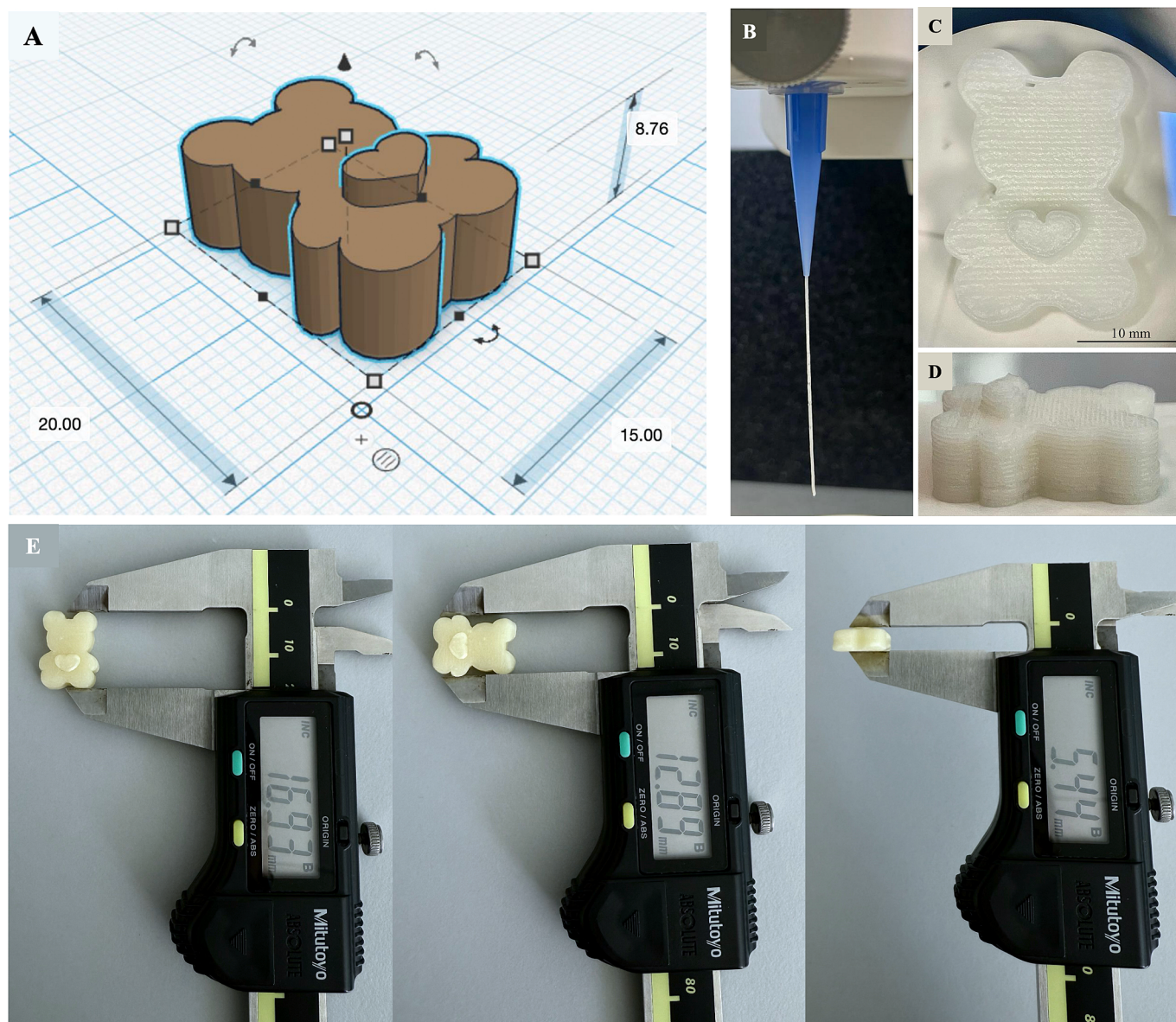


Fig. 1. A) CAD design of the 3DP gummy tablet. B) Images of the extruded filament and the 3DP gummy tablet at the optical microscope showing the layering of: C) the material from the top and D) lateral-side point of views. E) Dimensions of the dry 3DP gummy tablet. The dimensions are expressed in mm.

where F_1 is the max force registered after the first compression.

$$\text{Cohesiveness} = A_2/A_1 \quad (2)$$

Where A_2 and A_1 are the positive areas under the curve of the second and first peak of compression, respectively.

$$\text{Gumminess}(N) = \text{Hardness} * \text{Cohesiveness} \quad (3)$$

The assay was employed both to evaluate the best drying time under CaCl_2 environment after printing, but also to assess the texture retention after 1, 2, 7, 14 and 28 days of packaging under vacuum.

2.6.8. In vitro drug release

The dissolution test was performed according to Ph. Eur. 11th Ed. by a Dissolution system Agilent 708-DS (Cernusco sul Naviglio, Milano, Italy), using the paddle method. Before starting the experiment, each 3DP gummy tablet was cut by a scalpel in fragments to simulate chewing. Then, it was introduced in a vessel containing 1000 mL of simulated gastric fluid pH 1.2 (SGF), thermostated at $37.0 \pm 0.5^\circ\text{C}$, having the following composition (FU XII Ed.): 2 g NaCl, 80 mL HCl 1 M,

bidistilled water until 1000 mL. Paddle rotation was set to 50 rpm. The experiment was conducted for 120 min. Four mL of medium was drawn at established times (5, 10, 15, 20, 30, 45, 60, 90, 120 min) and replaced with 4 mL of fresh thermostated SGF. The same experiment was performed on AMOX powder (200 mg) used as control because of the lack on the market of solid formulations containing 200 mg of AMOX. Aliquots were analyzed immediately after sampling by UV-Vis spectrophotometry using a calibration curve in SGF ($\lambda_{\text{max}} = 228.0 \text{ nm}$; $r^2 = 0.99$). All dissolution experiments were carried out in triplicate.

2.6.9. In vitro permeability studies

In vitro permeability studies were carried out by employing a Franz-type static glass diffusion cell (15 mm jacketed cell with a flat ground joint and clear glass with a 12 mL receptor volume; diffusion surface area = 1.77 cm^2), equipped with a V6A Stirrer (PermeGear Inc., Hellertown, PA, USA). Aliquots (0.5 mL), withdrawn at 20 min from paddle apparatus, were placed in the donor compartment of the Franz cell. PermeaPad®, used as a model membrane for gastrointestinal absorption (Berben et al., 2018), was placed between the donor and receptor

chambers. The receptor compartment was composed of 12 mL of PBS phosphate buffer at pH 7.4 ($2.38 \text{ Na}_2\text{HPO}_4 \cdot 10 \text{ H}_2\text{O}$ g/L, $0.19 \text{ KH}_2\text{PO}_4$ g/L and 8.0 NaCl g/L) maintained at 37°C by means of a surrounding jacket and constantly stirred to assure a uniform drug concentration. At predetermined time intervals until 360 min (30, 60, 120, 180, 240, 300 and 360 min), samples (0.5 mL) were collected from the receptor compartment, replaced with the same amount of fresh medium and analyzed using HPLC (see section 2.6.10). The experiments were done in triplicate. The results of permeation studies are shown as a percentage of the cumulative permeated drug plotted as a function of time.

2.6.10. AMOX quantification by HPLC

The HPLC system consisted of two mobile phase delivery pumps (LC-10ADvp, Shimadzu, Japan), a UV-vis detector (SPD-10Avp, Shimadzu, Japan) and an autosampler (SIL-20 A, Shimadzu, Japan). A reversed phase C18 column (Luna, $4 \mu\text{m}$, $150 \text{ mm} \times 4.60 \text{ mm}$; Phenomenex, Bologna, Italy) was used as stationary phase, while the mobile phase consisted of K_2HPO_4 0.05 M (adjusted at pH 8.6 with H_3PO_4): acetonitrile (90:10 v/v). The injected volume was $20 \mu\text{L}$ and the detection wavelength was set at 230 nm. The chromatographic run followed an isocratic method with a mobile phase flow rate of 1 mL/min . In these conditions the retention time of AMOX was 5.1 min. For the calibration curve, AMOX stock solution (1 mg/mL) was prepared by dissolving 10 mg of AMOX in 10 mL mobile phase. The stock solution was diluted with the mobile phase to prepare solutions at different AMOX concentrations ($50\text{--}0.5 \mu\text{g/mL}$), which were injected. The determination coefficient (R^2) was then calculated to verify a linear response.

2.6.11. Statistical analysis

For permeations results, *t*-test was used to determine statistical significance. The criterion for statistical significance was $p < 0.05$.

3. Results and discussions

3.1. Gel composition optimization

3DP is a valuable technique for the development of customized paediatric oral formulations and PAM is an interesting manufacturing method to investigate as it allows the preparation of gummy dosage forms with desired shape, weight, and dimensions starting from a suitable semisolid matrix. The choice of excipients is also a crucial step in the design of gummies, as it is essential to use substances deemed safe for use in the paediatric population. With this in mind, the use of natural components could lead to the development of safe and environmentally friendly formulations. For this reason, gummies were realized starting from a pre-formulated gel using CS as the main matrix polymer. It is well known the corn starch capability to undergo gelation at 80°C thus, a hydrophilic gel having the following composition was prepared: CS 10 % w/w; Gly 30 % w/w and ultrapure water 60 % w/w. The composition was then modified introducing acacia honey as a plasticizing/flavouring/sweetening agent (Osuna et al., 2022; Valverde et al., 2022). Four different gels were prepared varying the honey amount (Table 1): 6 % w/w; 15 % w/w; 24 % w/w and 30 % w/w (in which Gly was totally replaced from honey).

3.2. Gel characterization

3.2.1. Sensory analysis

The objective of the sensory analysis was to select the most palatable gel composition useful for the preparation of the final dosage forms. For this preliminary evaluation the gels reported in Table 1 were used to prepare gummy tablets (Fig. S3, Supplementary material) by casting method (see section 2.3.). A blister pack containing five kinds of gummies was given to each participant who did not know which gel corresponded to which sample. Moreover, each participant was given instructions on how to carry out the analysis and a questionnaire for the

final evaluation. After the collection of all the responses, the final outcomes were expressed as %. The obtained results (Fig. S4, Supplementary material) show that all formulations were considered easy to chew. While the formulation that obtained the highest score in terms of taste was the sample 2 which contained the highest percentage of honey. Thus, GH30 gel was selected to produce the paediatric dosage forms.

3.2.2. Rheological properties

Within the framework of semisolid materials, the rheological characterization is essential for a successful PAM 3DP process. The ink's rheological properties play a crucial role in determining its response to applied pressures, flow through the nozzle, and ability to shape retention after deposition of the material on the printing bed, directly influencing the manufacturing outcome (Rau et al., 2023).

For this reason, both shear and oscillatory tests were carried out and results are reported in Fig. 2. The gel showed a good shear thinning behaviour, both with and without the presence of the drug (Fig. 2A). While oscillatory tests (Fig. 2C and D) highlighted the solid-like behaviour of the material showing a storage modulus (G') higher than the loss modulus (G''). G' registered at the linear viscoelastic region (LVR) was around 4370.1 Pa and 6136.9 Pa , for the unloaded and AMOX-loaded gel, respectively. Moreover, the inks presented a yield point (graphically recognizable as the region at which the curve deviates from linearity in amplitude sweep tests) and a cross over ($G' = G''$) at which point a stress of 722.9 Pa and 845.1 Pa was recorded for the gel without and with the drug, respectively. Fig. 2B presents the thixotropic behaviour of the ink when a low and high stress is consecutively applied to it through a 3ITT Osc-Rot-Osc test. Two following cycles were registered and the percentage of structure recovery (in terms of G') was 79.75 % and 60.03 % for the unloaded and loaded gel, respectively. These results suggest that the gel loses some of its elasticity when AMOX is incorporated, resulting in an ink that is stiffer. However, rheological analyses highlighted all the desirable properties of the material to be applied to the 3DP process and results were confirmed through the visual assessment of the ink's behaviour during the manufacturing of the 3DP gummy tablets (section 3.2.3).

3.2.3. Gummy tablets production by 3DP

Printing parameters were experimentally fine-tuned in terms of printing pressure (75 kPa) and printing speed (10 mm/s) to obtain the most desirable outcomes. Pressure was set at 75 kPa , to ensure a consistent extrusion of the material, leading to better layer adhesion and uniformity. Higher values resulted in over extrusion and lack of printing resolution while at lower values the gel was extruded unevenly since the material flow didn't suit the printing speed. 10 mm/s were selected as the best printing speed to achieve the most desirable printing resolution. However, increasing the printing speed can significantly reduce production time and enhance efficiency. One single gummy was completed in $\sim 16 \text{ min}$. Fig. 1B-D shows the final 3DP gummy tablet. A good shape fidelity and printing resolution were observed and the final dimensions resembled those defined on the CAD design suggesting a good accuracy of the manufacturing process.

3.3. 3DP gummies characterization

After the successful 3DP of the dosage forms, they were characterized to ensure quality and observation of official standards as reported in the Ph. Eur. 11th Ed.

3.3.1. Weight uniformity

Considering that non-official assays are available for gummy tablets, the "uniformity of mass of single dose preparations" prescribed by the Ph. Eur. 11th Ed. for tablets (weight $> 250 \text{ mg}$) was considered. Straight after printing one batch of 20 units, the 3DP gummy tablets were weighted and average mass calculated. Following the Ph. Eur. 11th Ed. assay prescription, no more than two single units should vary $\pm 5 \%$

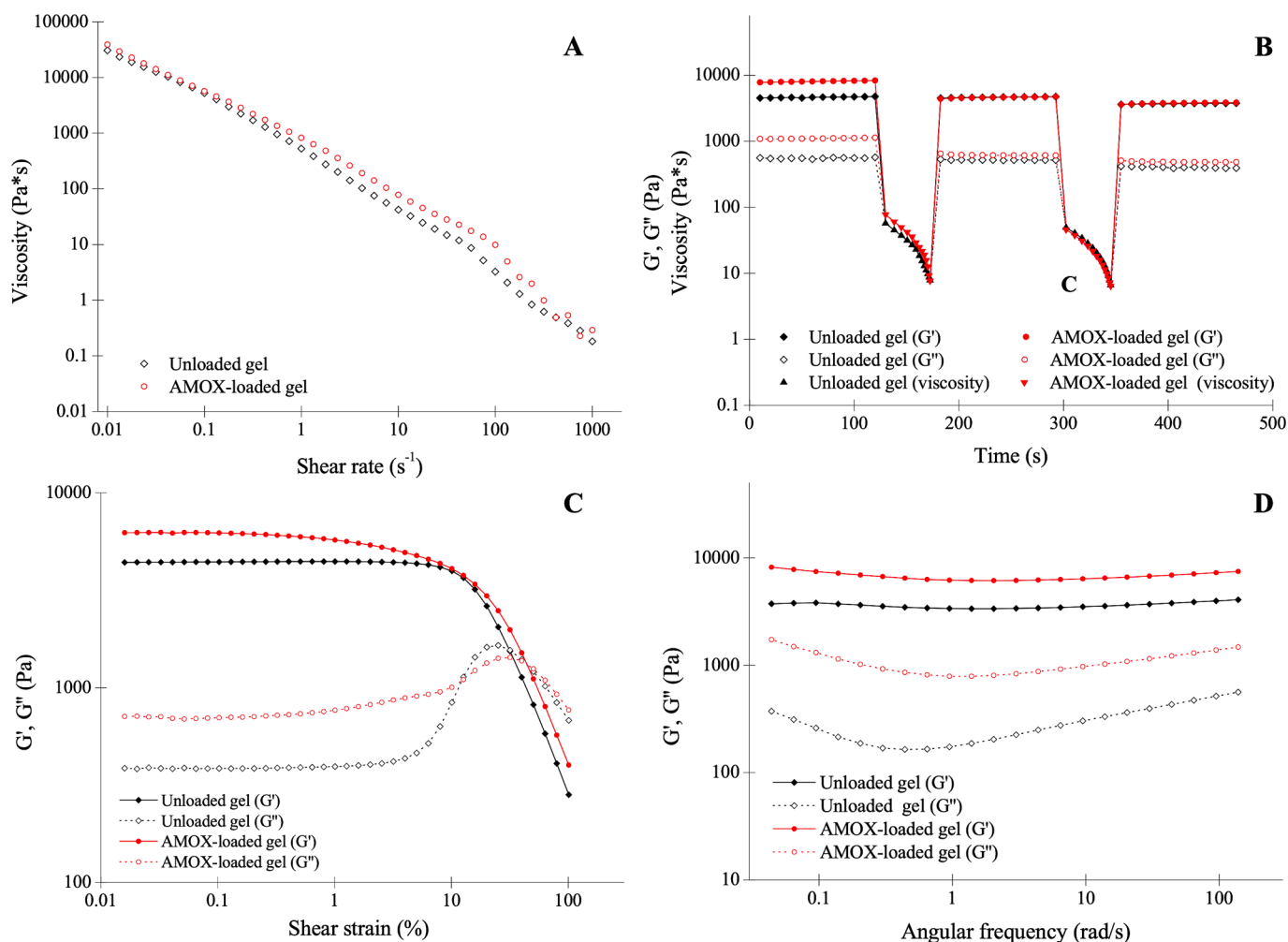


Fig. 2. A) Flow curves, showing the shear thinning behaviour of the gel. B) 3ITT Osc-Rot-Osc recovery test, showing the recovery of storage (G') and loss modulus (G'') of the gel. Trends of G' and G'' of the gel during C) amplitude sweep and D) frequency sweep tests.

from the average mass according to Table 2.9.5.-1 (Ph. Eur. 11th Ed.). Studying the weight's distribution (Fig. 3), only two dosage forms were found to be out of the given limits per batch, confirming the prerequisite for mass uniformity of the manufacturing method. On average, the weight for a single dosage form was 1.94 ± 0.12 g of the “wet” 3DP gummy tablets after printing and 1.07 ± 0.05 g after 72 h drying under CaCl₂ environment. The dimensions diminished slightly from 15.00 x 20.00 x 8.75 mm (width x length x height) of the “wet” gummy tablet (Fig. 1C, D) to 12.90 x 16.94 x 5.44 mm (width x length x height) of the dry one (Fig. 1E). Moreover, the appearance was not modified as detectable in Fig. 1E. Distribution of the “dry” weights around the average is also shown in Fig. 3.

3.3.2. Drug content and drug content uniformity assay

The measurement of drug content was carried out following the procedure described in par. 2.6.2. to evaluate drug incorporation in the 3DP gummy tablets. The expected value was 20 % by weight of drug, considering the weight of the dry 3DP gummy tablets (1.07 ± 0.05 g) and the theoretical AMOX content of 200 mg/single dose unit. The AMOX percentage found in the analysed formulations was 18.7 ± 0.5 %, according to the expected value.

The measurement of drug content uniformity was carried out complying with the “Uniformity of content of single-dose preparations” for tablets reported in Ph. Eur. 11th Ed. The obtained results (Fig. S5, Supplementary material) showed that the assay was satisfied measuring an AMOX amount in the admitted range of 85 % – 115 % of the average

content for the 3DP gummy tablets analyzed.

3.3.3. Fourier-Transform Infrared Spectroscopy (FT-IR)

ATR-FTIR was employed to investigate any possible chemical interaction among the formulation's components and to confirm the homogeneous distribution of AMOX in the 3DP gummy tablets. For this reason, the raw materials (CS, honey and AMOX), the unloaded and drug-loaded dosage forms were analyzed. Results are shown in Fig. 4A and are comparable to those found in literature (Li et al., 2025; Mahmood et al., 2025; Naiel et al., 2023). Being both glucides, CS and honey present analogies in the main FTIR signals. Particularly, a broad band in the range of 3400–3200 cm⁻¹ is attributed to the stretching vibration of OH groups, CH vibrational stretches are found around 2926 cm⁻¹ and a characteristic intense, broad absorption band at 1150–900 cm⁻¹ corresponds to the stretching vibrations of COC bonds of the glycosidic rings typical of polysaccharides. For honey a strong peak around 1643 cm⁻¹ is attributed to the stretching of C=O groups present in the molecules. The same peaks with no significant shifts in wavelength are clearly visible for both the unloaded and AMOX-loaded 3DP gummy tablets with the difference that the latter also presents the characteristic peaks of the drug. AMOX shows OH stretching with a broad band around 3400–3200 cm⁻¹ which is indicative of the presence of water molecules in the trihydrate form. Peaks at 1772 and 1685 cm⁻¹ correspond to the stretching of the carbonyl C=O group in the β -lactam ring and the peak at about 1576 cm⁻¹ is attributed to the stretching of C=O in the secondary amide. Moreover, peaks between 1500 and 1300 cm⁻¹ are related to C=C

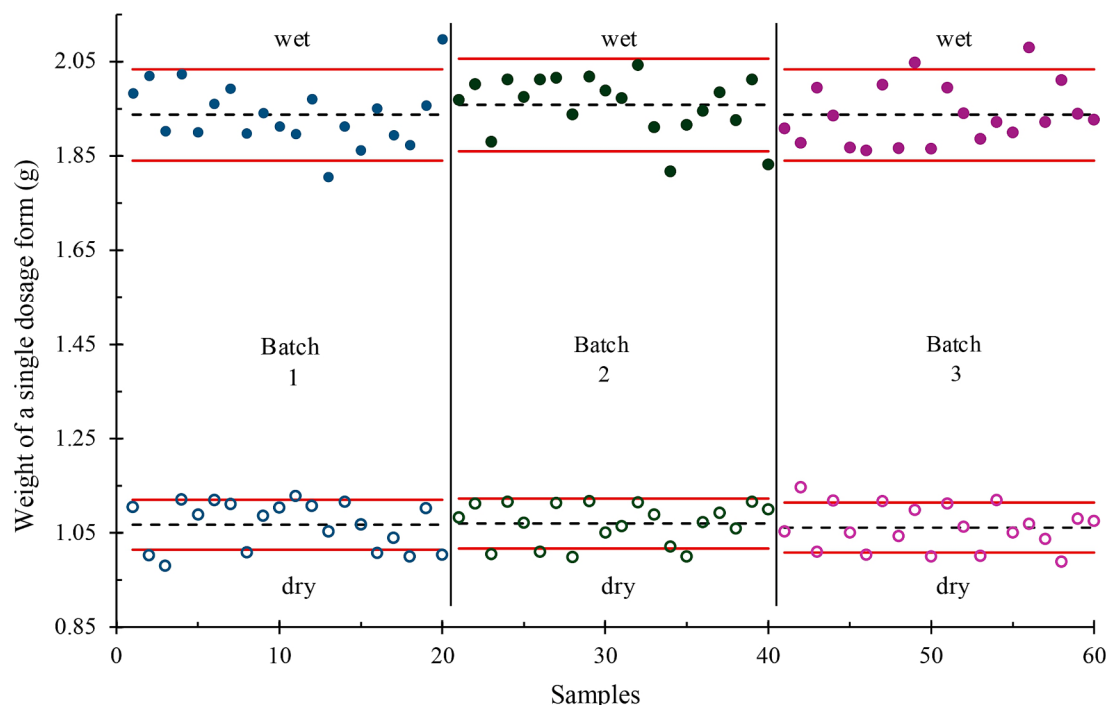


Fig. 3. Distribution of the 3DP gummy tablets' "wet" weights around the average and within the limits ($\pm 5\%$) given by the Ph. Eur. 11th Ed. for solid oral dosage forms. Each batch comprises 20 units. "Dry" weights' distribution is also shown.

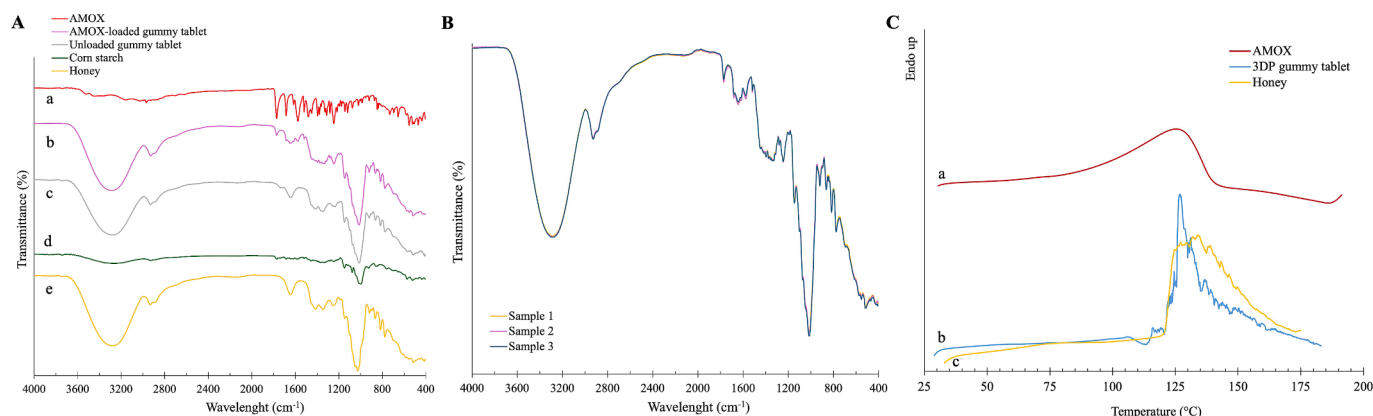


Fig. 4. A) FT-IR spectra of: a) pure AMOX, b) AMOX-loaded 3DP gummy tablet, c) unloaded 3DP gummy tablet, d) corn starch, e) acacia honey. B) FTIR spectra showing the homogeneous distribution of the drug in a 3DP gummy tablet. C) DSC thermograms of: a) pure AMOX, b) AMOX-loaded 3DP gummy tablet and c) acacia honey.

stretching of aromatic rings and NH bending vibrations while the region around 1246 cm^{-1} shows CN stretching vibrations associated with primary amines. Overall, the FTIR results showed that no new peak was generated, and no significant peak disappeared in the 3DP formulation. Therefore, it can be assumed that there was no major chemical interaction among the components.

As a final FTIR analysis, the homogeneous distribution of AMOX was determined by analyzing the spectrum of three sections of one 3DP gummy tablet. As shown in Fig. 4B, the three spectra display the characteristic peaks of AMOX with comparable intensities, only minor variations of $\sim 5\%$ in transmittance were seen. Thus, the results confirmed that AMOX is uniformly distributed within the gummies.

3.3.4. Differential scanning calorimetry (DSC)

DSC analysis was carried out to evaluate the crystallinity of the drug within the 3DP gummies. The thermogram of the pure drug was firstly recorded and then a single dosage form was fragmented and evaluated at

the DSC. As shown in Fig. 4C, a broad endothermic peak ($T_{\text{onset}} = 83.5^\circ\text{C}$, $T_{\text{peak}} = 126.5^\circ\text{C}$) related to the loss of water molecules in the crystal structure, was observed for the pure drug. The same event was not easily detectable in the 3DP gummy tablet due to the degradation of the other excipients present in the formulation such as acacia honey occurring at the same temperature. For this reason, PXRD analysis (section 3.3.5) was performed to better evaluate the crystallinity of the drug.

3.3.5. PXRD analysis

The PXRD patterns of the pure commercial AMOX confirms the high crystallinity of the starting material, showing several diffraction peaks at 12.15° , 15.20° , 16.25° , 17.20° , 18.03° degrees of 2θ angle (Fig. 5A). Importantly, the experimental pattern of the pure drug is very similar to the calculated pattern of the trihydrate structure deposited in the Cambridge Structural Database (Suzuki et al., 2022). Several diffraction peaks are detectable across all five sections of the gummies, suggesting

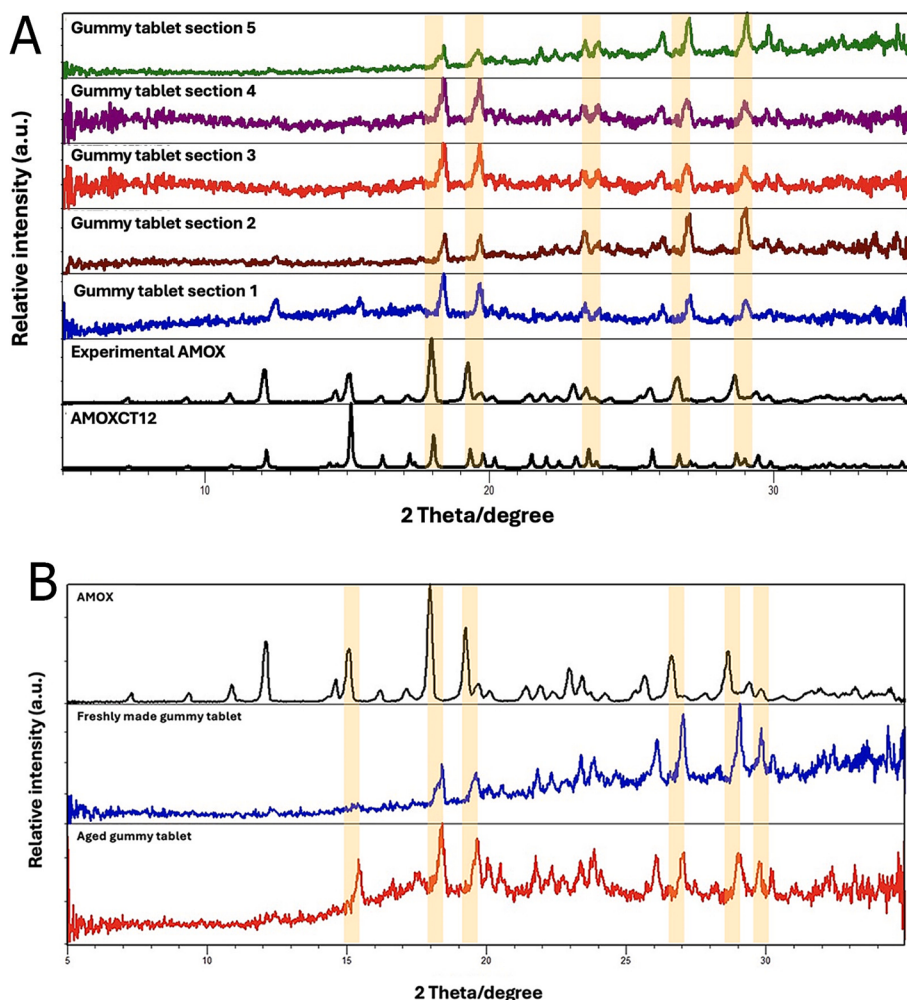


Fig. 5. A) PXRD patterns of the CSD-deposited structure (AMOXCT12), pure commercial AMOX, and five different sections of a freshly prepared AMOX-loaded 3DP gummy tablet. B) PXRD of pure AMOX (black) compared to freshly made (blue) and aged for 6 months (red) AMOX-loaded 3DP gummy tablet. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

that AMOX retains its crystalline structure within the matrix. The PXRD pattern appears slightly shifted, possibly due to the dispersion of the drug within a predominantly amorphous matrix. In order to assess AMOX stability over time, PXRD analysis was also performed on an aged 3DP gummy tablet, stored at R.T. in a vacuum package for 6 months. The data obtained from the sections of the aged gummy bear confirmed that AMOX remained in its original crystalline form, with no evidence of physical transformation or degradation (Fig. 5B).

3.3.6. Texture analysis

Concerning the texture evaluation, the tensile profile analysis (TPA) test was employed to identify the best drying conditions which would minimise the amount of water before packaging under vacuum while maintaining acceptable mechanical properties such as hardness and gumminess. Cohesiveness was also evaluated; this parameter indicates how well the product can withstand a second deformation after the first and it can be used to define the “gumminess” of the 3DP gummy tablets. Currently there is no standard and widely recognized chewability index for gummy tablets. However, this characteristic can help determine how easily and comfortably a gummy can be chewed and consumed (Adeleke and Abedin, 2024). Drying time was optimized at 72 h corresponding to 6.55 ± 0.65 % of water remaining into the dosage form and therefore to a notable increase in the gummy hardness. In fact, registered hardness after this drying time was 288.20 ± 15.43 N, which is considerably higher than the maximum value defined by FDA for chewable tablets

(117.68 N) (FDA, 2018). However, when the dosage unit was exposed to minimum amount (1 mL) of simulated salivary fluid (SSF, pH = 6.8, according to the FDA guidelines, 2018) (composition defined in Table 1S, supplementary material) for a short period of time (~30 sec) a significant reduction in hardness (>50 %) was recorded 150.52 ± 5.67 N. Moreover, prolonged exposure, especially in the presence of amylase (an enzyme found in human saliva), is likely to further reduce the hardness, thereby ensuring the palatability of the 3DP gummy tablets. Hardness of marketed gummy tablets was also evaluated and compared, resulting in 49.42 ± 3.26 N (Fig. 6). The same test was employed to determine the stability of the 3DP gummy tablets during packaging. Results of mechanical properties are listed in Table 3. The parameters showed constant values until the first 7 days, after that an increase in hardness, cohesiveness and thus, gumminess, which represents the strength needed to chew the gummy tablets, was observed. This was also evident observing the dosage units that resulted stiffer and less elastic. However, during the 28 days, only a small % of weight reduction, due to the residual water loss, was recorded (3.61 ± 0.99 %).

3.3.7. In vitro drug release

The obtained results (Fig. 7A) showed that, in the case of CTRL an almost complete dissolution of the drug was obtained within 10 min due to the high solubility of AMOX in SGF. It is possible to note that, starting from the sixtieth min, the % of drug in solution decreases and this could be attributed to the instability of AMOX in acidic media related to the

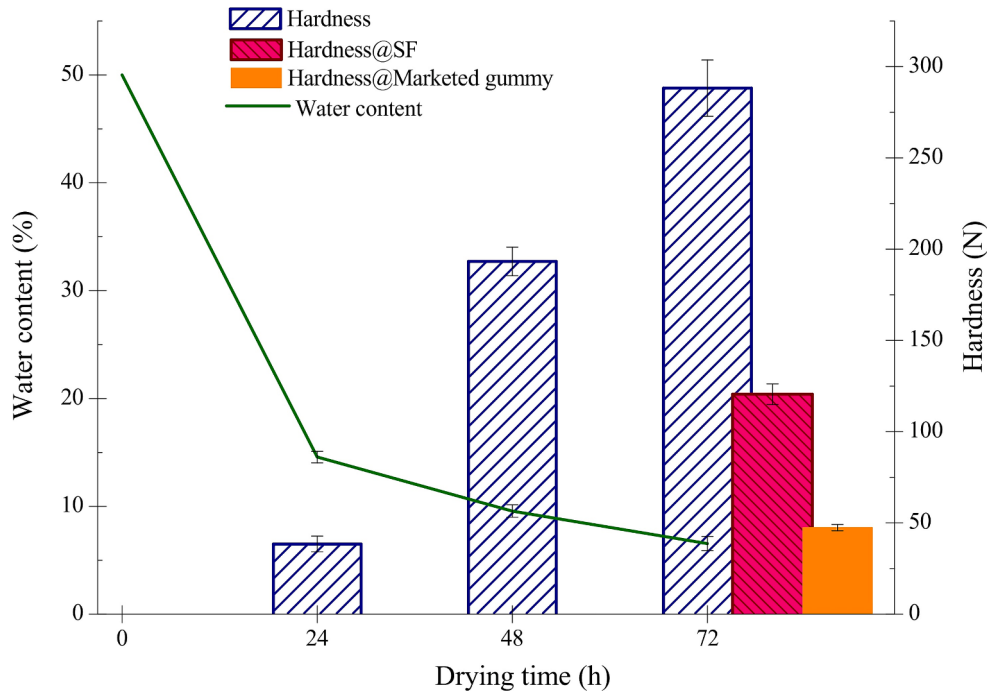


Fig. 6. Trends of hardness of the 3DP gummy tablet compared to water loss during drying under CaCl₂ environment. Hardness at 72 h of drying is also compared to the hardness of the dry 3DP gummy tablet exposed to SSF and to that registered for marketed gummies.

Table 3
Weight loss (%), hardness (N), cohesiveness and gumminess (N) registered for the 3DP gummy tablets under packaging during stability studies. The parameters were also recorded exposing the single units to SF.

TP (days)	Weight loss (%)	Hardness (N)	Hardness @SF (N)	Cohesiveness	Cohesiveness @SF	Gumminess (N)	Gumminess @SF (N)
0	43.45 ± 0.65	288.20 ± 15.43	150.52 ± 5.67	0.63 ± 0.01	0.56 ± 0.02	190.72 ± 7.25	68.13 ± 6.51
1	1.07 ± 0.22	288.87 ± 23.89	174.39 ± 11.90	0.59 ± 0.02	0.51 ± 0.02	170.48 ± 8.59	89.35 ± 9.87
2	2.04 ± 0.66	297.93 ± 12.54	200.92 ± 3.41	0.62 ± 0.01	0.59 ± 0.07	167.98 ± 9.70	117.70 ± 10.87
7	2.12 ± 0.93	300.55 ± 8.43	229.42 ± 9.01	0.59 ± 0.01	0.58 ± 0.01	188.57 ± 8.73	132.22 ± 6.73
14	1.73 ± 0.31	378.64 ± 15.32	275.93 ± 3.63	0.67 ± 0.01	0.68 ± 0.01	245.00 ± 6.95	188.26 ± 3.74
28	2.40 ± 0.37	453.05 ± 10.94	339.41 ± 11.57	0.73 ± 0.04	0.71 ± 0.02	347.76 ± 5.28	241.36 ± 7.14

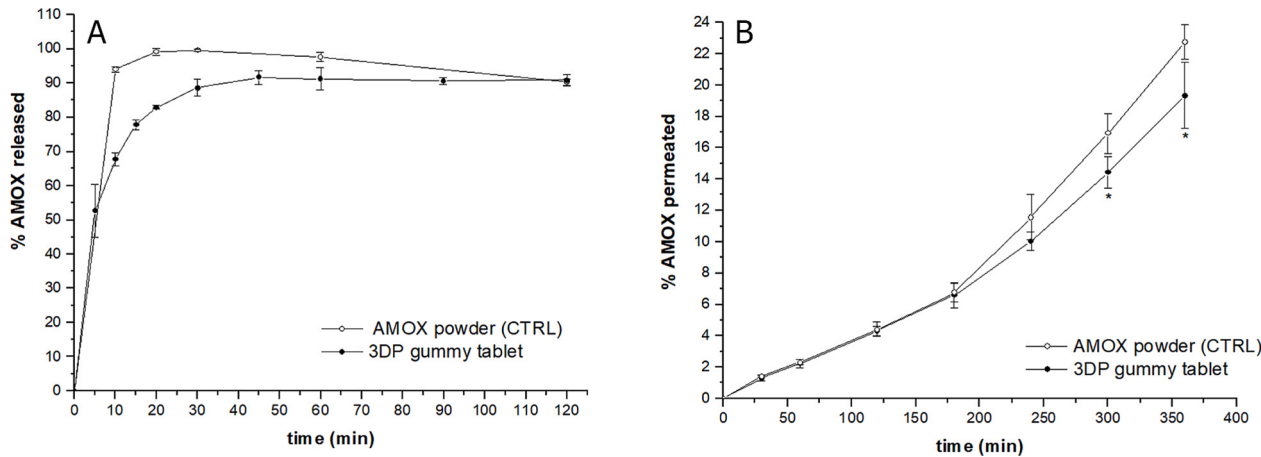


Fig. 7. A) AMOX dissolution profiles obtained both from AMOX powder (CTRL) and the 3DP gummy tablet in SGF pH 1.2. B) AMOX permeation profiles obtained from AMOX powder (CTRL) and the 3DP gummy tablet. Significance indicated by * = $p < 0.05$, compared to the CTRL.

degradation of the drug (Palma et al., 2016). To confirm this hypothesis, AMOX was solubilized in SGF (0.5 mg/mL) and the concentration measured after 120 min using the HPLC method described in section

2.6.10. The obtained results showed that at 120 min, AMOX concentration decreased by 9.62 ± 0.92 % compared to the starting concentration, suggesting AMOX degradation after exposure to the acidic fluid

SGF. In the case of the 3DP gummy tablet, AMOX dissolution appeared slowly and the rate determining step was represented by the drug diffusion from the tablet fragments. After 120 min the maximum AMOX released was approximately 90 % of the total. Moreover, it must be highlighted that, compared to the CTRL, the amount of drug in solution reached a plateau and did not decrease (as CTRL) suggesting that probably the formulation protects the drug from the acidic degradation.

3.3.8. *In vitro* permeability studies

The evaluation of drug permeability represents a key point for oral formulations given that it could predict the absorption of drug in the gastro-intestinal tract and consequently its bioavailability. In this study, PermeaPad® barrier was used as a model membrane for the prediction of AMOX oral absorption (Berben et al., 2018). PermeaPad® barrier was found to be a promising barrier for permeability testing of small molecules and also possesses high robustness against extreme pH values (Jacobsen et al., 2020). Moreover, this model barrier presents several advantages in terms of costs and time efficiency, even if it can only predict passive drug transport. Fig. 7B reports the percentage of the cumulative permeated drug plotted as a function of time for AMOX alone (CTRL) and the 3DP gummy tablet. As can be seen, until 240 min, the permeation profile of CTRL overlapped with that obtained for the gummy tablet ($p > 0.05$) and after 300 min only a slight difference was observed between the values of the two permeation profiles ($p = 0.04$). At the end of the study, the percentage of permeated drug was equal to 22.76 ± 1.12 % and 19.34 ± 2.10 % for the CTRL and the 3DP gummy tablet respectively. Overall, it can be assumed that the developed formulation assured AMOX permeation, with only a minimum variation in comparison with the drug alone.

4. Conclusion

Gummy formulations realized by 3DP technique represent an appreciable oral delivery system for paediatric patients. They show in fact, several desirable characteristics for this category of patients such as appealing, visual appearance, lack of need for swallowing or a reliable water source, and above all customizability. 3DP is a versatile and scalable technique exploitable in the pharmaceutical industry. The presented research detailed the successful development of a child-friendly gummy formulation with a “teddy bear” shape having a final AMOX amount of 200 mg/single dose unit, yellow in colour, visually attractive, and small enough to be easily consumed by the paediatric population. The “ink”, suitable for 3DP, was realized by the combination of CS and acacia honey. The optimized 3DP gummy tablets were subject to a deep characterization to highlight suitable properties and to ensure quality and observation of Pharmacopoeia standards including weight uniformity and drug content. AMOX was homogeneously distributed in the gummy tablets, maintaining its crystalline structure within the matrix as demonstrated by FTIR spectra and PXRD patterns, respectively. *In vitro* dissolution and permeability assays showed a maximum AMOX release of 90 % within 120 min and a promising permeation profile.

In conclusion, the 3DP gummy tablets described in this work can be a strong support for the successful management of AMOX worldwide since they could be useful to accommodate other commonly used antibiotics or drugs to improve healthcare in the paediatric population. The developed “ink” as well as the manufacturing technology employed are very versatile and could be exploited to produce customized formulations, changing the CAD design they could be produced formulations of different shape and dose (changing the final shape of the printed object as well as the amount of starch-gel used for printing), helpful to meet patient needs for the oral delivery of other drugs used in the paediatric field.

CRedit authorship contribution statement

Anna Imbriano: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Costanza Fratini:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Giulia Bondi:** Formal analysis, Data curation. **Ilenia D’Abbrunzo:** Formal analysis, Data curation. **Serena Bertoni:** Writing – review & editing, Formal analysis, Data curation. **Mattia Tiboni:** Writing – review & editing, Formal analysis. **Angela Abruzzo:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition. **Dritan Hasa:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition. **Cinzia Pagano:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Luca Casettari:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Funding

This study is part of the project “3D-printed antibiotic oral dosage forms for paediatric use” [p3Diatrics] under the Project of Relevant National Interest (PRIN 2022) call, funded by Ministero dell’Università e della Ricerca. Project ID: 2022FRNFMT.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijpharm.2025.125645>.

Data availability

Data will be made available on request.

References

- Adeleke, O.A., Abedin, S., 2024. Characterization of prototype gummy formulations provides insight into setting quality standards. *AAPS PharmSciTech.* 25, 155.
- Bialek, A., Krysztofiak, J., Hozakowska, A., Wojszel, Z., Osmalek, T., Wojtylko, M., Froelich, A., 2025. Novel soft dosage forms for paediatric applications: can we 3D-print them or not? *Gels.* 11, 187.
- Berben, P., Bauer-Brandl, A., Brandl, M., Faller, B., Flaten, G.E., Jacobsen, A.-C., Brouwers, J., Augustijns, P., 2018. Drug permeability profiling using cell-free permeation tools: Overview and applications. *Eur. J. Pharm. Sci.* 119, 219–233.
- Bernatoniene, J., Stabrauskienė, J., Kazlauskaitė, J.A., Bernatonyte, U., Kopustinskiene, D.M., 2025. The future of medicine: How 3D printing is transforming pharmaceuticals. *Pharmaceutics.* 17, 390.
- Challener, C., 2023. Overcoming challenges to formulation development for pediatric medicines. *Pharm. Technol.* 47, 20–25.
- FDA, 2018. Quality Attribute Considerations for Chewable Tablets Guidance for Industry. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quality-attribute-considerations-chewable-tablets-guidance-industry> (accessed 3 March 2025).
- Herrada-Manchón, H., Fernández, M.A., Aguilar, E., 2023. Essential guide to hydrogel rheology in extrusion 3D printing: how to measure it and why it matters? *Gels.* 9, 517.
- Holas, C., Chiu, Y.L., Notario, G., Kapral, D., 2005. A pooled analysis of seven randomized crossover studies of the palatability of cefdinir oral suspension versus amoxicillin/clavulanate potassium, cefprozil, azithromycin, and amoxicillin in children aged 4 to 8 years. *Clin. Ther.* 27, 1950–1960.
- Jacobsen, A.C., Nielsen, S., Brandl, M., Bauer-Brandl, A., 2020. Drug permeability profiling using the novel permeapad® 96-well plate. *Pharm. Res.* 37, 93.
- Juárez-Hernández, J.E., Carleton, B.C., 2022. Paediatric oral formulations: Why don’t our kids have the medicines they need? *Br. J. Clin. Pharmacol.* 88, 4337–4348.

- Kean, E.A., Adeleke, O.A., 2023. A child-friendly anti-infective gummy formulation: Design, physicochemical, micromechanical, and taste sensory evaluation. *Drug Deliv. Transl. Res.* 14, 1319–1337.
- Khan, D., Kirby, D., Bryson, S., Shah, M., Mohammed, A.R., 2022. Paediatric specific dosage forms: Patient and formulation considerations. *Int. J. Pharm.* 616, 121501.
- Lopalco, A., Manni, A., Keeley, A., Haider, S., Li, W., Lopodota, A., Altomare, C.D., Denora, N., Tuleu, C., 2022. In vivo investigation of (2-hydroxypropyl)- β -cyclodextrin-based formulation of spironolactone in aqueous solution for paediatric use. *Pharmaceutics*. 14, 780.
- Mahmod, Z., Zulkifli, M.F., Masimen, M.A.A., Ismail, W.I.W., Sharifudin, M.A., Amin, K. A.M., 2025. Investigating the efficacy of gellan gum hydrogel films infused with Acacia stingless bee honey in wound healing. *Int. J. Biol. Macromol.* 296, 139753.
- McCloskey, A.P., Bracken, L., Vasey, N., Ehtezaz, T., 2023. 3D printing – an alternative strategy for pediatric medicines. *Expert Rev. Clin. Pharmacol.* 16, 613–616.
- Mennella, J.A., Spector, A.C., Reed, D.R., Coldwell, S.E., 2013. The bad taste of medicines: overview of basic research on bitter taste. *Clin. Ther.* 35, 1225–1246.
- Malkawi, W.A., AlRafayah, E., AlHazabreh, M., AbulLaila, S., Al-Ghananeem, A.M., 2022. Formulation challenges and strategies to develop pediatric dosage forms. *Children*. 9, 488.
- Moreira, M., Sarraçuca, M., 2020. How can oral paediatric formulations be improved? A challenge for the XXI century. *Int. J. Pharm.* 590, 119905.
- Murugan, M., Ramasamy, S.K., Venkatesan, G., Lee, J., Barathi, S., Kandasamy, S., Sarangi, P.K., 2024. The comprehensive review on 3D printing- pharmaceutical drug delivery and personalized food and nutrition. *Food Chem.* 459, 140348.
- Naiel, B.H., El-Subruiti, G.M., Khalifa, R.E., Eltaweil, A.S., Omer, A.M., 2023. Construction of gastroretentive aminated chitosan coated (sunflower oil /alginate / i-carrageenan) floatable polymeric beads for prolonged release of Amoxicillin trihydrate. *J. Drug Deliv. Sci. Technol.* 84, 104534.
- Osuna, M.B., Michaluk, A., Romero, A.M., Judis, M.A., Bertola, N.C., 2022. Plasticizing effect of *Apis mellifera* honey on whey protein isolate films. *Biopolymers*. 113, e23519.
- Palma, E., Ellison, L., Meza, E., Griko, Y., 2016. Calorimetric evaluation of amoxicillin stability in aqueous solutions. *Mathews J. Pharm. Sci.* 2, 008.
- Pérez Gutiérrez, C.L., Cottone, F., Pagano, C., Di Michele, A., Puglia, D., Luzi, F., Dominici, F., Sinisi, R., Ricci, M., Viseras Iborra, C.A., Perioli, L., 2023. The optimization of pressure-assisted microsyringe (PAM) 3D printing parameters for the development of sustainable starch-based patches. *Polymers*. 15, 3792.
- Perotti, G.F., Tronto, J., Bizeto, M.A., Izumi, C.M.S., Temperini, M.L.A., Luga, A.B., Parra, D.F., Constantino, V.R.L., 2013. Biopolymer-clay nanocomposites: cassava starch and synthetic clay cast films. *J. Braz. Chem. Soc.* 25, 320.
- Qin, W., He, Y., Guo, Z., Zhang, L., Wu, L., Yin, X., Shaky, S., Maharjan, A., Tang, Y., Zhu, W., Zhang, J., 2019. Optimization of taste-masking on ibuprofen microspheres with selected structure features. *Asian J. Pharm. Sci.* 14, 174–182.
- Rampedi, P.N., Ogunrombi, M.O., Adeleke, O.A., 2024. Leading paediatric infectious diseases-current trends, gaps, and future prospects in oral pharmacotherapeutic interventions. *Pharmaceutics*. 16, 712.
- Ranmal, S., Tuleu, C., 2013. Demonstrating evidence of acceptability: the “catch-22” of pediatric formulation development. *Clin. Pharmacol. Ther.* 94, 582–584.
- Rau, D.A., Bortner, M.J., Williams, C.B., 2023. A rheology roadmap for evaluating the printability of material extrusion inks. *Addit. Manuf.* 75, 103745.
- Rodríguez-Pombo, L., Awad, A., Basit, A.W., Alvarez-Lorenzo, C., Goyanes, A., 2022. Innovations in chewable formulations: the novelty and applications of 3D printing in drug product design. *Pharmaceutics*. 14, 1732.
- Salunke, S., Giacoia, G., Tuleu, C., 2012. The STEP (safety and toxicity of excipients for paediatrics) database. Part 1-A need assessment study. *Int. J. Pharm.* 435, 101–111.
- Salunke, S., Brandys, B., Giacoia, G., Tuleu, C., 2013. The STEP (Safety and Toxicity of Excipients for Paediatrics) database: Part 2 – The pilot version. *Int. J. Pharm.* 457, 310–322.
- Santamaría, K.J., Anaya, B.J., Lalatsa, A., González-Barranco, P., Cantú-Cárdenas, L., Serrano, D.R., 2024. Engineering 3D printed gummies loaded with metformin for paediatric use. *Gels*. 10, 620.
- Seoane-Viano, I., Januskaite, P., Alvarez-Lorenzo, C., Basit, A.W., Goyanes, A., 2021. Semi-solid extrusion 3D printing in drug delivery and biomedicine: Personalised solutions for healthcare challenges. *J. Control. Release* 332, 367–389.
- Suzuki, H., Matsubara, D., Nakata, Y., Ito, M., Noguchi, S., 2022. C-H $\cdots$ S hydrogen bonds in ampicillin and amoxicillin crystals investigated by sulfur K-edge X-ray absorption near-edge structure spectroscopy and single-crystal X-ray structure analysis. *Chem. Pharm. Bull. (Tokyo)* 70, c22-00377.
- Synaridou, M.S., Monou, P.K., Zacharis, C.K., Fatouros, D.G., Panderi, I., Markopoulou, C.K., 2021. Amoxicillin chewable tablets intended for pediatric use: formulation development, stability evaluation and taste assessment. *Pharm. Dev. Technol.* 26, 978–988.
- Tegegne, A.M., Ayenew, K.D., Selam, M.N., 2024. Review on recent advance of 3DP-based pediatric drug formulations. *Biomed. Res. Int.* 2024, 4875984.
- Valencia, G.A., Luciano, C.G., Lourenço, R.V., do Amaral Sobral, P.J., 2018. Microstructure and physical properties of nano-biocomposite films based on cassava starch and laponite. *Int. J. Biol. Macromol.* 107, 1576–1583.
- Valverde, S., Ares, A.M., Stephen Elmore, J., Bernal, J., 2022. Recent trends in the analysis of honey constituents. *Food Chem.* 387, 132920.
- Vlachou, M., Siamidi, A., Protapapa, C., Sotiropoulou, I., 2023. A review on the colours, flavours and shapes used in paediatric 3D printed oral solid dosage forms. *RPS Pharm. Pharmacol. Rep.* 2, rqad009.
- Wüpper, S., Lüersen, K., Rimbach, G., 2021. Cyclodextrins, natural compounds, and plant bioactives—a nutritional perspective. *Biomolecules*. 11, 401.