AAPS PharmSciTech (2023) 24:88
https://doi.org/10.1208/s12249-023-02544-5

RESEARCH ARTICLE

Novel Advances in 3-D Printing Technology in Drug Delivery

Development of 3D DLP Printed Sustained Release Ibuprofen Tablets and Their Pharmacokinetic Evaluation in Rats

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Received: 19 December 2022 / Accepted: 26 February 2023 / Published online: 28 March 2023

Abstract

The objective of the present study was to develop digital light processing (DLP) 3D printed sustained release ibuprofen (IBU) tablets using 3D DLP printers for evaluation in *in vitro* release and *in vivo* pharmacokinetic studies with their *in vitro–in vivo* correlation. The resin formulation and printing parameters were optimized using quality by design (QbD) approach, and IBU tablets were printed using DLP printers which works at 385 and 405 nm wavelengths. Our results demonstrated that formulation consisting of polyethylene glycol diacrylate (PEGDA) 700, water, IBU, and riboflavin printed at 40-s bottom layer exposure time and 30-s exposure time produced tablets using both 385 and 405 nm wavelengths. *In vitro* dissolution studies showed > 70% drug release at the end of 24 h when printed at 405 nm wavelength with no significant difference between tablets printed at 385 nm. *In vivo* pharmacokinetic evaluation of the optimized 3D printed tablets printed at 405 nm at oral dose of 30 mg/kg in rats showed sustained release of IBU with significantly ($p < 0.05$) higher C_{max} of 30.12 ± 2.45 µg/mL and $AUC_{(0–24\ h)}$ of 318.97 ± 16.98 (µg/mL × h) compared to marketed IBU tablet (control). *In vivo–in vitro* correlation studies showed 80% of drug was absorbed *in vivo* within 3 h from the pulverized 3D printed tablet, whereas intact 3D tablet showed sustained release of IBU with > 75% IBU release in 24 h *in vitro*. Overall, IBU tablets fabricated using DLP printing demonstrated sustained release and enhanced systemic absorption with no significant difference in their release profile at different wavelengths.

Keywords 3D printing · ibuprofen · oral formulation · pharmacokinetics · tablets

Introduction

Personalized medicine is a concept that refers to making medicine specifically tailored to the needs of each individual patient. This is accomplished by considering each patient's physiological constitution, genetic makeup, and drug response when designing medications. These considerations make personalized medicine the ideal method of administering medications due to the unique biological, physical, and medical conditions of each individual patient [1]. Conventionally, medications are formulated with a one-size-fits-all approach to streamline the manufacturing process and maximize production efficiency. Although producing medications tailored to the needs of each individual person on a large scale was deemed inefficient by manufacturers, the emergence of research surrounding 3D printed pharmaceutical products has the potential to fulfill that role. One of the main advantages of utilizing 3D printing is the level of control over the physicochemical properties of manufactured tablets [2].

Three-dimensional (3D) printing including fused deposition modeling (FDM) and inkjet printing and hot melt extrusion coupled with FDM printing has been reported to develop oral tablets [3–7]. Stereolithography (SLA) and digital light processing (DLP) 3D printing have also demonstrated to be viable methods of fabricating tablets containing active pharmaceutical ingredients (API) with controllable release patterns [8]. Unlike other printing technologies, SLA

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and DLP printing utilizes a UV light source to project a series of two-dimensional (2D) cross-sections onto a liquid photoreactive resin into the desired shape. Parameters such as drug release profiles and mechanical strength can be controlled by altering the components of the resin formulation and printing parameters such as exposure time and light intensity with light-based printing. This method allows for tailorable tablet shapes and multilayered dosage forms which allow for modified release of the drug [8]. Current challenges of this process are limited availability of biocompatible excipients, photoinitiators, and other agents in the resin formulation generally recognized as safe for use in pharmaceutical products. Polyethylene glycol (PEG) is a US FDA-approved excipient utilized in many commercial pharmaceutical formulations. PEGylated compounds such as polyethylene glycol diacrylate (PEGDA) and polyethylene glycol dimethacrylate (PEGDMA) are widely used polymers in DLP printing applications due to their photoreactive functional acrylic groups that crosslink under ultraviolet (UV) irradiation [9]. Photoinitiators such as Ciba® Irgacure and TPO have been used, but these are not currently FDA-approved [10]. Riboflavin (or vitamin B2) is a common material that is biocompatible and water-soluble and can serve as a cost-effective photoinitiator for crosslinking by free-radical polymerization [11].

Current methods to modify the release rate of printed tablets include optimizing the ratio of PEG, PEGDA, and other excipients to control the crosslinking capability of the polymer network [12]. Due to the presence of unreactive PEG, the crosslinking density of the printed tablet is lowered which permits the ease of release of API and increases dissolution rate. Manipulating water and photoinitiator concentrations has also been utilized to control the crosslinking behavior of PEGDA hydrogels. Krkobabic *et al.* studied the effects of different hydrophilic excipients on drug release including NaCl and mannitol which improved the release of drug from DLP printed tablets [13]. Tablet geometry and shape have also been investigated for controllable release rate of paracetamol [14]. Researchers have also observed that geometry itself did not significantly influence the release of API, but the combination of the geometry, surface area, and surface area to volume ratio has the most significant effect on release profile [15]. Several studies have also investigated the effects of increasing the surface area of tablets by creating holes in DLP tablets to facilitate drug release [3]. Importantly, modifying the UV exposure time and intensity can be used to modify gelling behavior by the light source in printing extended-release tablets [16]. Although many investigators have reported the use of 3D printers in developing the tablets, there is only one 3D printed product out in the market (Spritam orodispersible tablet (contains levetiracetam)) [17]. Recently, Triastek, a pharmaceutical company, received FDA approval for T19 and T20 as an investigational new drug (IND) for the treatment of rheumatoid arthritis and cardiovascular and clotting disorders, respectively [18]. Additionally, there are limited reports of pharmacokinetic evaluation of 3D printed tablets and understanding the *in vitro–in vivo* correlation [17]. Therefore, there is a need to further explore the *in vitro* and *in vivo* correlation of 3D printed tablets. In the present study, ibuprofen (IBU) was chosen as the model drug for tablet fabrication. Ibuprofen is a relatively small (molecular weight of 206.28 Da) and lipophilic (log P of 3.48) API [19]. In this study, sustained release oral IBU tablets were fabricated using 3D DLP printing technology by optimizing the excipient concentrations and printing parameters including exposure time and intensity using a quality by design (QbD) approach. Further, the optimized IBU formulation was investigated in *in vitro* release studies and *in vivo* pharmacokinetic studies in rats. Finally, the *in vitro* and *in vivo* results were investigated for their *in vitro–in vivo* correlation using mathematical modeling.

Materials and Methods

Materials

Polyethylene glycol diacrylate (PEGDA) (average MW 700) and riboflavin were obtained from Sigma-Aldrich (St. Louis, MO). Polyethylene glycol (PEG) (average MW 400) was obtained from Fisher Scientific (Waltham, MA). Ibuprofen was obtained from Spectrum Chemical Mfg. Corp (Gardena, CA). UV spotlight was obtained from Agiltron. MicroDLP printer was obtained from Kudo3D (Dublin, CA). Phrozen Sonic 4 k 3D printer was obtained from Orion3D Printers (Temple, TX). The salts used to prepare the release media were purchased from Sigma-Aldrich and Fisher Scientific. TA.XT Plus Texture Analyzer was obtained from Stable Micro Systems (Surrey, UK).

Methods

Formulation of Resin for Tablet Printing

Briefly, riboflavin was dissolved in distilled water. Photopolymer PEGDA was then added to the mixture. Finally, IBU was added to the mixture and vortexed for 3 min until the drug completely solubilized in the resin. It was then centrifuged for 1 min at 1500 rpm to remove the bubbles from the resin.

3D Printing of IBU Tablets at 405 nm Wavelength

Using Fusion 360, a three-dimensional computer-aided design (CAD) model of a tablet with 10 mm in diameter

and 3 mm in thickness was created and saved as a stereolithographic (STL) file. This file was uploaded to a splicing software (Chitubox) where it was separated into multiple layers, each with a thickness of 25 µm, and then saved and uploaded to the Phrozen printer. The tablets were printed with a bottom layer exposure time of 40 s and a 30 s exposure time for the remaining layers. Finished tablets were then sprayed with isopropanol to clear off extra resin (Fig. 1).

3D Printing of IBU Tablets at 385 nm Wavelength

The same CAD model used in the Phrozen printer was used to print tablets on the MicroDLP printer. Kudo 3D software was used to splice the STL file of the tablet. The tablet file was separated into 120 layers each 25 µm thick, and an image of each layer was uploaded to the MicroDLP printer for printing. The same exposure times used on the Phrozen were used with the MicroDLP printer. Although the 3D model was spliced at a thickness of 25 µm, it was printed at a layer difference of 35 µm to ensure the tablets had suitable properties.

Dimensional Accuracy of 3D Printed Tablet

As mentioned before, the STL file of a tablet with 10 mm diameter and 3 mm thickness was imported in the printer software. After the printing process, tablets were sprayed with isopropanol to clear off extra resin. Further, the diameter and thickness of printed tablets were measured using digital caliper and compared with the CAD design of the tablet.

Formulation Optimization of IBU Tablets

Design of Experiment Variables related to the printing process included exposure time (bottom and other layers), and variables related to formulation of the resin including PEGDA concentration, water content, and PEG concentration were selected for the optimization of 3D printed IBU tablets. Pre-formulation studies were performed to determine the upper and lower limits to these parameters to use in the design of experiment (DOE). Box–Behnken design was then applied to the selected variables. Resulting formulations were printed using 385 nm wavelength printer with their respective printing parameters, and the effectiveness of each batch was determined based on the printability of each batch. Batches that did not successfully produce tablets were not analyzed further. Further, DOE batches which resulted in tablet fabrication were selected for IBU tablet fabrication. Batches consisting of 9.1% w/w IBU were then printed using a same 3D printer of 385 nm wavelength. Further, batches which resulted in tablets with no deformation were analyzed for hardness, drug release, and weight variation tests. Finally, the optimized batch which showed higher drug release compared to other batches and passed in hardness, friability, and weight variation test was selected to

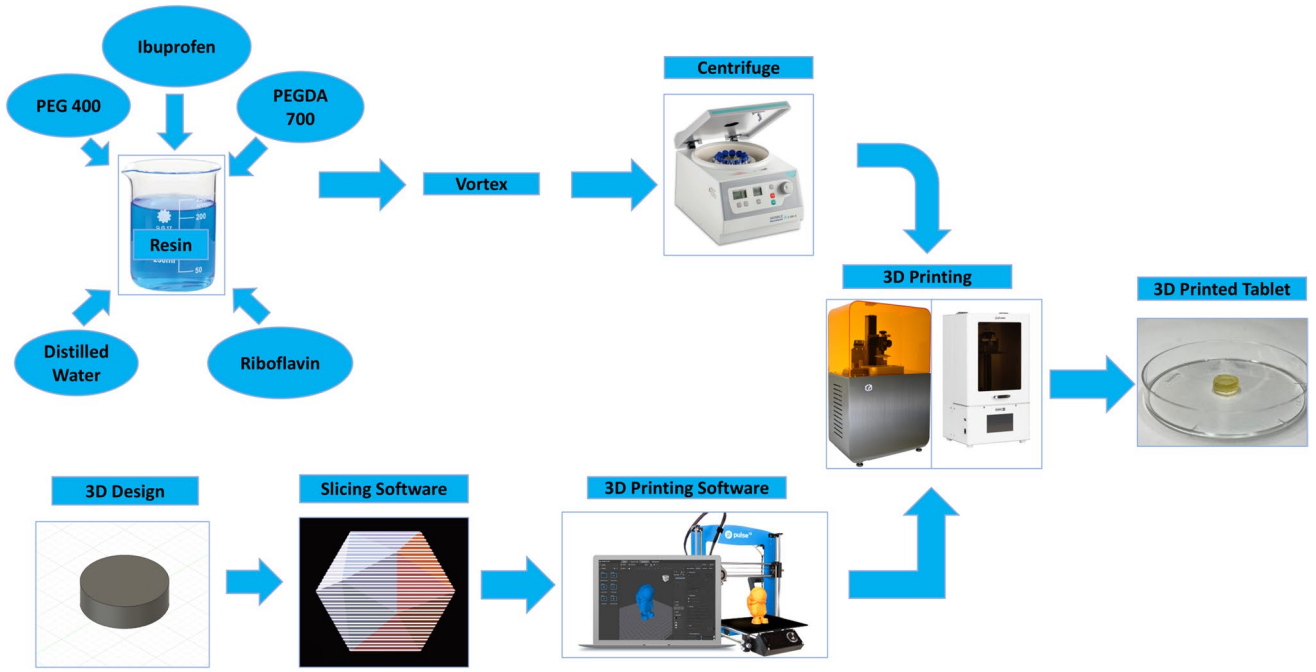

Fig. 1 3D printing steps of IBU tablet showing formulation of resin, creation of tablet design in the software, slicing the design in the slicing software, and importing the STL file in the printing software and finally printing the tablet using 3D printer

print at 405 nm wavelength 3D printer to evaluate the effect of wavelengths on printability, mechanical strength, and *in vitro* release profile of the IBU tablets.

Tablet Hardness Test Using Texture Analyzer Tablet hardness was measured using a TA.XT Plus Texture Analyzer equipped with a 50 kg load cell and the Exponent software. The force–distance profiles were generated based on an 8-inch diameter stainless steel ball point probe used to break the tablets. For each test, the probe migrates towards the sample at a pretest speed of 1 mm/s. Once the probe makes contact with the tablet and the instrument detects a trigger force of 5 g, the probe speed increases to the 2 mm/s test speed. At this point, the instrument begins recording the force with which the tablet is resisting the downward movement of the probe. This speed remains constant until the system senses a 10 kg decrease in force (occurs after the probe breaks through the tablet). The yield point was calculated through the software by identifying the maximum point on the force–time graph populated during the test, representing the maximum force applied to the tablet before it breaks. The elastic modulus was calculated graphically by determining the slope of the graph in the elastic region. A macro was created along with the project that automatically calculated these parameters immediately after each test.

Tablet Friability Test Friability testing was performed as per the US Pharmacopeia guidelines using a CS-2 Tablet Friability Tester [20]. Enough tablets needed to create a total mass of approximately 6.5 g were collected and weighed. Further, the tablets were subjected to 100 rotations at 25 rpm. The tablets were then weighed again, and the percent change in mass was calculated and recorded.

Weight Variation of Tablets To determine the weight variation within the batches of tablets printed, 10 tablets were selected and weighed. Once tablets were weighed, the average mass value was calculated as well as the extent to which each individual tablet varied from the average. The average percent variance and the standard deviation of the variance were also calculated.

Differential Scanning Calorimetry (DSC) Briefly, optimized IBU tablets (batch 10 printed at 405 nm wavelength) were pulverized in a mortar and pestle, and the powder was added in an aluminum pan. IBU API was also collected and placed into a similar container to compare to the tablet sample to observe the effects of polymers and excipients on the drug. A blank sample, and empty aluminum pan, was used as a reference for the samples. Each sample was subjected to increasing heat at 10 ℃/min from 20 to 200 ℃ in the presence of a constant supply of nitrogen gas.

Ibuprofen was characterized using a DSCQ100 calorimeter (TA Instruments, New Castle, DE). Thermal analysis software was utilized to analyze data generated by the DSC test (Universal Analysis 2000, TA Instruments). Tablet samples were obtained by pulverizing tablets in a mortar and pestle and transferring those contents to an aluminum pan. Each sample was subjected to a temperature increase of 10 ℃/min over a range of 20–200 ℃ in the presence of a constant supply of nitrogen.

***In Vitro* Drug Release Kinetics** IBU release from the fabricated 3D tablets was conducted using the Vankel Varian 10–1200 Dissolution System with paddle apparatus. The testing parameters used were based largely on USP standard protocols along with some modifications. One tablet was placed in each of the vessels, each filled with 500 mL of a 6.8 pH release media ($n = 3$). The paddles were set to rotate at 75 rpm, and the vessel was kept at a temperature of 37 ± 0.05 °C. Samples of 250 µL were collected at specified time points (15 min, 30 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 12 h, and 24 h). After each sample was collected, an equal amount of blank release media was added back in order to minimize changes in pH and sink conditions within each vessel. Samples were analyzed for IBU content using HPLC.

HPLC Method All the samples were analyzed for IBU content using Waters e2695 HPLC with a Waters 1525 Binary Pump and 717 Plus Autosampler (Waters Corporation, MA, USA). IBU was analyzed using a mobile phase of 70% acetonitrile and 30% 2.5 pH acidified water at a flow rate of 1 mL min^{-1} with a sample injection volume of 20 µL. Samples eluted from a reverse phase C_{18} column with a retention time of 6.529 ± 0.053 min. Data was observed at the absorption maximum wavelength of 220 nm [21]. Calibration curve was obtained over a range of 2–100 µg/mL and a linear correlation, with a correlation coefficient of 0.9985 was found.

***In Vivo* Pharmacokinetic Characterization** Sprague–Dawley (SD) rats (body weight 250 ± 10 g, Charles River, USA) were housed in cages for a minimum of 3 days prior to beginning of the study and had free access to food and water. Rats were randomly divided into two groups ($n = 3$): optimized 3D printed IBU tablets (batch 10 printed at 405 nm wavelength) and marketed IBU tablets. Further, tablets were triturated and dissolved in distilled water. The rats were fasted for 12 h prior to the experiments, and after 2 h of dosing of formulations, they were given access to food. Thirty mg/kg dose of IBU was given by oral gavage. Serial blood samples (200 µL) were taken

from the tail vein at time points of 1, 2, 4, 8, 18, and 24 h post-dosing. The whole blood was collected into heparin-coated tubes and centrifuged at 4 °C at 12,000 rpm for 5 min to obtain plasma. The plasma samples were kept frozen at − 80 °C until analysis [22, 23]. Analyzed samples were subjected to non-compartmental and compartmental pharmacokinetic analysis using nonlinear regression (GraphPad Prism) and evaluated for an *in vitro–in vivo* correlation using the Wagner–Nelson deconvolution method [24].

Statistical and PK Analysis All raw data results have been expressed as the mean ± standard deviation for at least three repetitions. Two-way analysis of variance (ANOVA) analysis was used for the comparison among multiple groups followed by Tukey's multiple comparison test, whereas Student's *t* test analysis was used for the comparison between two groups. The mean differences were considered significant in all experiments valued at $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$.

Table I Central Composite Design of the Experiment Depicts the Different Experimental Batches with Constant Concentration of 0.01% w/w Riboflavin and Their Corresponding Printing Parameters for the Evaluation of Printability into a Tablet

Batch No	Exposure time (s)	PEG 400 (%w/w)	Water (%w/w)	PEGDA (%w/w)
1	10	0	19.99	80
2	10	58.5	19.99	21.5
3	50	0	19.99	80
4	50	58.5	19.99	21.5
5	10	29.25	9.99	60.75
6	10	29.25	29.99	40.75
7	50	29.25	9.99	60.75
8	50	29.25	29.99	40.75
9	30	0	9.99	90
10	30	0	29.99	70
11	30	58.5	9.99	31.5
12	30	58.5	29.99	11.5
13	30	29.25	19.99	50.75
14	30	29.25	19.99	50.75
15	30	29.25	19.99	50.75

Results

Design of Experiment

The DOE resulted in 15 formulations with different concentrations of materials and printing parameters as shown in Table I. Riboflavin was maintained at 0.01% w/w, and the bottom layer exposure time stayed constant at 40 s. Other constant variables included the use of the same printing file, parameters, and the printer. As mentioned before, all 15 batches were printed using the 3D printer at 385 nm wavelength with blank resins (without IBU). Only batches 3, 6, 7, 8, 10, 11, 13, 14, and 15 printed successfully. Further, 9.1% w/w IBU was added in the resin to each of the previously mentioned batches that passed the first line of evaluations and printed with the same printer at 385 nm wavelength for further analysis (Table II). Our printability results showed that addition of IBU resulted in printing of batches 3, 7, and 10 with no significant difference in the dimensions of tablet design (diameter of 10 mm and thickness of 3 mm). Further, the optimized batch 10 was selected and printed at 405 nm wavelength to assess the effect of wavelength on printing, mechanical properties, and release profile of IBU tablets.

Dimensional Accuracy of 3D Printed Tablet

Batches 3, 7, and 10 printed at 385 nm wavelength showed no difference in the diameter and thickness as compared to the designed tablet CAD file with 10 mm diameter and 3 mm thickness. Optimized batch 10 printed using 405 nm wavelength DLP printer also showed diameter of 10 ± 0.06 mm and thickness of 3 ± 0.03 mm with no significant difference as compared to the designed tablet CAD file (Fig. 2).

Hardness Testing Using Texture Analyzer

Batches 3, 7, and 10 printed using 385 nm wavelength printer were analyzed for hardness testing using texture analyzer. Data showed that batch 7 had the lowest average yield point of 3.50 ± 0.55 kg, followed by batch 10 with 13.90 ± 0.41 kg and batch 3 with 16.13 ± 1.66 kg yield point. The elastic modulus values for batches 3, 7, and 10 were 11,383.686 ± 825.627, 3650.022 ± 410.09, and 11,384.412 ± 386.56 g/mm, respectively. Additionally, the

Table II IBU Resin Formulations 3, 7, and 10 Showing Different Proportions of PEG 400 and PEGDA

Batch	IBU (%w/w)	PEG 400 (%w/w)	Water (%w/w)	Riboflavin (%w/w)	PEGDA (%w/w)
3	9.1	—	18.18	0.01	72.71
7	9.1	26.59	9.1	0.01	55.2
10	9.1	—	27.27	0.01	63.62

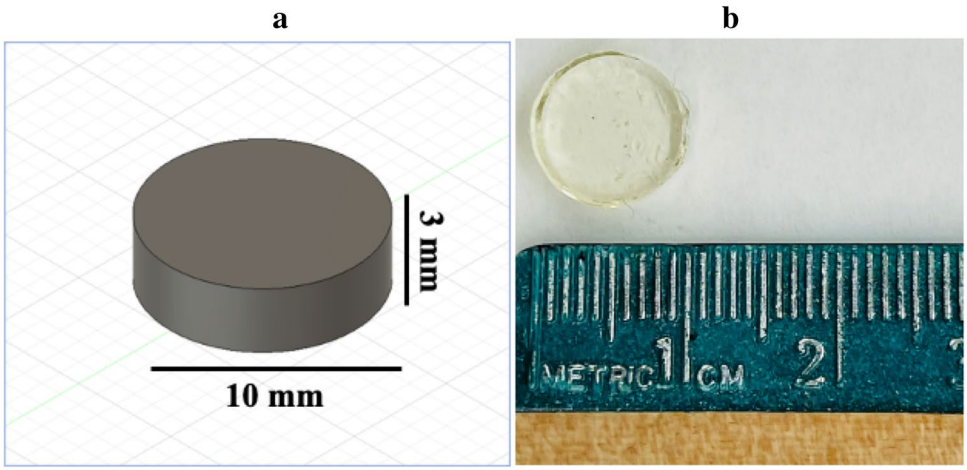

Fig. 2 **a** CAD file of tablet design with 10 mm diameter and 3 mm thickness. **b** 3D DLP printed IBU tablet showing the similar dimensions as CAD file with 10 mm diameter and 3 mm thickness

toughness of batches 3, 7, and 10 were 2240.83 ± 338.6, 325.78 ± 68.83, and 1644.80 ± 64.00 g*mm, respectively. Optimized batch 10 printed using 405 nm wavelength printer showed yield point, elastic modulus, and toughness of 11.87 ± 0.95 kg, 10,567.961 ± 282.12 g/mm, and 1598.12 ± 83.25 g*mm, respectively (Fig. 3).

Weight Variation and Friability Test

According to the USP guideline, tablets pass the weight variation test if the average tablet weight difference before and after the test is in the range of 0–10%. Tablets weight variation test showed that batches 3, 7, and 10 printed at 385 nm wavelength printer exhibited accepted weight variation values of 1.85 ± 1.33, 4.19 ± 2.96, and 1.77 ± 0.99%, respectively, as per the USP guidelines. According to the USP guideline, tablets pass the friability test if the average tablet weight difference before and after the test is in the range of 0–1%. Friability testing conducted on batches 3, 7, and 10 printed at 385 nm wavelength printer resulted in percent change in mass values of 0.97 ± 0.02, 0.69 ± 0.01, and 0.75 ± 0.02%, respectively, which were in the accepted range as per the USP guideline. Finally, the optimized batch 10 printed at 405 nm wavelength passed in all the tablet evaluation parameters including weight variation with 2.02 ± 0.41% average weight change after the test and

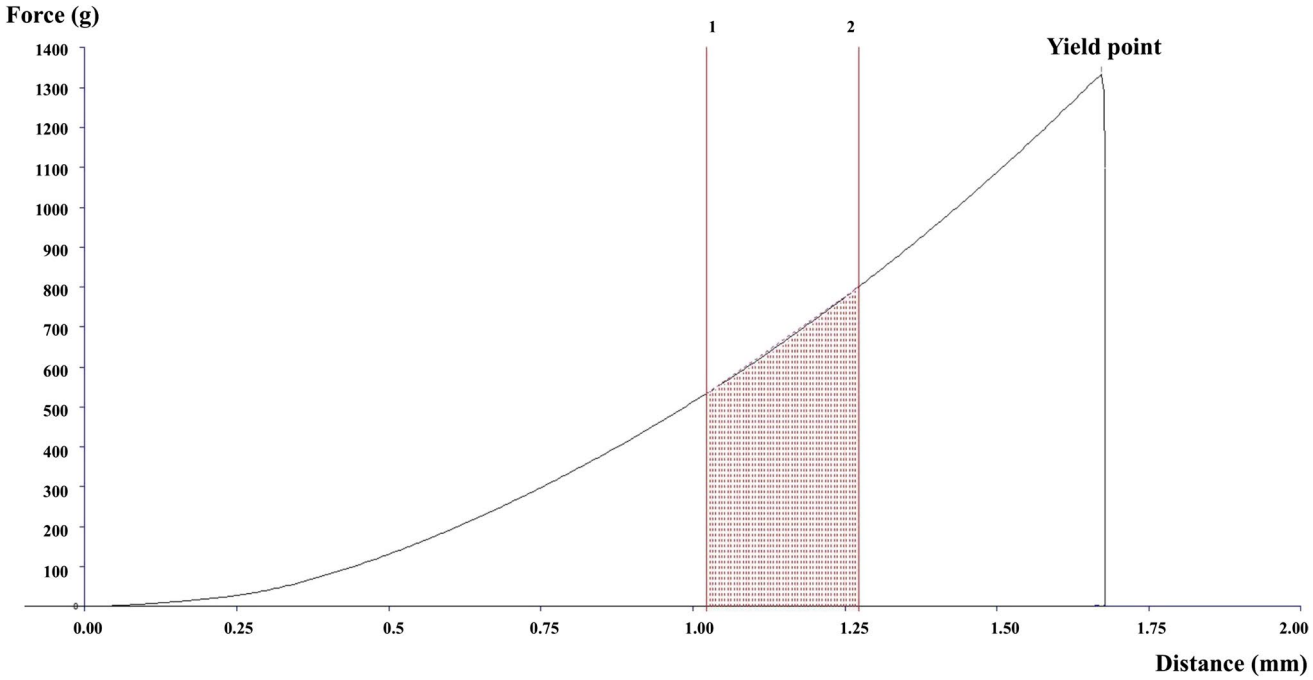

Fig. 3 Hardness test using texture analyzer showing force *vs* distance graph to calculate elastic modulus, yield point, and toughness of a tablet

friability testing with 0.96 ± 0.02% average weight change after the test.

Differential Scanning Calorimetry

Figure 4 compares the DSC thermograms of the IBU API alone to the optimized 3D printed tablet which contains IBU, PEGDA700, riboflavin, and distilled water. The thermogram of the ibuprofen API showed an endothermic peak at 80 °C, indicating its melting point, whereas the thermograph of the 3D printed tablet did not show a peak at the same temperature of the API (Fig. 4).

In Vitro Release Study

The results showed that batches 3, 7, and 10 printed using 385 nm wavelength printer demonstrated release of 18.12 ± 2.56, 30.66 ± 4.78, and 33.04 ± 2.99%, respectively, at the end of 8 h. After 24 h, batch 10 had the highest release of 64.12 ± 1.35% followed by batch 7 with 51.36 ± 1.51% release and batch 3 with 45.53 ± 0.88% (Fig. 5). Batch 10 (printed at 385 nm wavelength) which showed higher drug release compared to batch 3 and 7 was then selected for further studies. Batch 10 was then printed using 405 nm wavelength printer and analyzed for the effect of printing at different wavelength *in vitro* release profile of IBU tablets.

Effect of DLP Printing of IBU Tablets at Different Wavelengths

The drug release profiles were compared on tablets printed at 385 nm and 405 nm wavelengths printers. After 12 h,

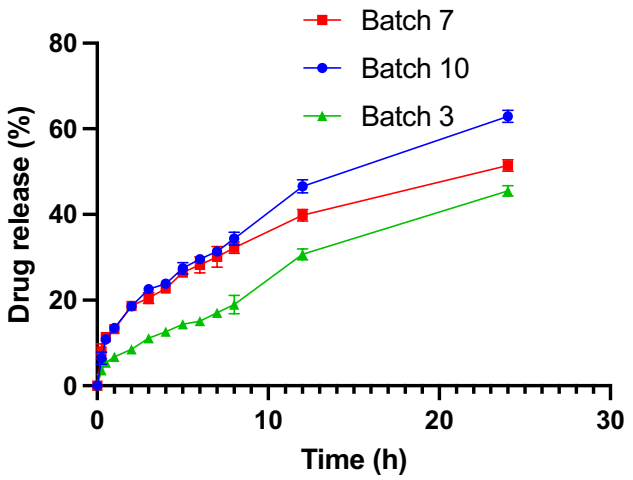

Fig. 5 *In vitro* release study showing more than 60% drug release in pH 6.8 release media from batch 10 (9.1% w/w IBU, 27.27% w/w water, 0.01% w/w riboflavin, 63.62% w/w PEGDA) as compared to 3 (9.1% w/w IBU, 18.18% w/w water, 0.01% w/w riboflavin, 72.71% w/w PEGDA) and 7 (9.1% w/w IBU, 26.59% w/w PEG 400, 9.1% w/w water, 0.01% w/w riboflavin, 55.2% w/w PEGDA) with no significant difference between batch 3 and 7 at the end of 24 h

the 385 nm and 405 nm wavelength printed tablets showed burst release of 45.00 ± 2.25% and 54.00 ± 0.27% of IBU, respectively. Moreover, tablets printed at 405 nm wavelength which showed 79.00 ± 1.15% of drug release was not scientifically high as compared to 385 nm wavelength printed tablets which showed 67.00 ± 3.17% IBU release at the end of 24 h *in vitro* drug release study (Fig. 6). The percent release of ibuprofen was evaluated to determine its mechanism of drug release (i.e., first-order, zero-order, Higuchi

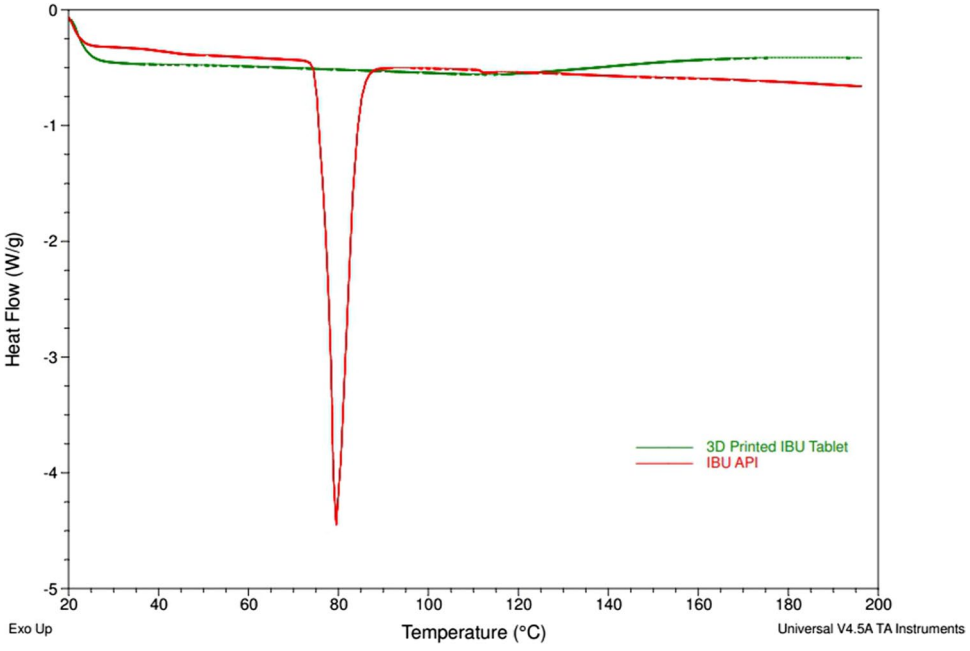

Fig. 4 DSC thermograms of IBU API and 3D printed IBU tablet showing prominent endothermic peak in IBU API thermogram at the melting point temperature and shifting of the endothermic peak in case of 3D printed IBU tablet

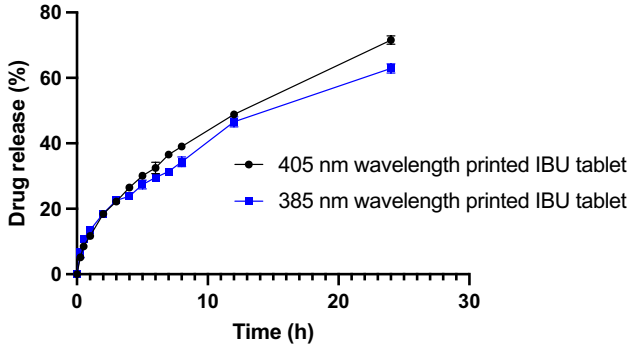

Fig. 6 Effect of different wavelengths used for 3D printing IBU tablets showing no significant difference in percent drug release at the end of 24-h study in *in vitro* dissolution study

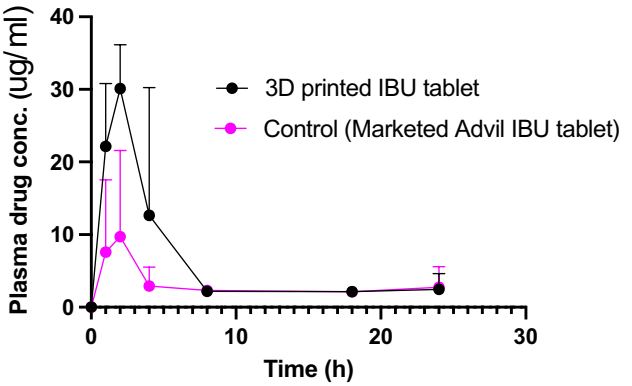

Fig. 7 Plasma drug concentration *vs* time profile in *in vivo* PK study in SD rats after the oral dose of 30 mg/kg showing significant increase in AUC in case of 3D printed IBU tablet as compared to marketed IBU tablet at the end of 24-h study

and Korsmeyer-Peppas models). The curves generated from 405 nm wavelength and 385 nm wavelength printed tablets exhibited a Higuchi release pattern with the R^2 value being equal to 0.999 and 0.9978, respectively (Figs. 1 and 2 in supplementary file).

In Vivo Pharmacokinetic Studies

Animal group consisting of optimized 3D printed IBU tablets printed at 405 nm wavelength showed a peak plasma concentration (C_{max}) of 30.124 µg/mL after 2 h (T_{max}). The rats dosed with the marketed ibuprofen formulation (control) exhibited C_{max} of 9.715 µg/mL after T_{max} of 2 h Additionally, the total AUC for the 3D printed tablet and control groups were 318.97 µg/mL*h and 66.56 µg/mL*h, respectively, and their mean resident times were 15.75 and 12.08 h, respectively (Fig. 7).

In Vitro–In Vivo Correlation (IVIVC)

An analysis of the *in vitro–in vivo* relationship comparing the intact tablet in a dissolution apparatus and the pulverized resin in water formulation yielded the percent absorbed *in vivo* versus the percent released *in vitro*. We observed that 80% of absorption *in vivo* was completed in under 3 h, whereas the intact tablet formulation required 24 h to reach 80% completion and demonstrated the sustained release properties of the 3D printed resin (Fig. 8).

Discussion

Today, various researchers have reported the development of oral 3D tablet formulation due to its potential to revolutionize personalized medicine. Kadry *et al*. studied the fabrication of modified release tablets using DLP printing, Krkobabić *et al.* demonstrated 3D DLP printing of atomoxetine hydrochloride tablets using photoreactive suspensions, Stanojević *et al.* studied tailoring atomoxetine release rate from DLP 3D printed tablets using artificial neural networks, and Tan *et al.* studied fully customizable 3D printed tablets of multiple APIs including paracetamol, phenylephrine hydrochloride, and diphenhydramine hydrochloride [1, 8, 9, 12]. Additionally, 3D LCD tablet printing has also been reported by Madˇzarevi´c *et al.* in which they showed 3D printed tablet at 405 and 450 nm visible wavelengths at different exposure time did not show any significant difference in the drug release profile of the ibuprofen tablet [16]. 3D printing is a new technology in manufacturing of pharmaceutical solid oral dosage forms; as of today, only one 3D printed oral dosage form (Spritam (levetiracetam)) is approved by the FDA. So far, there is limited literature available on the formulation and development of 3D printed tablets with their pharmacokinetic (PK) evaluations and *in vitro–in vivo* correlation [17]. Therefore, there is a need to explore the formulation, pharmacokinetic, and *in vitro–in vivo* correlation aspects of 3D printed oral tablets because of numerous advantages of the 3D printing technology including personalized medication. In the present study, 3D sustained release IBU tablets were formulated and optimized using 3D DLP printers at UV and visible wavelengths with enhanced drug release and were further evaluated in pharmacokinetic studies in rodents with their *in vitro–in vivo* correlation.

One of the main drawbacks of light-based 3D printing methods like DLP and SLA printing is that there are limited materials that can be used to formulate resin. The polymers must possess photoreactive groups which have crosslinking ability when exposed to UV light. That limited selection of materials is further accentuated when formulating pharmaceuticals since biocompatibility is an additional factor to be considered. The first component of the resin is PEGDA 700,

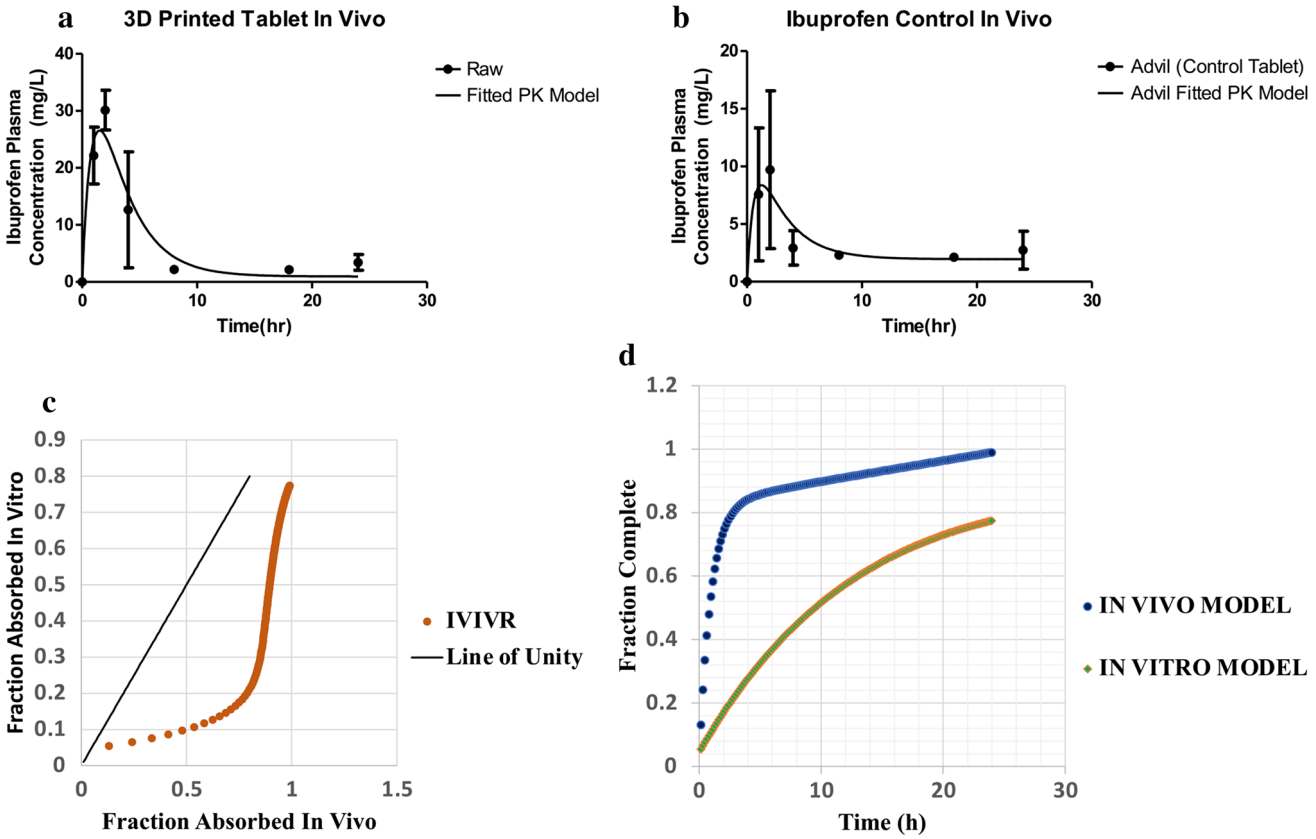

Fig. 8 **a** Nonlinear PK model fit in 3D printed IBU tablet. **b** Nonlinear PK model fit in marketed Advil IBU tablet. **c** *In vitro–in vivo* correlation between 3D printed IBU tablet showing fraction absorbed *in vitro vs in vivo*. **d** *In vitro–in vivo* correlation showing fraction of drug release and absorbed as a function of time

which serves as the photopolymer in this formulation due to its photoreactive acrylic groups that crosslink when exposed to UV radiation. This property of PEGDA led to the widespread use of PEGDA 700 and other PEGylated polymers such as PEGDMA 500 in formulating resins for DLP printing [4]. Riboflavin was used as a photoinitiator in this formulation that creates highly reactive free radicals by converting light energy into chemical energy. These free radicals induce photopolymerization and cause the photopolymers to crosslink. Riboflavin (vitamin B2) was selected because of its cost-effectiveness, water solubility, biocompatibility, and its demonstrated capabilities as a photoinitiator in other works [11]. Water and PEG 400 serve as hydrophilic excipients commonly used in tablet formulations to assist with dissolution and consequently the release of the API in DLP printing. These excipients have also been used in 3D printing of tablets by other investigators including Madˇzarevi ˇ c *et al.* and Madzarevic *et al.* [16]. Water, PEGDA 700, and PEG 400 concentrations and exposure time were selected as the experimental variables for DoE to optimize with constant riboflavin concentration and bottom layer exposure time constant.

Our DOE results showed that batches 3, 7, and 10 were able to crosslink and print IBU tablets with the similar dimension of 10 mm diameter and 3 mm thickness as CAD file using 3D DLP printers. This suggests that exposure time of ≥ 30 s with PEGDA 700 concentration ≥ 60.75% w/w played an important role in printing completely crosslinked IBU tablets with no deformation in the print. These initial printing steps were crucial for determining whether the resin formulation could print a tablet without deformation in shape or size. It has been well reported that photo-crosslinking polymer concentration and exposure time are important parameters to be considered in 3D DLP printing [12, 25]. Madzarevic *et al.* also employed a similar method to test out different combinations of resin ingredients to determine the most optimal resin formulations for printing the tablet [11]. Hardness testing using texture analyzer provided a more accurate assessment of the mechanical strength of the tablet. These results indicated no significant differences in yield point, elasticity, and toughness between the batches 3 and 10. Batch 7, however, had yield point, elasticity, and toughness values that were significantly lower than both batches 3 and 10. This was expected since the batch 7 resin had the

lowest concentration of PEGDA 700 (60.25% w/w) compared to batches 3 and 10 (80% and 70% w/w, respectively). Low photopolymer concentration might have resulted in weaker crosslinking, which also led to low mechanical strength of the tablet. This trend has been demonstrated in other works that have investigated the effects of different components such as photopolymer and various hydrophilic excipients on 3D printed tablet quality [13, 14]. Krkobabić *et al.* who studied the effect of hydrophilic excipients on the internal structure and release profile of the DLP printed paracetamol tablet showed that mannitol concentration significantly affected the tablet printing process. They found that mannitol, although it assisted release of paracetamol at high concentrations, also made it difficult to print. They also found that the addition of NaCl and water had significant improvements in the release of the API at high PEGDA concentrations [13]. Our DSC studies suggested that IBU was completely dissolved into the resin formulation since the endothermic peak seen in the API thermogram was absent in 3D printed IBU tablet thermograms. Similar phenomenon has been observed by other investigators including Fanous *et al.* who showed the absence of the caffeine endothermic peak in the thermogram of 3D printed caffeine tablets [26].

Our *in vitro* dissolution study revealed that the formulation 10 showed significantly ($p < 0.05$) higher drug release at the end of 24 h as compared to formulation 3 in pH 6.8 buffer. This suggests that photo-crosslinking polymer concentration and exposure time also affected the release profile of the tablet which also has been reported in the literature [8]. Moreover, formulation 10 had significantly higher water concentration as compared to formulation 3 which might have led to enhanced drug release. This difference in release profiles is consistent with other studies which observed an increase in the concentration of hydrophilic excipients such as water and PEG400 is directly proportional to increased drug release [13, 15]. It is well reported in the literature that PEG 400 is a highly hydrophilic polymer [27].

Photoinitiated polymerization is a process in which light source activates the photoinitiator (at its λ_{max}) and generates reactive species (free radicals or ions) which then induces polymerization reaction of monomers [28, 29]. Riboflavin has been reported to have two wavelengths: 365–371 (UV region) and 442–444 nm (visible region) at which it shows maximum absorbance [30, 31]. Therefore, formulation 10 optimized using wavelength of 385 nm (UV region) was further investigated at wavelength, 405 nm (visible region), to evaluate if the wavelength affects the printability, mechanical properties, and release profile of the IBU from the 3D printed tablet. Our results showed no significant differences in the yield point, toughness, and elasticity values obtained through texture analysis (formulation 10) of IBU tablet printed at wavelength 405 and 385 nm. Additionally, results of weight variation and release profile did not show any significant differences. Similar results were also observed by Madˇzarevíc *et al.* who studied the effect of different visible wavelengths (405 and 450 nm) on release profile of 3D printed ibuprofen tablet consisting of riboflavin as a photoinitiator [16]. Hence, our studies along with Madˇzarevíc *et al.* give the scientific community an overall understanding of the impact of tablet printing at wavelengths ranging from 385 to 450 which is not currently available.

Further, 405 nm wavelength printed tablets were selected for *in vivo* pharmacokinetic evaluation. Our PK study results showed significant ($p < 0.05$) increase in AUC in the case of 3D printed tablets as compared to commercially available ibuprofen tablets. Moreover, increased IBU absorption indicated that excipients in the formulation, including PEGDA, enhanced solubility of IBU which led to increased IBU absorption into the systemic circulation. Shah *et al.* who studied the pharmacokinetic profile of ibuprofen at different doses in the rats showed C_{max} about 50 µg/mL after 50 mg/kg intravenous dose to the rats [32]. Additionally, in a report by Dewland *et al.* who studied the bioavailability of ibuprofen from different commercially available ibuprofen tablets showed maximum systemic absorption of about 32 µg/mL after a single dose of 2×200 mg of ibuprofen from a standard ibuprofen tablet in healthy human volunteers [33].

Our PK results showed C_{max} of 30 µg/mL after 30 mg/kg oral dose to SD rats. In evaluating an *in vitro–in vivo* correlation, we expected the pulverized resin to demonstrate rapid availability of drug *in vivo* compared to that observed *in vitro*, where the fraction absorbed *in vivo* was dependent on solubility or permeability limitation rather than release from the resin [34, 35]. On the contrary, not only was the resin very successful at solubilizing IBU (which is relatively insoluble in water), but also allowed for sustained release of drug residing within the resin matrix. This result was consistent with Krkobabic *et al.* who demonstrated sustained release of acetaminophen over 8 h from PEGDA-based 3D printed tablets [13]. An *in vitro–in vivo* relationship involving 3D printed tablets has not yet been much reported. Siyawamwaya *et al.* prepared a 3D printed, tritherapeutic tablet matrix for controlled release but dosed the whole tablet in large pigs [36]. We intentionally compared intact tablets *in vitro* to crushed tablets *in vivo* for two reasons: first, crushing the tablet was a practical way of dosing the tablet formulation orally in rats. In addition, this allowed us to explore the extent that sustained release properties would be maintained independent of bulk erosion, i.e., without Higuchi kinetics. We conducted nonlinear regression modeling of our *in vitro* data which revealed that Higuchi release kinetics were also approximated by a combination of concentration-dependent first-order release and pseudo-steady state zero-order release constants (0.071 ± 0.003 h^{-1} and 0.3642 ± 0.082%/h, respectively). This provided mechanistic evidence of sustained release properties which

was also observed through nonlinear regression *in vivo* (Ka = 1.06 ± 0.48 h^{-1} and Ko = 0.3873 ± 1.13 mg/h). Interestingly, the *in vitro* data could only be fit with a zero-order lag-time component of 12.15 h, whereas no lag time was able to be fit with the *in vivo* data. The zero-order lag *in vitro* was consistent with surface release occurring before pore diffusion [37]. This phenomena of first- and zero-order dual release mechanisms has been previously described with biodegradable matrices, where there is a coupling of matrix erosion and pore diffusion mechanisms and contributed to sustained release through 24 h both *in vitro* and *in vivo* [38].

Overall, in this study, IBU resin formulations and its corresponding printing parameters were optimized to print IBU tablets using the 3D DLP printer. IBU tablets printed at different wavelengths did not affect the release profile of the IBU. 3D printed IBU tablets with PEGDA-based resins showed enhanced systemic absorption of IBU as compared to the marketed IBU tablet in an *in vivo* study. An *in vitro–in vivo* relationship evaluation demonstrated that 3D printed resins can provide sustained release properties through 24 h.

Conclusion

In the present study, sustained release IBU tablets were successfully manufactured using DLP printing technology. Drug release was significantly enhanced in 24 h *in vitro* release study by optimizing the excipient concentrations and the printing parameters using QbD approach. Optimized 385 nm wavelength 3D printed IBU tablet containing 27.27% w/w water with no PEG 400 did not show significant difference in the drug release profile as compared 405 nm wavelength printed tablet in *in vitro* release study. Further, the 3D printed tablet showed enhanced systemic IBU absorption as compared to marketed IBU tablets in pharmacokinetic studies with sustained release pattern as suggested in *in vitro–in vivo* correlation study.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1208/s12249-023-02544-5.

Author Contribution Keb Mosley-Kellum: substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work and drafting the work or revising it critically for important intellectual content.

Arvind Bagde: substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work and drafting the work or revising it critically for important intellectual content.

Shawn Spencer: substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work.

Satyanarayan Dev: substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work.

Mandip Singh: final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The authors are thankful to the National Institute on Minority Health and Health Disparities of the National Institutes of Health (grant/award number U54 MD007582) and the NSFCREST Center for Complex Materials Design for Multidimensional Additive Processing (CoManD) (grant/award number:1735968) for providing the funding for this research work.

Data Availability Data will be made available on request.

Declarations

Conflict of Interest The authors declare no competing interests.

Ethics approval The Institutional Animal Care and Use Committee (IACUC) at Florida A&M University, FL approved all animal protocols that were observed in this study (Protocol number: 020-04).

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