Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: http://ees.elsevier.com

3D printed gummies: Personalized drug dosage in a safe and appealing way

Helena Herrada-Manchón [a,b,*], David Rodríguez-González [a,b], M. Alejandro Fernández [b], Marc Suñé-Pou [c,d], Pilar Pérez-Lozano [c,d], Encarnación García-Montoya [c,d], Enrique Aguilar [a]

[a] Centro de Innovación en Química Avanzada (ORFEO-CINQA), Instituto Universitario de Química Organometálica "Enrique Moles", Departamento de Química Orgánica e Inorgánica, Universidad de Oviedo, C/ Julián Clavería, 8, 33006 Oviedo, Asturias, Spain
[b] Fundación Idonial, Parque Científico y Tecnológico de Gijón, Avda. Jardín Botánico, 1345, 33203 Gijón, Asturias, Spain
[c] Departamento de Farmacia, Tecnología Farmacéutica y Físico Química, Facultad de Farmacia y Ciencias de la Alimentación, Universidad de Barcelona, Avda. Joan XXIII, 27-31, 08028 Barcelona, Spain
[d] IDIBELL-UB Research Group, Pharmacotherapy, Pharmacogenomics and Pharmaceutical Technology, L'Hospitalet de Llobregat, Barcelona, Spain

ARTICLE INFO

Keywords
Personalized medicine
3D printed drugs
3D printed gummies
Medication adherence
Ranitidine hydrochloride

ABSTRACT

Obtention of customized dosage forms is one of the main attractions of 3D printing in pharmaceuticals. In this sense, children are one of the groups within the population with a greater need for drug doses adapted to their requirements (age, weight, pathological state…), but most 3D printed oral dosages are solid forms and, therefore, not suitable for them. This work developed patient-tailored medicinal gummies, an alternative oral dosage form with eye-catching appearance and appropriate organoleptic characteristics. Four inks were formulated, characterised and 3D printed by means of syringe-based extrusion mechanism. Different tests were performed to ensure reproducibility of the process and validate work methodology for dosage unit fabrication applying basic manufacturing standards. Rheological test helped in evaluating inks printability. Visual characterization concluded that drugmies, apart from a high fidelity in the 3D model shape reproduction, had a bright and uniformly coloured appearance and a pleasant aroma, which made them highly appetising and attractive. The printed gummy oral dosages complied comfortably with the mass uniformity assay regardless of the formulated ink used or the 3D model selected for printing. Ranitidine hydrochloride individual contents were determined using uv–vis spectrophotometry, showing successful results both in dose accuracy, uniformity of drug content and dissolution.

1. Introduction

Inter-individual variability, due to both genetic and environmental factors, makes drug response different between patients (Schork, 2015). For this reason, concepts of "patient-specific" or "tailored" dosing are emerging as an alternative to the traditional pharmaceutical industry mass production. In this sense, 3D printing has proved to be a manufacturing technique with great potential since it allows the creation of three-dimensional objects, layer by layer, with total freedom of form and design (Awad et al., 2018; Norman et al., 2017; Trenfield et al., 2018). Thus, dosages adapted to each patient can be printed without incurring additional costs since the easily modification of the infill density or the size of the figure allow the acquisition of the desired drug dose with no need of ink reformulation. Moreover, through these manufacturing technologies, complex custom shapes can be achieved, providing an alternative potential to the release and absorption profiles of drugs (Goyanes et al., 2016, 2015a; Okwuosa et al., 2017; Sadia et al., 2018), as well as pills containing multiple drugs with defined immediate and sustained release profiles (Goyanes et al., 2015b; Khaled et al., 2015a, 2015b).

Just as happens with conventional-manufactured medicines, most of published works on 3D printed medicines respond to solid oral formulations that must be swallowed whole, except for some alternative approaches to chewable doses (Goyanes et al., 2019; Rycerz et al., 2019). Solid oral dosages, although widely accepted by society, are inconvenient for patients with swallowing difficulties or uncooperative, such as children or old people. The lack of will to swallow solid forms is also common in healthy adults, who do not communicate it to doctors, and the treatment ends up failing without considering alternative therapy solutions. In all these cases, compliance and medication adherence are directly affected, contributing to a greater occurrence of medical complications and decreasing patient's quality of life (Barbara Akpanudo, 2014; Beck et al., 2005; Fields et al., 2015).

This work presents a novel option to enhance the complacency and willingness of the end-user costumer to take the medication as planned: patient-tailored medicinal gummies or 'drugmies'; a dosage form

* Corresponding author at: Fundación Idonial, Parque Científico y Tecnológico de Gijón, Avda. Jardín Botánico, 1345, 33203 Gijón, Asturias, Spain.
E-mail address: helena.herrada@idonial.com (H. Herrada-Manchón)

https://doi.org/10.1016/j.ijpharm.2020.119687
Received 30 April 2020; Received in revised form 18 July 2020; Accepted 20 July 2020
Available online xxx
0378-5173/

with eye-catching appearance and appropriate organoleptic characteristics that can improve treatment adherence and reduce psychological impact of the disease, especially in children (Gardiner and Dvorkin, 2006; Lajoinie et al., 2017; Volovitz et al., 2000).

With this aim, new semi-solid drug-loaded inks had been developed and printed through syringe-based extrusion 3D printing, an additive manufacturing technology where a programmed stepper motor moves a plunger with a linear motion and extrusion rate is controlled through motor velocity (Guo et al., 2019). In extrusion 3D printing, rheological properties of the materials chosen as printing inks are considered a key factor in controlling the printability and crucial to create figures with precise geometries. In this sense, it has been widely reported that shear-thinning and thixotropic fluids are highly desirable (Azam et al., 2018; Li et al., 2016; Y. Liu et al., 2019a; Z. Liu et al., 2019b; Yang et al., 2018), as they can be easily extruded through a narrow nozzle and then, rapidly recover the viscosity and mechanical strength necessary to support the next layer extruded.

The formulated thermo-reversible inks combine several hydrocolloids and common gelling agents (Brenner et al., 2015; Liu et al., 2013; Saha and Bhattacharya, 2010) with an Active Pharmaceutical Ingredient (API). In this case, the API selected was ranitidine hydrochloride, an histamine-2 receptor antagonist (H2RA) that inhibits gastric acid secretion, thereby reducing gastric contents volume and increasing intragastric pH (Orenstein et al., 2002; Sandritter, 2003). The drug exhibits polymorphism and has been reported to exist in two crystalline states, named form1 and form 2, although bioavailability and therapeutic efficacy of both forms are equivalent (Chieng et al., 2006; Mirmehrabi et al., 2004). Ranitidine is a first-line treatment for peptic ulcer disease and gastroesophageal reflux disease in children, with a variable dosage depending on the age, weight, and clinical condition of the patient. Some European countries have a specific medicinal product for children, commonly a syrup containing 15 mg/ml of ranitidine (Ameen et al., 2006). In other countries, instead, ranitidine syrup is an officinal formula –a product made in the pharmacy following the pharmacopoeia prescriptions (Nahler, 2017)–, delaying the start of treatment due to its elaboration process. Moreover, dosage of oral liquids has been carried traditionally with calibrated dosing cups, dosing spoons or syringes, which although they are an inexpensive solution, have been associated with human errors that compromise proper dosage and patient safety (Crawford et al., 2018; Ryu and Lee, 2012).

The need of personalize the dose according to the patient and their requirements, the lack of commercial options available and the high rate of human error in dosing, make ranitidine hydrochloride the perfect candidate to show the possibilities of 3D printing technologies as alternative to generate drugmies dosages, and the corresponding validation of this work methodology for dosage unit fabrication applying basic manufacturing standards and studies.

2. Materials and methods.

2.1. Materials.

Ranitidine hydrochloride (CAS no. 66357–59-3), xanthan gum (CAS no.11138–66-2), strawberry essence and purified water (CAS no.7732–18-5) were purchased from Fagron Ibérica SAU, Terrassa, Spain. Gelatin, from porcine skin (CAS no. 9000–70-8) was purchased from Sigma-Aldrich Química S.L., Tres Cantos, Madrid. Carrageenan (Gelification Iota®) was acquired through Guzmán Gastronomía SL, Barcelona, Spain. Corn starch (Maizena®, Unilever España S.A), liquid sweetener (Edulcorante de mesa líquido, Hacendado), food colouring (Colorante alimentario Vahiné®, McCormik España S.A.) and deionized water (Agua desionizada 5L, Auchan Retail España S.L.) were purchased from a local convenience store. Quantitative paper filters (A070603, Prat Dumas, France) used in analytical tests were purchased to Labbox Labware S.L., Vilassar de Dalt, Spain.

2.2. Ink preparation.

Four different thermo-reversible inks were prepared by combining different hydrocolloids and other well-known gelling agents. Compositions differed mainly in the presence or absence of corn starch and ranitidine among all the ingredients (Table 1). Sweeteners and other excipients were used to improve the organoleptic characteristics and palatability of the formula.

Firstly, gelatin was hydrated with purified water and melted in a bath at 40 ± 2 °C. Meanwhile, required amount of ranitidine and corn starch (if needed) were dissolved in purified water and gradually added to a container with the weighed quantity of carrageenan and xanthan gum. Once a homogeneous paste was formed, molten gelatin was added and gently mixed. Finally, strawberry essence, liquid sweetener and food colouring were incorporated to the mix. Slow manual mixing during all the process is highly recommended to avoid air incorporation to the ink.

The formula was left at rest in a bath at 60 ± 2 °C for 60 min, until the bubbles disappeared. Inks containing corn starch were maintained at 70 ± 2 °C for 60 min to enable starch gelatinization. During this time, the container was wrapped with food grade plastic protective film to prevent the water loss.

Printer-compatible syringes (BD 3 ml Syringe Luer-Lok™Tip; Benton, Dickinson and Company, Belgium) were filled while inks remained hot (liquid) and stored in the fridge at 4 °C until use.

2.3. Rheological analysis.

Rheological characterization of ink samples was carried out with a controlled stress rheometer (Discovery HR-2, DHR, TA Instruments, USA) equipped with a parallel plate (25 mm diameter, 1 mm gap) and a controlled convection/radiant heating oven for stable temperature control (Environmental Test Chamber, ETC, TA Instruments, USA).

The formulations were warmed up in a 30 °C bath during 30 min before testing to form a more flowable state that would allow them to be handled without excessively damaging the internal structure of the fluid and preventing air entrapment. A plastic spatula was used to load samples with same amount of ink (0,5ml approximately).

The shear-viscosity tests were conducted in flow ramp mode with the shear rate increasing from 0.01 to 100 1/s within 120 s at temperatures of 23 °C and 37 °C. Thixotropy was measured at 37 °C through a shear recovery tests consisting in 3 different steps: a low shear rate of 0.4 1/s for 120 s, followed by a high shear rate at 100 1/s for 40 s and finally, a low shear rate of 0.4 1/s for 120 s. Structural regeneration

Table 1
Detailed composition of the inks.

	F1	F2	F3	F4
	R(-)CS(+)	R(+)CS(+)	R(-)CS(-)	R(+)CS(-)
Ranitidine HCl (g)	**0**	**1.004**	**0**	**1.004**
Corn starch (g)	**1.500**	**1.500**	**0**	**0**
Carrageenan (g)	0.600	0.600	0.600	0.600
Xanthan gum (g)	0.075	0.075	0.075	0.075
Gelatine (g)	2.400	2.400	2.400	2.400
Liquid sweetener (g)	1.000	1.000	1.000	1.000
Strawberry essence (g)	0.150	0.150	0.150	0.150
Food colouring (g)	0.150	0.150	0.150	0.150
Purified water (to 30 g)	24.125	23.121	25.625	24.621

*In the codes listed for formulation column; R and CS stands for ranitidine hydrochloride and corn starch, respectively.

of inks was determined as the percentage of viscosity obtained during the first 40 s and the 120 s in the third step (after high shear rate), based on the average viscosity obtained in the last 40 s of the first step, where equilibrium viscosity was reached. Linear viscoelastic behaviour was studied using small-amplitude oscillatory shear (SAOS) tests. As a previous step to obtaining the mechanical spectra or frequency sweeps, the linear viscoelastic interval (LVR) was determined by means of amplitude sweeps in a strain interval of 0.1 to 100% and at a fixed frequency of 1 Hz. Frequency sweep analysis were performed at 23 °C and 37 °C, with angular frequency ranging from 0.1 to 10 rad/s at a constant deformation of 0.5% strain (within the linear viscoelastic range, LVR).

In every test, average data of three replicates were used to plot the curves. Results were recorded and processed by a Trios software (Trios Rheology Software, TA Instruments, USA).

2.4. Drug characterization.

2.4.1. Differential scanning calorimetry (DSC).

Samples of pure ranitidine hydrochloride and drug-containing inks (F2 and F4), were thermally analysed using differential scanning calorimeter (DSC). Thermograms were obtained using a DSC822e Differential Scanning Calorimeter (Mettler-Toledo, USA), under a nitrogen gas flow of 50 ml/min. Samples were crimped in an aluminium sample pan and heated at a rate of 3 °C/min and 10 °C/min from 0 to 160 °C.

2.4.2. X-ray diffraction (XRD).

XRD analysis was performed using a X'Pert Pro MPD X-ray diffractometer (PANalytical, UK). The samples of pure ranitidine hydrochloride and drug-loaded inks (F2 and F4) were filled into a zero-background sample holder (ZBH), compressing them to obtain smooth and uniform surfaces. Measurements were carried out from 5 to 50° 2θ, at a constant scanning speed of 0.02°/s.

2.5. 3D printing process.

Drugmies were manufactured using a syringe-based extrusion 3D printer (bIDO-I, Idonial Technological Center, Spain) (Fig. 1). Stereolithography models (.STL files) were downloaded from MakerBot's Thingiverse, an open platform with Creative Commons licensed designs. Three different figures –disk shaped tablet, heart, and gummy bear– were used (Supplementary Data, Fig.S1). Open source slicing software (Slic3r) was employed to convert stereolithography (.stl) format files to .gcode extension files, the printer readable format. The same temperatures (37 ± 2 °C for the printhead and 15 ± 2 °C for the printing bed) and main printing parameters (8 mm/s nozzle moving speed, rectilinear infill pattern and 45° infill angle) were set for all figures except layer height and infill density. Layer height was reduced from 0.50 mm to 0.45 mm for acquiring a greater definition in more complex figures. Furthermore, in order to create two drugmies with same appearance but different final weight, gummy bear 3D model infill density was reduced from 80% to 65% to print some batches. Disk and heart-shaped figures had a fixed 80% infill density value. An extended list of printing parameters is included in Supplementary Data. Stainless steel, blunt end dispenser tips (Fisnar, United Kingdom) with 0.51 mm inner diameter (21G) were used as printing nozzles. Prior to printing process, ink syringes were tempered by introducing them in a 37 °C bath for 30 min. Print head temperature was set up to 37 °C to keep the ink fluid enough to be extruded through the nozzle and correctly draw the paths made by the printer. Print bed temperature was adjusted to 15 °C to ensure ink temperature-induced gelification in situ. A thermographic camera (Optris® PI 230; Optris GmbH, Germany) allowed the visualization of fluid-to-solid inks transition. Flat glass pieces were used as printing support to remove the figures easily from the printing bed, facilitate cleaning tasks and reduce waiting time between printing process.

2.6. Mass uniformity assay of 3D printed gummy oral dosages.

Twenty figures of each 3D model (disk, heart, gummy bear 65% and gummy bear 80%) were printed using the same formula (R(-)CS(+)) and weighed individually using a digital precision balance (FH-200, GRAM, Spain) to test the mass uniformity regardless of the 3D design chosen. Also, mass uniformity independently of the ink used was checked by printing twenty more figures of R(+)CS(+), R(-)CS(-) and R(+)CS(-), each with a different 3D model (heart, gummy bear 80% and gummy bear 65%, respectively). Different and random cartridges (syringes) were chosen within the same batch to print each of the figures. Making an approach to European Pharmacopoeia technical procedures, average mass was determined, and individual mass deviations were checked based on the monograph 'Uniformity of mass of single-dose preparations' (European Directorate for the Quality of Medicines & HealthCare (EDQM), 2013a). In this method, the products failed if greater than 2 of the individual tablet weights deviated by more than 5% from the average weight and, if one tablet weight devi-

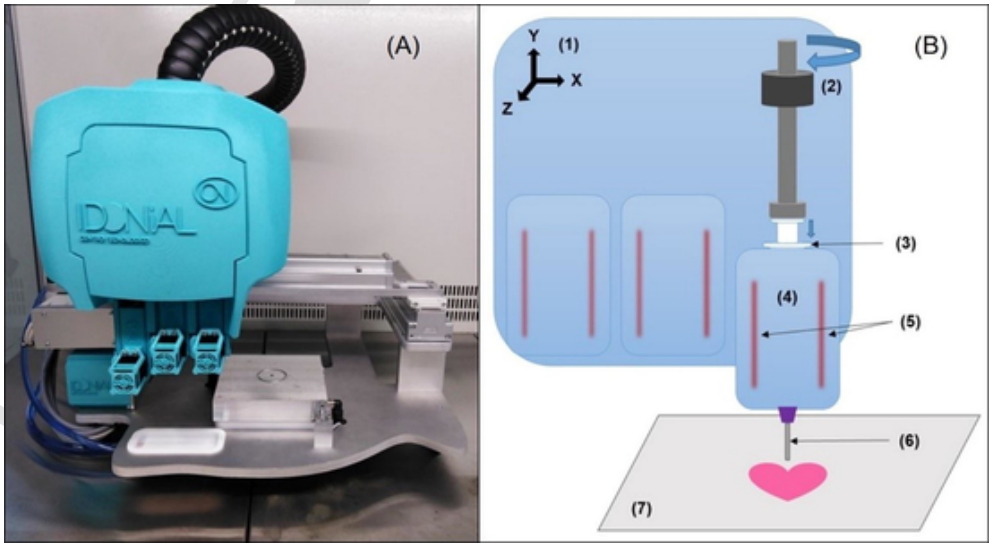

Fig. 1. (A). Photograph of bIDO-I 3D printer. (B). Schematic diagram of bIDO-I 3D printer: (1) Movable print head support (X-Y-Z motion). (2) Syringe-based extrusion unit. (3) Syringe (ink reservoir) and plunger. (4) Individual print head. (5) Print head temperature regulation system. (6) Nozzle. (7) Thermo-regulated print bed.

ated by more than 10% from the average weight. The assay applicable to tablets was chosen as there is no specific one for chewable tablets.

2.7. Visual characterization and handling of drugmies.

The visual appearance of mass uniformity assay printed figures (section 2.6) was analysed to assess the organoleptic characteristics and to check the level of accuracy in the 3D model reproduction and design reproducibility. Handling of gummy dosages was straightforward tested, checking if figures remained undamaged when were removed from the printing bed and if they could be easily manipulated with the hands without leaving any remains that may lead to a loss of dosage drug content.

2.8. Drug content analysis of 3D printed gummy oral dosages.

For ranitidine containing inks ((R(+)CS(+) and R(+)CS(-)), drug individual contents of ten dosage units were determined using uv–vis spectrophotometry (Agilent Cary 60 UV–Vis, Agilent, United States). Food colouring was not included in these batches to ensure a proper quantification. Colorant ʎmax determinations are available in Supplementary Data. Different and random syringes were chosen within the same batch to print each of the figures.

2.8.1. Linearity and calibration curve of ranitidine.

A standard ranitidine stock solution was prepared diluting an accurate amount of 10 mg of ranitidine in 100 ml of deionized water. Seven dilutions (D1-D7) were obtained by transferring different aliquots of 100 μg/ml stock solution to volumetric flasks and diluted to mark with deionized water. One of the dilutions (D6, 16 μg/ml) was scanned between 200 and 400 nm and ʎmax at 313.0 nm was determined, same as reported in bibliography (Moffat et al., 2011). A calibration curve for ranitidine was obtained by measuring the absorbance of D1-D7 dilutions at the ʎmax (Fig.S10). All lectures were carried out in triplicates.

2.8.2. Determination of dosage drug content.

In order to assess the ranitidine content of the drugmies, each unit was weighed and diluted in deionized water in a 500 ml volumetric flask, just after being printed. The flask was kept in a 37 ˚C bath with magnetic stirring (850 rpm) until the gummy dosage was completely dissolved (30 min). Then, a filtered aliquot of 1 ml was diluted in 20 ml of deionized water and measured at ʎmax to determine ranitidine concentration. All lectures were carried out in triplicates.

2.8.3. Evaluation of content uniformity.

Technical procedures of the European Pharmacopoeia were taken as a reference to assess whether the individual ranitidine contents were within limits set with reference to the average content of the printed gummies sample.

Specifically, the Ph. Eur. monograph 'Uniformity of content of single-dose preparations' method was employed to determine the uniformity of content. In this standard, the preparation complies with the test if each individual content is between 85% and 115% of the average content. The preparation fails if more than one individual content is outside these limits or if one individual content is outside the limits of 75% to 125% of the average content (European Directorate for the Quality of Medicines & HealthCare (EDQM), 2013b; Madathilethu et al., 2018). Again, the test suitable to tablets was chosen as chewable tablets do not have a specific one.

2.9. Dissolution testing.

Drug release profiles from printed gummies were determined with a USP-II apparatus (Erweka D700, Germany). The dissolution method from USP monograph for ranitidine tablets (USP 43-NF 38) was used, as no specific assay is established for chewable dosages. For this assay, USP tolerances establish that not less than 80% of the contained amount of ranitidine must be dissolved in 45 min. Each dosage, containing about 30 mg of ranitidine, was placed in a vessel with purified water as the dissolution media (900 ml), maintained at 37˚± 0.5 ˚C with a stirring rate of 50 rpm. Samples were taken at 5, 10, 15, 30, 45, 60, 90 and 120 min; and filtered previous determination of the amount of dissolved ranitidine through uv–vis spectrophotometry (Specord 205, Analytical Jena, Germany). Six dosages of each ranitidine loaded ink ((R(+)CS(+) and R(+)CS(-)) were analysed. Again, food colouring was not included to ensure a proper ranitidine quantification.

3. Results

3.1. Rheological characterization and printability assessment of the inks

For the preparation of drugmies, four inks were formulated and used in different tests to ensure process reproducibility and validate work methodology. Two of them contained ranitidine hydrochloride as active pharmaceutical ingredient and the other two were used as a control to observe how API presence affected inks printability or final printed figure characteristics.

The flow curves (Fig. 2A-B) reflected shear thinning behaviour of the inks, highly convenient for fluids to be extruded through a nozzle. Also, thermo-reversible behaviour was demonstrated since viscosity values fell with temperature increase. Both properties were pursued in the selection of formula components and were quite expected as they are common in gelatin or carrageenan-based gels. Shear recovery tests (Fig. 2C-D) revealed strong thixotropic behaviour of the inks since all the formulas were able to rapidly build up large percentage of their viscosity; which was substantially reduced after the exposure to a high shear rate (100 1/s) during 40 s. A fact of special relevance was that, both in flow curves and in thixotropy tests, F1 (R(-)CS(+)) and F2 (R(+)CS(+)) had almost the same rheological behaviour. In this way, it could be assumed that the corn starch contained in the formula cushioned the effect that ranitidine hydrochloride had on the fluid rheology which, by contrast, was clearly observed in non-starch inks (F3 vs F4). Regarding the SAOS tests, firstly, the amplitude sweeps were used to determine the linear viscoelastic region (LVR) of the different inks and thereby ensure that all the oscillatory tests were carried out without destroying the internal structure of the sample (Supplementary data, Fig. S2). The frequency sweeps (Fig. 2E-F) showed that the inks had viscoelastic properties with a typical weak-gel behaviour, since storage modulus (G') values were higher than loss modulus (G") values, regardless of the formulation chosen or the temperature at which the measurements were made. In parallel, it was observed that the addition of corn starch caused higher storage modulus values, which are related to a better self-supporting ability and higher mechanical strength of the ink (Huang, 2018; Li et al., 2016; Liu et al., 2018).

3.2. Drug characterization

The physical form of ranitidine hydrochloride within the formulated inks was investigated using thermal and diffractometry methods. Thermal analysis (DSC) of ranitidine hydrochloride exhibited a peak at 143–145 ˚C, corresponding to the melting point and confirming the crystalline state of the drug (Chieng et al., 2009, 2006; Ramachandran et al., 2011). In the case of the drug-loaded inks, thermograms with a heating rate of 10 ˚C/min showed overlapped peaks which disap-

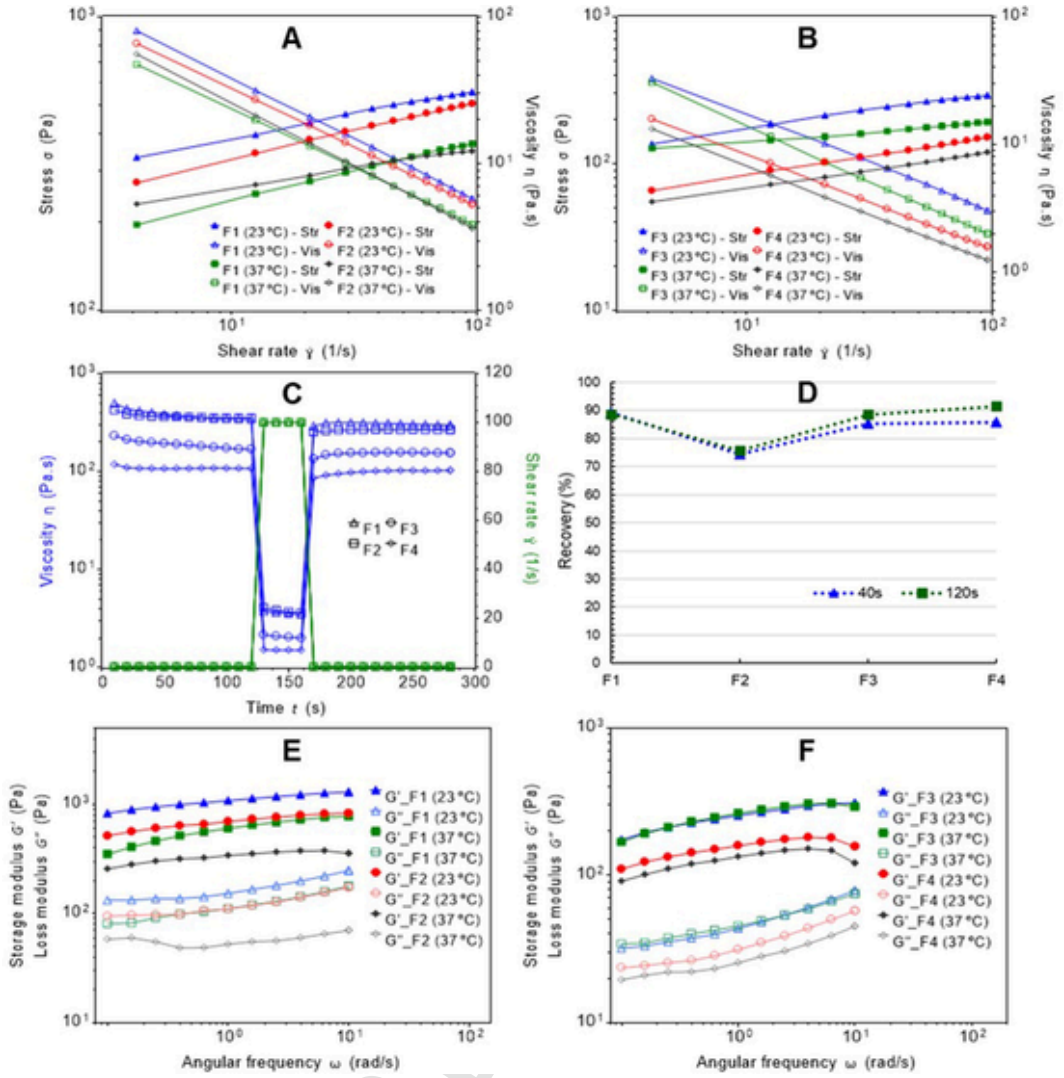

Fig. 2. Rheological tests: (A-B) Shear stress and viscosity profiles (flow curves) for the inks from 0.01 to 100 1/s within 120 s at temperature of 23 °C and 37 °C. (C-D) Shear recovery test for inks thixotropy evaluation and percentage of viscosity recovery of the inks 40 s and 120 s after a high shear rate. (E-F) Storage modulus (G') and loss modulus (G") of different inks conducted at 23 °C and 37 °C.

peared with a slower heating rate (Supplementary data, Fig. S12-S13). In thermograms made at 3 °C/min only a broad endothermic transition was observed around 90 °C (Fig. 3A), probably due to the loss of moisture, suggesting that ranitidine was present as a solid solution or amorphized state within the ink matrix (Kajjari et al., 2011; Palekar et al., 2019). In that way, X-ray diffractograms of pure ranitidine exhibit characteristic intense peaks at $2\theta = 20°$ and 23.5°, also representing the crystalline nature of the drug specifically in form 2. Again, these characteristic peaks were not observed in the formulated inks (Fig. 3B) indicating the conversion of ranitidine to the amorphous form (Chieng et al., 2006; Skowyra et al., 2015).

3.3. Printing process and visual analysis of drugmies.

All the inks could be used to produce different models of 3D printed drug dosages (Supplementary data, Videos V1-V4). Print head and print bed temperature regulation system enabled the management of inks thermo-responsive behaviour, reducing the viscosity by means of a higher temperature in the syringe and a rapid induced gelification in a cold fabrication platform for a solid-state recovery of the ink (Fig. 4). A review of printed figures appearance was made taken different 3D models (disk, heart, gummy bear) and formulas into consideration (Supplementary data, Tables S8-S9). All the gummy oral dosages printed reproduced the 3D models with very high fidelity, as projected and measured sizes were almost equal (Table 2). The visual appearance of the ink was influenced by the presence of corn starch, obtaining a whitish-pastel shade coloured inks, less transparent than the starch-free formulas. Otherwise, the presence of the ranitidine hydrochloride did not vary inks colour. In any case no particles, spots or heterogeneously coloured parts were seen, confirming both the suitability of the formula and its elaboration process.

The printing parameters introduced in the slicing program established the final appearance of the figure, determining points such as the level of detail obtained or the smoothness of the surface. Simpler figures with flat final surface, like heart and disk models, only had a smooth surface finish if the top layer parameter was set to 'solid' —which means that infill density of the layer is 100%—. Solid top layer was not relevant in printed gummy bears, which had a higher level of details in the final layers. Layer height reduction in gummy bear 3D model-derived dosages helped in the acquisition of a greater figure definition. Moreover, drugmies from same 3D model were visually identical to the point that any possible defect or mark derived from the printing process appeared in all figures equally (Supplementary data, Fig. S5-S8). In that way, gummy bear shaped dosages printed with differ-

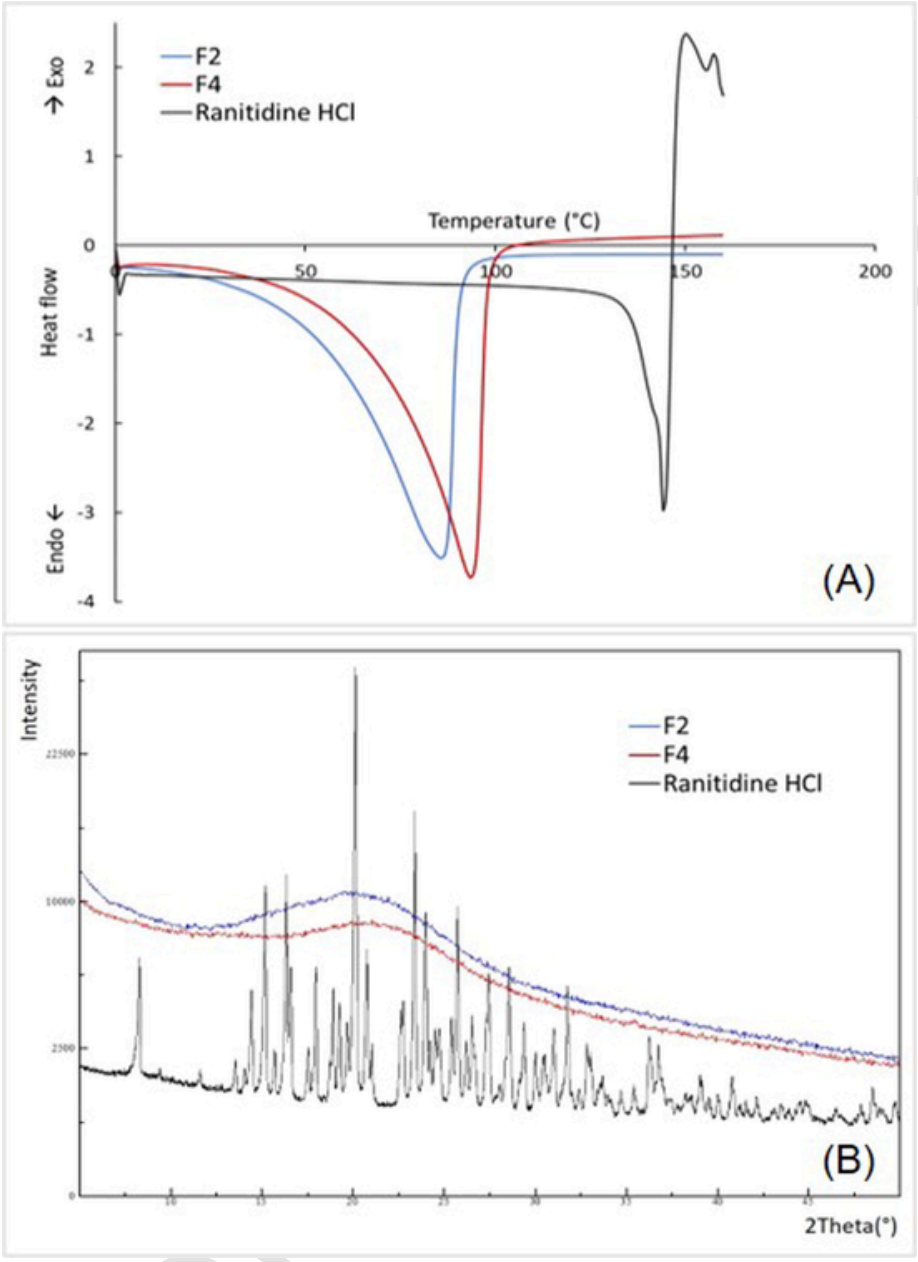

Fig. 3. DSC thermograph (A) and XRD spectra (B) of pure ranitidine hydrochloride and ranitidine-containing inks (F2 and F4).

ent infill density (80% vs 65%) were also difficult to identify at first glance, but instead they differed, as expected, in weight, manipulability and gumminess, which was greater in the denser figure (Supplementary data, Fig. S9 and Videos V5-V8).

Removing figures from the glass printing support without being broken was easy in all the cases, but faster in corn starch derived inks, as was expected because of the higher mechanical strength of this inks revealed in rheological tests. Overall, just a couple of minutes after printing process ended were needed to ensure the complete solidification of the ink throughout the figure. All the drugmies, once cold enough, could be trouble-free handled (Fig. 5).

3.4. Mass and content uniformity of drugmies

Individual weights of every 3D printed gummy dosage were used to calculate upper and lower limit mass values, according to the standard, for each model selected. All the weights fitted the limits and complied with the acceptance criteria, as none of the individual masses deviated from the average mass by more than 5% (Supplementary data, Tables S4-S7). Therefore, mass uniformity of drugmies was acquired regardless of 3D model selected or the formula used (Table 3).

In the same way, drug content and dose accuracy of drugmies printed with the two different ranitidine formulations —R(+)CS(+) and R(+)CS(-)— were determined (Table 4). Dose accuracy represented a successful outcome as values were higher than 90%. Content uniformity of the two batches of ranitidine drugmies widely complied with the standards since the measured content range were, in both cases, within the 85–115% marked by the general monograph. However, it is also necessary to indicate that although all the gummy dosages for this test were printed with same weight (800 mg approximately), theoretical API dose observed varied depending on the ink used. This was due to the fact that a greater amount of water was lost by evaporation during starch gelatinization process of R(+)CS(+) and the resulting formula had a slightly higher ranitidine hydrochlo-

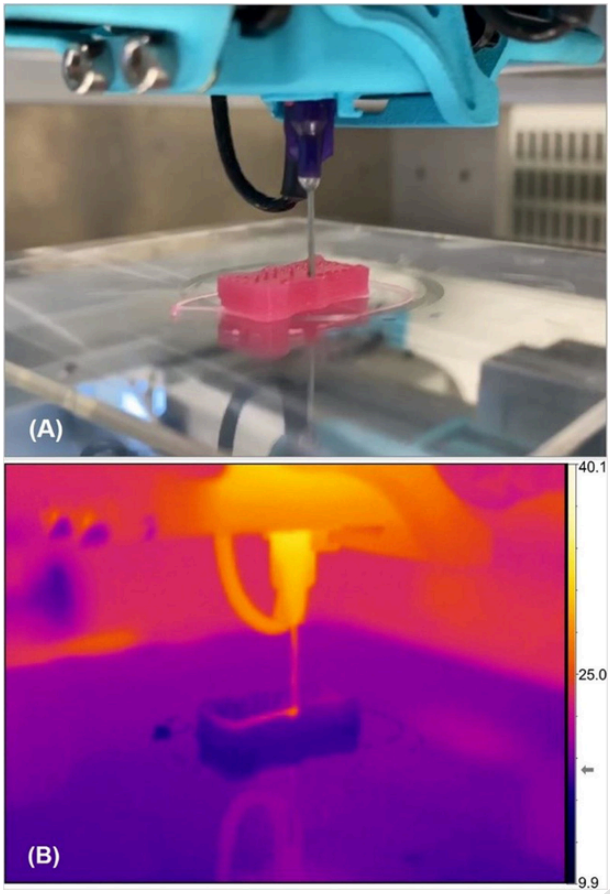

Fig. 4. (A) Printing process of a gummy dosage. (B)Thermographic image of the temperature-induced in situ gelation of the ink.

Table 2
Projected and measured sizes of the different 3D models.

3D Model	Projected size (mm)	Length (mm) ± SD	Width (mm) ± SD	Height (mm) ± SD
Disk	15.0x15.0x4.5	15.01 ± 0.01	15.00 ± 0.00	4.27 ± 0.07
Heart	19.6x16.5x3.0	19.59 ± 0.04	16.45 ± 0.06	2.94 ± 0.07
Gummy Bear (80% infill)	20.8x11.2x7.8	20.56 ± 0.06	10.97 ± 0.05	7.44 ± 0.08
Gummy Bear (65% infill)	20.8x11.2x7.8	20.44 ± 0.08	10.98 ± 0.04	7.42 ± 0.08

ride concentration (Supplementary Data, Tables S12–S14), but uniform in its entirety.

3.5. Dissolution test and drug release profiles.

The dissolution studies are commonly used to simulate in vitro behaviour of the pharmaceutical dosages and to predict its bioavailability and effectiveness. As can be seen in the Fig. 6, although both formulations released practically 100% of their content after 120 min, the resulting dissolution profiles were entirely different. On the one hand, F4 (R(+)CS(-)) released fast the API and concentrations close to 100% after 15 min were obtained, giving place to a more immediate release-like profile. On the other hand, F2 (R(+)CS(+)) showed a more extended-release of ranitidine, achieving only a 60% dissolved after 45 min. Although corn starch is usually employed in pharmaceutical tablet formulations due to the disintegrant properties (Adjei et al., 2017; Hartesi et al., 2016), the gelatinization step during the ink manufacturing process caused the opposite effect. In this case, gelatinized starch formed a more closely packed gel structure that act like a more resistant barrier to drug release, affecting the dissolution profile (Xu et al., 2014). Despite of the fact that F2 would not comply the USP specifications chosen for this work, this extended-release profile could be used as a new approach in designing oral ranitidine sustained forms.

4. Discussion

In this study, we explored the creation of 'drugmies', an alternative pharmaceutical form obtained through extrusion 3D printing that, besides containing a customized dose of active ingredient, had a better acceptance in some more demanding population sectors, such as children. Previous approaches to chewable dosages already demonstrated the importance of the figure design by using varied colours of cylindrical dosages (Goyanes et al., 2019) or either depositing semi-solid inks within a mould filled with a solidifying liquid matrix (Rycerz et al., 2019). In the present work, besides combining different models with greater complexity and more eye-catching form, the final aspect of the dosage has been greatly improved to make it as attractive as possible, not only by the colour, but also by the bright smooth finished surfaces, the gumminess, the manipulability and the touch when handling them.

The 3D printer used had the capability to successfully print different designs introduced with all formulated inks, as it has a precise deposition control and a proper user-friendly operating software. Print head and print bed temperature regulation system enabled the management of inks thermo-responsive behaviour, reducing the viscosity by means of a higher temperature in the syringe and a rapid induced gelification in a cold fabrication platform for a solid-state recovery of the ink. The four suggested formulas resisted the extrusion process without flocculation, phase separation or irreversible rupture of the internal structure of the gel. DSC and XRD suggested that ranitidine hydrochloride exists in amorphous form within the ink matrix. Rheological tests also confirmed the suitability of the inks for the 3D printing technology used, as they showed shear thinning behaviour and a proper viscosity recovery. In this way, the inks that contained starch in its composition turned out to be the most appropriate, having a more rapid restructuring that provides a faster acquisition of the necessary mechanical strength to support the next extruded layer and also, to remove the figure from the printing bed when the printing process is finished. In this type of inks, in addition, the presence of ranitidine hydrochloride and its effect on the behaviour of the ink were cushioned. This finding opens the possibility of studying the use of this formula as a vehicle for the dosage of other active ingredients, which would facilitate the handling of the printer for the end user and would save time to the healthcare staff, because the more suitable printing parameters would be already specified and would not have to be investigated.

Drugmies had creative and eye-catching shapes, and a final appearance that did not differ from that of a conventional fruit gummy. The colour was homogeneous and bright, necessary aspects for a greater acceptance by the patient. On this issue, a non-uniform distribution of it could not only draw the attention from an aesthetic point of view, but also be associated with a lack of content uniformity, a low quality of the dosage or deterioration process. Likewise, no unpleasant odour that could cause rejection or could indicate a chemical alteration of any ink component, with the consequent effects on therapeutics that may appear, was detected.

All the gummy oral dosages reproduced the 3D models with very high fidelity and all the printed figures complied comfortably with the mass and content uniformity assays regardless of the 3D model selected, consolidating the reproducibility of the process for dosage unit fabrication and ensuring the obtention of the planned doses. Thus, ad-

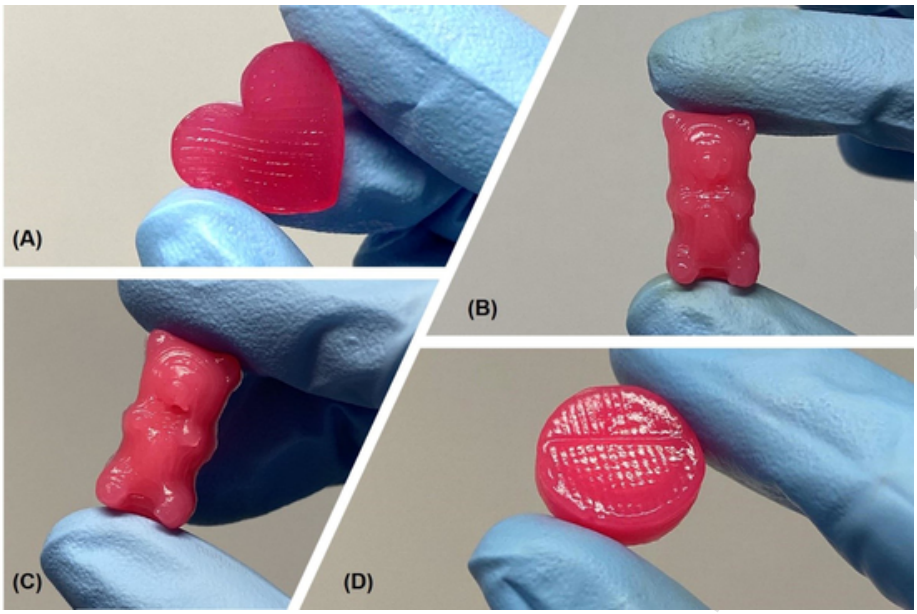

Fig. 5. Trouble-free handling of drugmies printed from different 3D models: (A) heart, (B) gummy bear with 80% infill density, (C) gummy bear with 65% infill density, (D) disk. Figures (B) and (C) have an identical appearance but differ in weight and mechanical strength.

Table 3
Printed dosage weights and mass uniformity compliance limits.

Formula	Model	Mean weight (g) ± SD	Weight compliance limits (g)
F1 - R(-)CS(+)	Disk	0.835 ± 0.004	0.793 – 0.877
	Heart	0.615 ± 0.011	0.584 – 0.646
	Gummy Bear (80% infill)	1.239 ± 0.008	1.177 – 1.301
	Gummy Bear (65% infill)	1.131 ± 0.005	1.075 – 1.188
F2 - R(+)CS(+)	Heart	0.774 ± 0.007	0.735 – 0.812
F3 - R(-)CS(-)	Gummy Bear (80% infill)	1.288 ± 0.004	1.223 – 1.352
F4 - R(+)CS(-)	Gummy Bear (65% infill)	1.126 ± 0.007	1.070 – 1.182

justing ranitidine hydrochloride dose to the patient could be easily done, with safety and reliability, simply by choosing a 3D model and its size —a bigger size, a higher dose— or varying the filling density of the figure, since a reduction in the infill percentage lead to a decrease in figure final weight and therefore, a smaller amount of active ingredient.

Finally, dissolution studies revealed different drug release profiles of the inks derived from the starch content. A faster ranitidine release was obtained in starch-free formulas, while a slower and more extended release was achieved by adding corn starch among the components and allowing its gelification during the formulation process. Thereby, these results could be used to develop a new approach in 3D printed oral sustained forms.

5. Conclusions.

In this work, the use of additive manufacturing by syringe-based extrusion 3D printing for gummy oral dosages was investigated. This novel dosage form exhibited an attractive, funny, and appetising visual appearance in addition to acceptable structural features allowing easy handling and intake. In the context of process repeatability and work method validation for dosage unit fabrication, a preliminary assessment was conducted by applying basic manufacturing standards. Even though the production of this 3D printed oral gummy dosages was an experimental approach, just small weight variations were detected, fitting standards that only well-established tableting technology reproduce. Ability of drugmies to contain a given dose of API and dose uniformity evaluation also reported favourable results. In a clinical setting, this approach will empower healthcare staff with the capability to provide specific dosing by changing the size, infill density or design of the printed figure, avoiding common errors derived from dosing liquid medication. Drugmies could enhance treatment adherence and help to decrease the emotional impact of the disease in children.

Table 4
Drug content accuracy and individual content range of printed dosages.

Formula	Theoretical dose (mg) ± SD	Measured dose (mg) ± SD	Dose accuracy (%) ± SD	Individual content compliance range (%)	Measured individual content range (%)
F2 - R(+)CS(+)	32.18 ± 0.092	32.15 ± 1.19	99.90 ± 3.68	85.00 – 115.00	94.96 – 107.13
F4 - R(+)CS(-)	28.25 ± 0.092	26.24 ± 1.43	92.88 ± 5.11	85.00 – 115.00	88.07 – 106.19

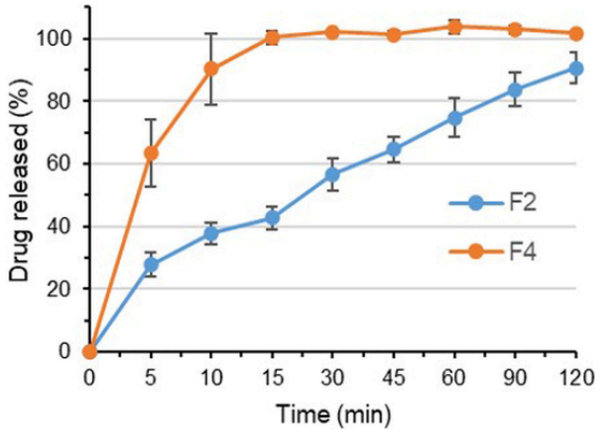

Fig. 6. Drug dissolution profiles of gummy dosages printed with F2 and F4 formulas.

CRediT authorship contribution statement

Helena Herrada-Manchón: Conceptualization, Methodology, Software, Validation, Investigation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **David Rodríguez-González:** Methodology, Investigation. **M. Alejandro Fernández:** Conceptualization, Writing - review & editing, Project administration, Funding acquisition. **Pilar Pérez-Lozano:** Validation, Investigation, Resources, Resources. **Encarnación García-Montoya:** Validation, Investigation, Resources. **Enrique Aguilar:** Conceptualization, Methodology, Resources, Writing - review & editing, Supervision, Funding acquisition.

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.

Acknowledgements

We are grateful to the Ministerio de Economía y Competitividad (MINECO, Spain), AEI and FEDER (CTQ-2016-76794-P, PID2019-107580 GB-100), and Science, Technology and Innovation Plan of Principado de Asturias and FEDER (Programa Asturias-IDI/2018/000060 and GRUPIN-IDI/2018/000231) for financial support.

The authors would like to acknowledge the technical support received by Dr. Ana Belén García-Delgado with Agilent Cary 60 UV-Vis spectrophotometer, Dr. Olvido Iglesias and Prof. Carlos González-Sánchez in rheological tests, and by Servicios Científico-Técnicos of Universidad de Oviedo (in XRD and DSC).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2020.119687.

References

Adjei, F K, Osei, Y A, Kuntworbe, N, Ofori-Kwakye, K, 2017. Evaluation of the Disintegrant Properties of Native Starches of Five New Cassava Varieties in Paracetamol Tablet Formulations. J. Pharm. 2017, 1–9. doi:10.1155/2017/2326912.

Ameen, V Z, Pobiner, B F, Giguere, G C, Carter, E G, 2006. Ranitidine (Zantac®) syrup versus ranitidine effervescent tablets (Zantac® EFFERdose®) in children: A single-center taste preference study. Pediatr. Drugs 8, 265–270. doi:10.2165/00148581-200608040-00005.

Awad, A, Trenfield, S J, Gaisford, S, Basit, A W, 2018. 3D printed medicines: A new branch of digital healthcare. Int. J. Pharm. 548, 586–596. doi:10.1016/j.ijpharm.2018.07.024.

Azam, S M R, Zhang, M, Mujumdar, A S, Yang, C, 2018. Study on 3D printing of orange concentrate and material characteristics. J. Food Process Eng. 41, 1–10. doi:10.1111/jfpe.12689.

Barbara Akpanudo, V S, 2014. "Doc, I Just Can't Swallow Pills": HIV Infected Patients and Pill Phagophobia. J. AIDS Clin. Res. 5. doi:10.4172/2155-6113.1000348.

Beck, M H, Cataldo, M, Slifer, K J, Pulbrook, V, Guhman, J K, 2005. Teaching Children with Attention Deficit Hyperactivity Disorder (ADHD) and Autistic Disorder (AD) How to Swallow Pills. Clin. Pediatr. (Phila) 44, 515–526. doi:10.1177/000992280504400608.

Brenner, T, Tuvikene, R, Fang, Y, Matsukawa, S, Nishinari, K, 2015. Rheology of highly elastic iota-carrageenan/kappa-carrageenan/xanthan/konjac glucomannan gels. Food Hydrocoll. 44, 136–144. doi:10.1016/j.foodhyd.2014.09.016.

Chieng, N, Aaltonen, J, Saville, D, Rades, T, 2009. Physical characterization and stability of amorphous indomethacin and ranitidine hydrochloride binary systems prepared by mechanical activation. Eur. J. Pharm. Biopharm. 71, 47–54. doi:10.1016/j.ejpb.2008.06.022.

Chieng, N, Zujovic, Z, Bowmaker, G, Rades, T, Saville, D, 2006. Effect of milling conditions on the solid-state conversion of ranitidine hydrochloride form 1. Int. J. Pharm. 327, 36–44. doi:10.1016/j.ijpharm.2006.07.032.

Crawford, C, Anderson, M, Cooper, G, Jackson, G, Thompson, J, Vale, A, Thomas, S H L, Eddleston, M, Bateman, D N, 2018. Overdose in young children treated with anti-reflux medications: Poisons enquiry evidence of excess 10-fold dosing errors with ranitidine. Hum. Exp. Toxicol. 37, 343–349. doi:10.1177/0960327117705430.

European Directorate for the Quality of Medicines & HealthCare (EDQM), 2013a. 2.9.5. Uniformity of Mass of Single-Dose Preparations, in: European Pharmacopoeia. 8.0. pp. 297–298.

European Directorate for the Quality of Medicines & HealthCare (EDQM), 2013b. 2.9.6 Uniformity of Content of Single-Dose Preparations, in: European Pharmacopoeia. 8.0. pp. 298–299.

Fields, J, Go, J T, Schulze, K S, 2015. Pill Properties that Cause Dysphagia and Treatment Failure. Curr. Ther. Res. - Clin. Exp. 77, 79–82. doi:10.1016/j.curtheres.2015.08.002.

Gardiner, P, Dvorkin, L, 2006. Promoting medication adherence in children. Am. Fam, Physician, p. 74.

Goyanes, A, Kobayashi, M, Martínez-Pacheco, R, Gaisford, S, Basit, A W, 2016. Fused-filament 3D printing of drug products: Microstructure analysis and drug release characteristics of PVA-based caplets. Int. J. Pharm. 514, 290–295. doi:10.1016/j.ijpharm.2016.06.021.

Goyanes, A, Madla, C M, Umerji, A, Duran Piñeiro, G, Giraldez Montero, J M, Lamas Diaz, M J, Gonzalez Barcia, M, Taherali, F, Sánchez-Pintos, P, Couce, M L, Gaisford, S, Basit, A W, 2019. Automated therapy preparation of isoleucine formulations using 3D printing for the treatment of MSUD: First single-centre, prospective, crossover study in patients. Int. J. Pharm. 567, 118497. doi:10.1016/j.ijpharm.2019.118497.

Goyanes, A, Robles Martinez, P, Buanz, A, Basit, A W, Gaisford, S, 2015. Effect of geometry on drug release from 3D printed tablets. Int. J. Pharm. 494, 657–663. doi:10.1016/j.ijpharm.2015.04.069.

Goyanes, A, Wang, J, Buanz, A, Martínez-Pacheco, R, Telford, R, Gaisford, S, Basit, A W, 2015. 3D Printing of Medicines: Engineering Novel Oral Devices with Unique Design and Drug Release Characteristics. Mol. Pharm. 12, 4077–4084. doi:10.1021/acs.molpharmaceut.5b00510.

Guo, C F, Zhang, M, Bhandari, B, 2019. A comparative study between syringe-based and screw-based 3D food printers by computational simulation. Comput. Electron. Agric. 162, 397–404. doi:10.1016/j.compag.2019.04.032.

B. Hartesi A. Sriwidodo M., Chaerunisaa, A.Y., Starch as pharmaceutical excipient Int. J. Pharm. Sci. Rev. Res. 41 2016 59 64

Huang, C Y, 2018. Extrusion-based 3D Printing and Characterization of Edible Materials. University of Waterloo. doi:10.1016/j.clay.2010.10.028.

Kajjari, P B, Manjeshwar, L S, Aminabhavi, T M, 2011. Semi-Interpenetrating Polymer Network Hydrogel Blend Microspheres of Gelatin and Hydroxyethyl Cellulose for Controlled Release of Theophylline. Ind. Eng. Chem. Res. 50, 7833–7840. doi:10.1021/ie200516k.

Khaled, S A, Burley, J C, Alexander, M R, Yang, J, Roberts, C J, 2015. 3D printing of tablets containing multiple drugs with defined release profiles. Int. J. Pharm. 494, 643–650. doi:10.1016/j.ijpharm.2015.07.067.

Khaled, S A, Burley, J C, Alexander, M R, Yang, J, Roberts, C J, 2015. 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles. J. Control. Release 217, 308–314. doi:10.1016/j.jconrel.2015.09.028.

Lajoinie, A, Janiaud, P, Henin, E, Gleize, J C, Berlion, C, Nguyen, K A, Nony, P, Gueyffier, F, Maucort-Boulch, D, Kassaï Koupaï, B, 2017. Assessing the effects of solid versus liquid dosage forms of oral medications on adherence and acceptability in children. Cochrane Database Syst. Rev. 2017. doi:10.1002/14651858.CD012783.

Li, H, Liu, S, Lin, L, 2016. Rheological study on 3D printability of alginate hydrogel and effect of graphene oxide. Int. J. Bioprinting 2, 10–12. https://doi.org/10.18063/IJB.2016.02.007.

Liu, X, Wang, Y, Yu, L, Tong, Z, Chen, L, Liu, H, Li, X, 2013. Thermal degradation and stability of starch under different processing conditions. Starch/Staerke 65, 48–60. doi:10.1002/star.201200198.

Liu, Y, Yu, Y, Liu, C, Regenstein, J M, Liu, X, Zhou, P, 2019. Rheological and mechanical behavior of milk protein composite gel for extrusion-based 3D food printing. Lwt 102, 338–346. doi:10.1016/j.lwt.2018.12.053.

Liu, Z, Bhandari, B, Prakash, S, Mantihal, S, Zhang, M, 2019. Linking rheology and printability of a multicomponent gel system of carrageenan-xanthan-starch in extrusion based additive manufacturing. Food Hydrocoll. 87, 413–424. doi:10.1016/j.foodhyd.2018.08.026.

Liu, Z, Zhang, M, Bhandari, B, 2018. Effect of gums on the rheological, microstructural and extrusion printing characteristics of mashed potatoes. Int. J. Biol. Macromol. 117, 1179–1187. doi:10.1016/j.ijbiomac.2018.06.048.

Madathilethu, J, Roberts, M, Peak, M, Blair, J, Prescott, R, Ford, J L, 2018. Content uniformity of quartered hydrocortisone tablets in comparison with mini-tablets for paediatric dosing. BMJ Paediatr. Open 2, 1–7. doi:10.1136/bmjpo-2017-000198.

Mirmehrabi, M, Rohani, S, Murthy, K S K, Radatus, B, 2004. Solubility, dissolution rate and phase transition studies of ranitidine hydrochloride tautomeric forms. Int. J. Pharm. 282, 73–85. doi:10.1016/j.ijpharm.2004.05.031.

A.C. Moffat M.D. Osselton B. Widdop Clarke's Analysis of Drugs and Poisons in pharmaceuticals, body fluids and postmortem material Fourth edi. ed. 2011 Pharmaceutical Press London 10.1007/978-94-009-8066-2_9

G. Nahler Dictionary of Pharmaceutical Medicine Fourth. ed 2017 Springer International Publishing, Cham Dictionary of Pharmaceutical Medicine 10.1007/978-3-319-50669-2

Norman, J, Madurawe, R D, Moore, C M V, Khan, M A, Khairuzzaman, A, 2017. A new chapter in pharmaceutical manufacturing: 3D-printed drug products. Adv. Drug Deliv. Rev. 108, 39–50. doi:10.1016/j.addr.2016.03.001.

Okwuosa, T C, Pereira, B C, Arafat, B, Cieszynska, M, Isreb, A, Alhnan, M A, 2017. Fabricating a Shell-Core Delayed Release Tablet Using Dual FDM 3D Printing for Patient-Centred Therapy. Pharm. Res. 34, 427–437. doi:10.1007/s11095-016-2073-3.

S.R. Orenstein J.L. Blumer H.M. Faessel J.A. McGuire K. Fung B.U.K. Li J.E. Lavine J.E. Grunow W.R. Treem A.A. Ciociola Ranitidine, 75 mg, over-the-counter dose: Pharmacokinetic and pharmacodynamic effects in children with symptoms of gastro-oesophageal reflux 2002 Pharmacol. Ther Aliment 10.1046/j.1365-2036.2002.01243.x

Palekar, S, Nukala, P K, Mishra, S M, Kipping, T, Patel, K, 2019. Application of 3D printing technology and quality by design approach for development of age-appropriate pediatric formulation of baclofen. Int. J. Pharm. 556, 106–116. doi:10.1016/j.ijpharm.2018.11.062.

Ramachandran, S, Thirumurugan, G, Dhanaraju, M D, 2011. Development and evaluation of biodegradable chitosan microspheres loaded with ranitidine and cross linked with glutar aldehyde. Am. J. Drug Discov. Dev. 1, 105–120. doi:10.3923/ajdd.2011.105.120.

Rycerz, K, Stepien, K A, Czapiewska, M, Arafat, B T, Habashy, R, Isreb, A, Peak, M, Alhnan, M A, 2019. Embedded 3D Printing of Novel Bespoke Soft Dosage Form Concept for Pediatrics. Pharmaceutics 11, 630. doi:10.3390/pharmaceutics11120630.

Ryu, G S, Lee, Y J, 2012. Analysis of liquid medication dose errors made by patients and caregivers using alternative measuring devices. J. Manag, Care Pharm https://doi.org/10.18553/jmcp.2012.18.6.439.

Sadia, M, Arafat, B, Ahmed, W, Forbes, R T, Alhnan, M A, 2018. Channelled tablets: An innovative approach to accelerating drug release from 3D printed tablets. J. Control. Release 269, 355–363. doi:10.1016/j.jconrel.2017.11.022.

Saha, D, Bhattacharya, S, 2010. Hydrocolloids as thickening and gelling agents in food: A critical review. J. Food Sci. Technol. 47, 587–597. doi:10.1007/s13197-010-0162-6.

Sandritter, T, 2003. Gastroesophageal reflux disease in infants and children. J. Pediatr. Heal. Care 17, 198–205. doi:10.1067/mph.2003.59.

Schork, N J, 2015. Personalized medicine: Time for one-person trials. Nature. doi:10.1038/520609a.

Skowyra, J, Pietrzak, K, Alhnan, M A, 2015. Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing. Eur. J. Pharm. Sci. 68, 11–17. doi:10.1016/j.ejps.2014.11.009.

Trenfield, S J, Awad, A, Goyanes, A, Gaisford, S, Basit, A W, 2018. 3D Printing Pharmaceuticals: Drug Development to Frontline Care. Trends Pharmacol. Sci. 39, 440–451. doi:10.1016/j.tips.2018.02.006.

Volovitz, B, Dueñas-Meza, E, Chmielewska-Szewczyk, D A, Kosa, L, Astafieva, N G, Villaran, C, Pinacho-Daza, C, Laurenzi, M, Jasan, J, Menten, J, Leff, J A, 2000. Comparison of oral montelukast and inhaled cromolyn with respect to preference, satisfaction, and adherence: A multicenter, randomized, open-label, crossover study in children with mild to moderate persistent asthma. Curr. Ther. Res. - Clin. Exp. 61, 490–506. doi:10.1016/S0011-393X(00)80032-6.

Xu, H, Shi, M, liu, Y, Jiang, J, Ma, T, 2014. A Novel In Situ Gel Formulation of Ranitidine for Oral Sustained Delivery. Biomol. Ther. (Seoul) 22, 161–165. doi:10.4062/biomolther.2013.109.

Yang, F, Zhang, M, Bhandari, B, Liu, Y, 2018. Investigation on lemon juice gel as food material for 3D printing and optimization of printing parameters. LWT - Food Sci. Technol. 87, 67–76. doi:10.1016/j.lwt.2017.08.054.