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Digital light processing (DLP) 3D printing technique applied in the fabrication of two-layered tablets: the concept of a combined polypill

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Abstract

Ever since 3D printing was introduced to the field of pharmacy, it has caused a paradigm shift from the manufacturing of large-scale to small batches of medicines tailored accordingly to the specific needs of patients. This study aimed to formulate and fabricate two-layered 3D tablets using the digital light processing (DLP) technique. Hydrochlorothiazide (HHT,5%,w/w) and warfarin sodium (WS,5%,w/w) were selected as model drugs. The printing process was initiated with 0.1% of photoinitiator, at a constant ratio of poly(ethylene glycol)diacrylate and poly(ethylene glycol) 400, 1:1, with the addition of water (10%,w/w). Single-layered tablets of 8.00 mm diameter and 1.50 mm thickness, containing HHT and WS respectively, were successfully printed, as well as combined two-layered 3D tablets, with each of the active substances in separate layers. Dissolution tests of single-layered tablets showed immediate, but incomplete release of WS (81.47±1.47%, after 45min), and prolonged and complete release of HHT (98.17±3.11%, after 8h), while significantly slower and incomplete release of both drugs from the combined two-layered 3D tablets was observed. The absence of drug-polymer interaction and presence of a layered cross-sectional tablet structure were confirmed. DLP technique enables simple and rapid fabrication of combined two-layered 3D tablets, while further optimization of formulation factors is necessary to achieve complete drug release.

Key words: DLP technique, hydrochlorothiazide, warfarin sodium, combined two-layered 3D tablets, personalized medicine

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Introduction

Three-dimensional (3D) printing as an additive manufacturing technology has the potential to revolutionize the field of manufacturing by transforming 3D models into reality based on a successive layering mechanism (1, 2). Since its introduction in the drug manufacturing field, 3D printing has captured the attention of the scientific and professional public, contributing to the progressive research of this technology and its potential applicability in the pharmaceutical field, opening the door to completely new approaches, not only in the way drugs are created, used and produced, but also with strong tendencies to make personalized medicine more realistic and approachable (3, 4).

The American Society for Testing and Materials (ASTM) International has classified 3DP technologies into seven main categories: vat polymerization, binder jetting, material jetting, powder bed fusion, extrusion of material, directed energy deposition, and sheet lamination (5). Amid the mentioned technologies, vat photopolymerization provides 3D objects of high resolution without operating with high temperature ranges, which makes it suitable for thermosensitive drugs (2). The focus of this study was on a vat polymerization technique known as digital light processing (DLP) 3D printing. In this technique, a digital micromirror is used to gradually expose and solidify an entire layer of liquid photopolymer solution following a layer-by-layer mechanism. (6, 7). After each successive layer is printed, the build platform is immersed in a tank filled with photopolymer solution, ensuring that each successive layer is cured by the light source and adheres to the previous one, until the process of printing the object is complete. (8). Based on the fact that the layers are formed due to light irradiation, one of the main drawbacks limiting the application of this technique is photosensitivity of the drugs, as well as the confined number of available photocrosslinkable polymers (6, 9). So far, reported studies have confirmed the potential of the DLP technique to provide innovative, non-conventional drug dosage forms (10, 11), as well as small batches of tablets with desirable drug release profiles and flexibile dosing regimens (8, 12), creating an opportunity for the pharmaceutical industry to switch from a “one size fits all” approach to the fabrication of patient-tailored drugs (4, 8, 13).

Over the past few years, researchers have put a lot of effort into developing a new platform that could enable flexible dosing regimens and dosage forms with different drug combinations (14). It has been recognized that 3D printing technologies have the potential to individualize drug therapy by combining multiple drugs into a single dosage form or polypill in a wide variety of shapes, sizes, geometries and other customized features (14, 15). A recently conducted pilot study has shown that the concept of a combined polypill could reduce patient pill burden, which in turn could lead to improved patient adherence and therapeutic outcomes (16). Compared to convetional tablets with fixed drug combinations, which typically contain fixed strengths on a large commercial scale and are therefore unsuitable for therapies that require flexible dose adjustments or drug combination(s), 3D printed tablets combine multiple active substances into a single dosage form with different geometric shapes, and due to the physical separation of the

drugs, it is possible to achieve tunable doses and release profiles for each drug individually, as well as to co-formulate potentially incompatible drugs (14, 17, 18).

To the best of our knowledge, the potential of the DLP 3D printing technique in the manufacturing of polypills has not yet been reported in the literature; therefore, this study aimed to formulate and fabricate two-layered 3D tablets that combine two different drugs, hydrochlorothiazide (HHT) and warfarin sodium (WS) into a single 3D tablet, in order to investigate the pertinence of the DLP 3D printing technique to the concept of a combined polypill. HHT and WS have been chosen as drug candidates due to their common administration in the therapy of cardiovascular diseases (CVD) (19). Moreover, WS belongs to the class of drugs that require dose titration due to its narrow therapeutic index (19), which makes it an ideal candidate for the individualization of therapy.

Experimental part

Materials

Poly (ethylene glycol) diacrylate (PEGDA, average MW 700) was obtained from Sigma-Aldrich, Tokyo, Japan. Poly (ethylene glycol) (PEG 400, average MW 400) was purchased from Fagron B.V., Rotterdam, The Netherlands. Hydrochlorothiazide (HHT, MW 297.7) and warfarin sodium (WS, MW 330.3) were kindly donated by Galenika AD, Belgrade, Serbia. Diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide (DPPO) was obtained from Sigma-Aldrich, Steinheim, Germany.

Methods

Preparation of Photopolymer Solutions

HHT and WS were chosen as model drug substances commonly used together in the treatment of CVD. PEGDA was used as a photopolymerizing monomer, which in the presence of a low amount photoinitiator (DPPO) forms a polymeric matrix of printed tablets. PEG 400 was added to improve drug release and as a co-solvent for the drugs. Purified water was used as a vehicle for drug substances.

Two formulations of the same quantitative composition were prepared (Table I). PEGDA and PEG 400 were maintained at a constant 1:1 (w/w) ratio, with the addition of 10% (w/w) of water. HHT or WS was then added to the solution at a concentration of 5% (w/w), while DPPO (0.1%, w/w) was added at the very end. The solution was thoroughly mixed until complete dissolution of the drug was achieved, and transferred into the printer.

Table I Composition (%, w/w) of photopolymer solutions

Tabela I Sastav (%, m/m) fotopolimernih rastvora

Formulation / Substance	CF	
	F1	**F2**
HHT	5.00	-
WS	-	5.00
PEGDA	42.45	42.45
PEG 400	42.45	42.45
DPPO	0.10	0.10
Water	10.00	10.00

3D Printing of Tablets

A cylindrical-shape 3D model of tablets, with a diameter of 8.00 mm and thickness of 1.50 mm, was created in the Autodesk fusion software version 2.0.8809 (Autodesk Inc, San Rafael, CA, USA) and exported as a stereolithography file (.stl) into the 3D printer software (Chitubox, version 1.7.0). A Wanhao Duplicator 8 printer (Wanhao, Zhejiang, China) equipped with a 405 nm UV lamp was used for tablet printing. First, 3D tablets were printed from individual formulations – HHT tablets, formulation F1 and WS tablets, formulation F2 (hereinafter referred to as single-layered tablets), while combined two-layered 3D tablets were fabricated from both formulations separately, in a two-step printing process. The single-layered WS tablet was printed on the top of the previously printed single-layered HHT tablet, using the same 3D printing file. Formulation F1, in the resin tank, was easily replaced by formulation F2, the build platform was restored to its previous position and the printing process restarted.

Preliminary experiments were carried out in order to optimize the process and establish printing parameters that enabled fast and effective fabrication of 3D tablets. Based on these results, all tablets were printed with the parameters shown in Table II.

Table II Parameters of printing process

Tabela II Parametri procesa štampanja

Parameter	Value
Layer height	0.1 mm
Bottom layer count	5
Exposure time	40 s
Bottom exposure time	40 s
Bottom lift distance	5 mm
Lifting distance	5 mm
Bottom lift speed	60 mm/min
Lifting speed	60 mm/min
Retract speed	150 mm/min

Mass and Dimension Variation

After being removed from the build platform, the printed tablets were washed with 2-propanol and wiped with a tissue to eliminate uncured liquid from the surface. 3D tablets were then weighed on an analytical balance (Kern & Sohn, Germany) and measured (length/diameter and thickness) using a digital caliper (Vogel Germany GmbH & Co. KG, Kevelaer, Germany). Measurements were performed on 10 tablets.

Determination of Drug Content

UV/VIS spectrophotometry (Evolution 300, Thermo Fisher Scientific, Waltham, MA, USA) was used to determine the drug content, at a wavelength of 273 nm (corresponding to the highest molar absorbance of HHT) and 307 nm (corresponding to the highest molar absorbance of WS). For standard preparation, 10 mg of HHT or WS was dissolved in 10 mL of absolute ethanol, shaken in an ultrasonic bath Bandelin-Sonorex RK102H (Sonorex-Bandelin, Berlin, Germany) for 15 min at room temperature, cooled and then filtered through 0.45 μm filters (Millipore, Bedford, MA, USA). Adequate dilution of the prepared standard solutions in distilled water was provided. For determination of drug loading in the combined two-layered 3D tablets, single drug-loaded layers (i.e., single-layered tablets) were crushed (n = 3), according to the methodology of Xu et al. (2020). The mass of each sample equivalent to an average mass of a single-layered tablet was weighed and dissolved in a volumetric flask with 10 mL of absolute ethanol and shaken in an ultrasonic bath for 15 min. Samples then underwent the same procedure as described for standard preparation. The analysis was performed in triplicate, while the obtained drug content was calculated as a percentage of the theoretical drug content with standard deviation (SD).

In Vitro Drug Release Testing

Dissolution profiles were obtained using a mini-paddle USP-II Erweka DT 600 (Erweka, Langen, Germany) apparatus. 3D tablets (n = 2) were placed in 250 mL of distilled water for 8 h. The rotation speed of the paddles was set to 50 rpm, and the tests were carried out at 37 ± 0.5 °C. Aliquots (4 mL) were withdrawn at time intervals of 15, 30, 45, 60, 120, 180, 240, 300, 360, 420 and 480 minutes, and immediately replaced with the same amount of fresh medium. All samples were filtered through 0.45 μm filters, and the released amounts of HHT and WS were determined by HPLC method using a Dionex Ultimate 3000 (Thermo Scientific, USA) HPLC system. Analyses were conducted under the following experimental conditions: C18 column (250 × 4.6 mm, 5 μm), mobile phase consisting of 50:50 (v/v) mixture of 0.1% (v/v) phosphoric acid in water and acetonitrile, at a flow rate of 1.2 ml/min, an injection volume of 20 μl, a detection wavelength of 215 nm, and a column temperature of 30 °C. All experiments were performed in duplicate.

Differential Scanning Calorimetry (DSC)

DSC was carried out on a DSC 1 instrument (Mettler Toledo, Giessen, Germany). Pure active substances and pulverized single-layered tablets were precisely weighed (5–

7 mg), placed in aluminum pans and subjected to heating at 10 °C/min in the range from 0 to 250 °C (WS) and 0 to 350 °C (HHT), under constant nitrogen gas flow of 50 mL/min. An empty aluminum pan was used as a reference. STARe software (version 12.10, Mettler, Toledo) was used to analyze the acquired data. DSC analysis was conducted to investigate the physical properties of HHT and WS within the printed 3D tablets.

Polarized light microscopy

The internal structure of both single-layered and combined two-layered 3D tablets, before and after dissolution testing, was visually examined by an Olympus BX53-P polarized microscope (Olympus, Tokyo, Japan) with UPLFLN4XP and UPLFLN10XP objectives. Images were taken by the cellSens Entry Version 1.14 software (Olympus, Tokyo, Japan).

Fourier-Transform Infrared Spectroscopy (FTIR)

The assessment of potential drug-polymer interactions was performed by FTIR spectroscopy. Analyses of thoroughly pulverized single-layered 3D tablets and pure materials, as references, were conducted with a Nicolet iS10 (Thermo Scientific,Waltham, MA, USA) FTIR spectrometer, equipped with a single reflection ATR system (Smart iTR, Thermo Scientific, Waltham, MA, USA) with a diamond plate and ZnSe lens. The spectra were recorded from 4 000 to 650 cm^{-1}, using a resolution of 2 cm^{-1}.

Results and Discussion

Cylindrical single-layered and combined two-layered 3D tablets of constant diameter and thickness were successfully printed with a DLP 3D printer (Figure 1). In about 10 minutes, 15 objects were printed at once, confirming the fact that the DLP 3D printing technique offers a simple and fast way to produce small batches of tablets at room temperature (8, 10, 12, 20). 3D tablets with a fine surface and the same color as the initial photopolymer solution were obtained (Figure 1).

The measured weight, diameter and thickness of 3D tablets are shown in Table III. All tablets were uniform in dimensions, while the combined two-layered 3D tablets showed the greatest variations in dimensions and mass. Such results may be explained by the fact that the printing process was conducted in two steps, meaning that the previously printed layer of HHT tablets was used as a bottom base for the layer of WS tablets, which might have caused additional solidification around the initially created 3D model and resulted in the expansion of the diameter. Robles-Martinez et al. (2019) reported similar results, where multi-layered cylindrical polypills containing six-different drugs obtained by the vat photopolymerization 3D printing technique showed greater variations in real dimensions compared to the targeted ones (14). The percentage of obtained drug content in single-layered HHT tablets was lower (82.63 ± 0.19) compared to drug content in single-layered WS tablets (107.32 ± 0.53). As for the drug content in HHT, similar results were published by Xu et al. (2020), where the lower drug loading in 3D tablets than that

in the photopolymer solution occurred due to incomplete drug extraction from the cross-linked polymeric matrix (9).

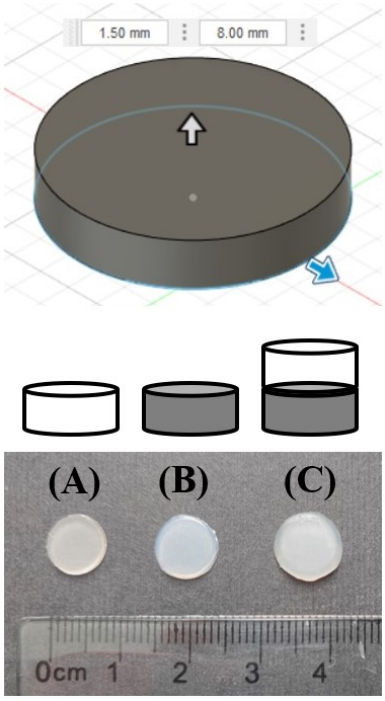

Figure 1. **Cylindrical 3D model of tablets created in Autodesk fusion software and printed single-layered (A) WS tablets, formulation F2 and (B) HHT tablets, formulation F1 and (C) combined two-layered 3D tablets, formulation CF**

Slika 1. **Cilindrični 3D model tableta kreiran u *Autodesk fusion* programu i odštampane jednoslojne (A) WS tablete, formulacija F2 i (B) HHT tablete, formulacija F1 i (C) kombinovane dvoslojne 3D tablete, formulacija CF**

Table III Measured weight, diameter and thickness of 3D tablets (mean ± SD)

Tabela III Masa, prečnik i debljina 3D tableta (srednja vrednost ± SD)

Formulation	Weight (mg)	Diameter (mm)	Thickness (mm)
F1	100.96 ± 5.93	9.15 ± 0.39	1.32 ± 0.04
F2	92.54 ± 3.61	8.74 ± 0.21	1.37 ± 0.05
CF	186.89 ± 12.06	10.01 ± 0.46	2.06 ± 0.16

After the dissolution test, the 3D tablets remained intact, showing no signs of erosion or disintegration, which is consistent with the previously reported results (8, 10, 11). Dissolution profiles for single-layered and combined two-layered 3D tablets are shown in Figure 2.

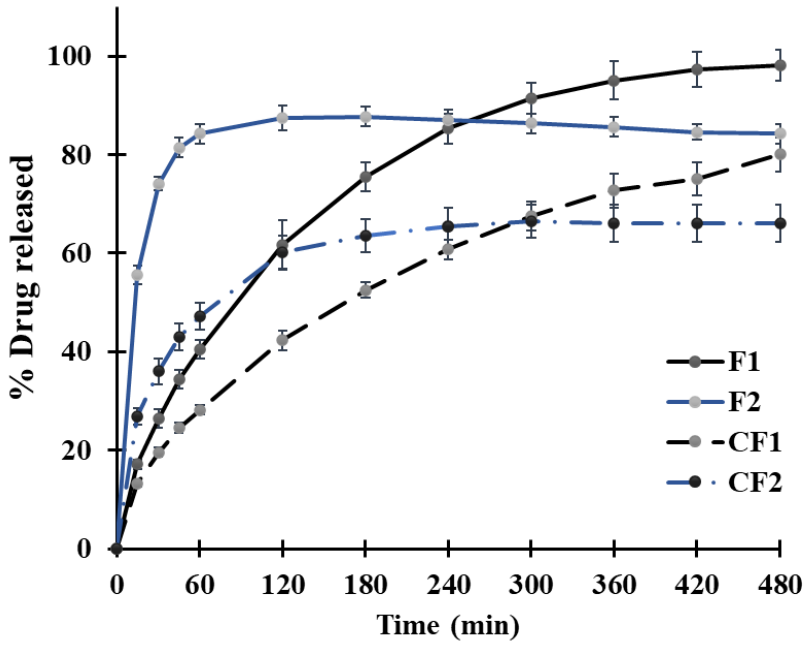

Figure 2. **Dissolution profiles of fabricated single-layered (F1 and F2) and combined two-layered (CF1 and CF2) 3D tablets**

Slika 2. **Profili brzine rastvaranja lekovite supstance iz jednoslojnih (F1 i F2) i kombinovanih dvoslojnih (CF1 i CF2) 3D tableta**

According to Chapter 5.17.1, Recommendation on dissolution testing, in the European Pharmacopoeia Edition 10.2, the acceptance criteria at level S1, for conventional-release dosage forms, are that at least 80% of the active substance is released within a specified time, typically 45 min or less, while for prolonged-release dosage forms the acceptance criteria are usually expected to consist of three time points or more. The 1st specification point corresponds to a dissolved amount typically of 20% to 30 % of drug, the 2nd specification point corresponds to around 50% of dissolved drug, and the final specification point is intended to ensure almost complete release, more than 80% of drug. According to the acceptance criteria, single-layered WS tablets (F2) showed immediate release – more than 80% of WS was released within 45 min, while single-layered HHT tablets (F1) showed prolonged drug release – approximately 20% to 30% of the drug was released after 30 minutes, about 50% of the drug between the first and second hour, and a plateau was achieved after five hours (Figure 1). The differences in drug dissolution rates between HHT and WS may be attributed to their aqueous solubilities: 0.70 mg/mL for HHT (21), and more than 7 g/mL for WS (22). WS was rapidly dissolved from the outer layers of the tablet, based on its high-water solubility, while about 13% of the drug was captured inside the inner layers of the tablet and caused incomplete release of WS. Studies have shown that formulation and geometrical factors, such as PEGDA/PEG ratio and surface area to volume ratio (SA/V), also affect drug dissolution rate from polymeric matrix (6, 11). Compared to single-layered tablets, combined two-layered 3D tablets showed significantly slower drug release, which may

be explained by the fact that in combined two-layered 3D tablets the surface area between the two attached tablets was blocked and therefore unavailable for drug dissolution. Consequently, the SA/V ratio was decreased, which affected the dissolution rates of both drugs from the combined two-layered 3D tablets (CF1 and CF2). Further research on increasing the drug dissolution rate from combined two-layered 3D tablets is necessary, and formulation strategies that promote higher drug release, such as increasing PEG 400 or water concentration, should be considered (6, 11).

DSC analysis was conducted to determine whether the drug was suspended or dissolved within the polymeric matrix. DSC thermograms of pure drug substances and formulations are presented in Figure 3. The DSC thermogram of pure HHT (Figure 3a) showed an endothermic peak at 271.6 °C, corresponding to its melting point, and another exothermic one, with a peak temperature of 311.5 °C, related to its degradation (23). A typical DSC spectrum of WS in amorphous form is shown in Figure 3b. A broad endotherm at around 100 °C, corresponding to the moisture loss, and a small endotherm peak at approximately 160–165 °C, representing the glass transition temperature of amorphous WS, were observed (24). The absence of typical HHT or WS peaks in the thermograms of the pulverized single-layered tablets (F1 or F2) indicates that the HHT or WS were dispersed in an amorphous form or dissolved in the polymer. However, the dissolution of drug crystals due to the high temperatures reached during DSC analysis cannot be neglected, and therefore polarized light microscopy was further performed.

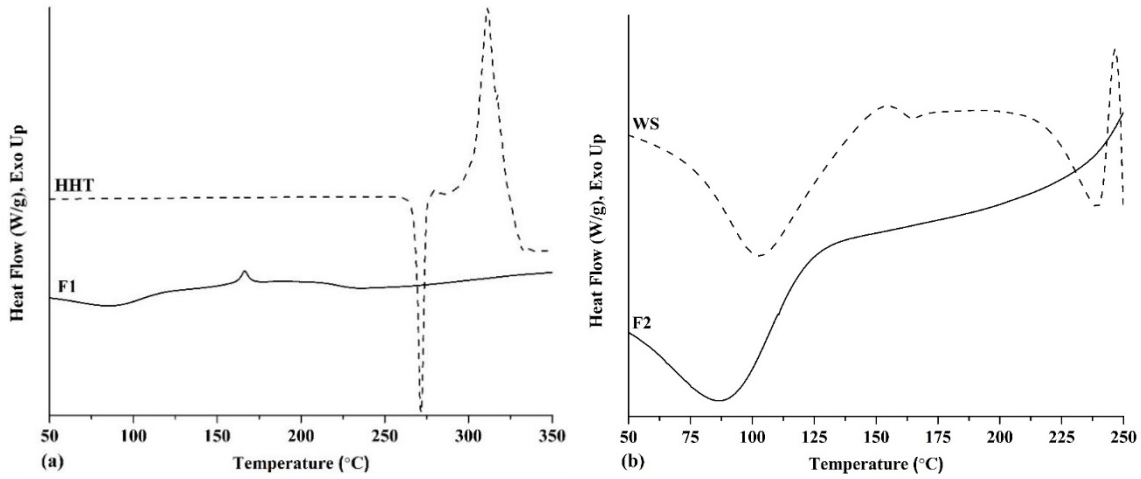

Figure 3. DSC thermograms of: (a) pure HHT and formulation F1 and (b) pure WS and formulation F2

Slika 3. DSC termogrami: (a) čistog HHT i formulacije F1 i (b) čistog WS i formulacije F2

Cross-sections of printed tablets, before and after the dissolution test, obtained by polarized-light microscope are presented in Figure 4. Crystals of the drugs were not found in the cross-sections of both single-layered (F1 and F2) and combined two-layered (CF)

tablets indicating that the drug did not crystallize in the photoreactive solution during the process of 3D printing (12). Parallel layers were observed in all printed tablets, both before and after the dissolution test, confirming the fact that the tablets were obtained in a layer-by-layer manner, and without signs of disintegration after the dissolution test. In Figure 4c, the difference between the two separate tablets (single-layered WS and single-layered HHT tablet) attached to each other can be clearly distinguished. In all formulations, after the dissolution test, longitudinal channels caused by drug diffusion from the polymeric matrix were observed, which is in accordance with the obtained drug release results.

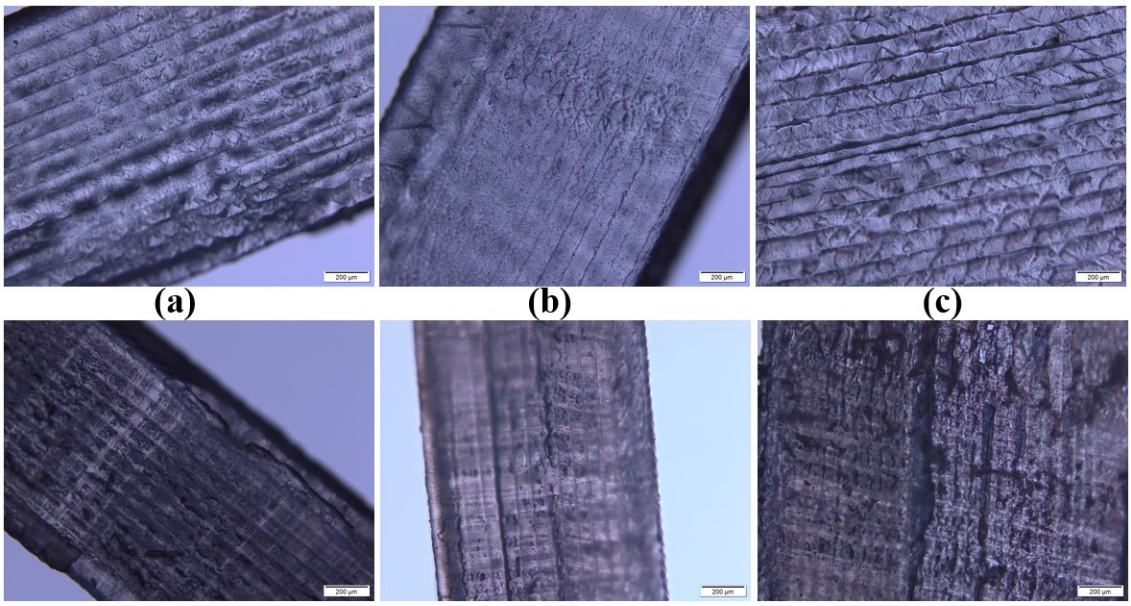

Figure 4. **Cross-sections of tablets before (above) and after (below) dissolution testing, respectively: (a) F1; (b) F2; (c) CF**

Slika 4. **Poprečni preseci tableta pre (iznad) i nakon (ispod) ispitivanja brzine rastvaranja lekovite supstance, redom: (a) F1; (b) F2; (c) CF**

An unexpected photopolymer-drug reaction has been reported in the literature, emphasizing that compatibility between drug and photoreactive monomer should be carefully considered and investigated (9). Accordingly, to confirm that no interactions between drugs and polymers had occurred, FTIR analysis was conducted, and the FTIR spectra of PEGDA, PEG 400, HHT, WS and pulverized tablets (F1 and F2) are presented in Figure 5. PEG 400 showed characteristic peaks at 3445 cm^{-1} (O-H stretching), 2866 cm^{-1} (C-H stretching) and 1096 cm^{-1} (C-O-C ether stretching) (25), all of which can be distinguished in the spectra of the printed tablets, as well. PEGDA exhibited characteristic peaks at 2866 cm^{-1} (CH3 stretching), 1721 cm^{-1} (C=O stretching) and 1636 cm^{-1} (acrylate C=C stretching) (10, 26). The C=C bonds were converted to C-C bonds as a result of the photopolymerization reaction, and therefore the acrylate bond peaks at 1636 cm^{-1} in the

spectra of the printed tablets were absent (25). The spectrum of pure HHT showed a band in the region of 1602 cm^{-1}, which corresponds to overlapping absorption bands associated with deformations of C–C bonds and C=C bonds of the aromatic ring, while those at 1334, 1319 and 1165 cm^{-1} were related to the SO_2 group of sulfonamides, and the one at 1123 cm^{-1} was related to the SO_2 heterocyclic ring (23). All the characteristic peaks of HHT were identified in the spectrum of the powdered tablets (F1), except those at 1165 and 1123 cm^{-1}, which were overlapped by the dominant broad C-O-C ether band of PEG 400. A large band at 1701 cm-1 corresponds to the stretching vibrations of the two C=O bonds of WS, while the bands at 1597 cm^{-1} and 1506 cm^{-1} correspond to C=C stretching. The out-of-plane bending vibrations of C–H of the phenyl rings were observed at 899, 756 and 700 cm^{-1} (27). All the bands were found in the spectrum of the powdered tablets (F2), confirming that interactions between drugs and polymers did not occur during the process of 3D printing.

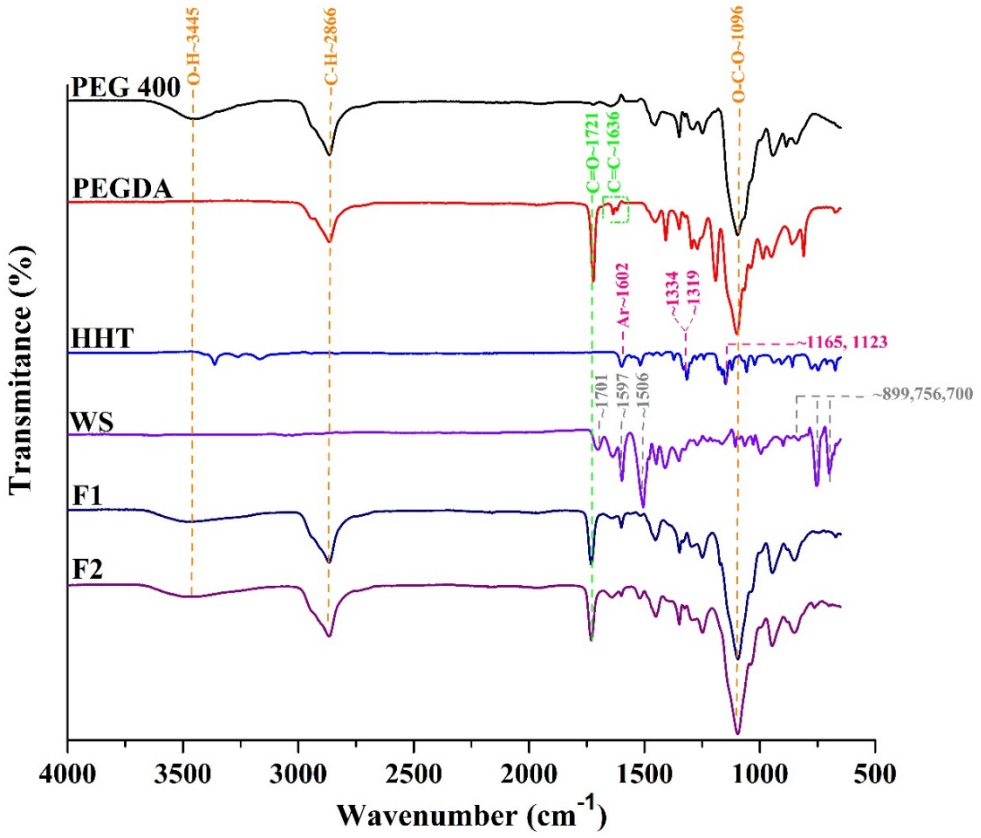

Figure 5. FTIR spectra of PEG 400, PEGDA, HHT, WS and pulverized tablets (F1 and F2)

Slika 5. FTIR spektri PEG 400, PEGDA, HHT, WS i sprašenih tableta (F1 i F2)

Conclusion

For the first time, a commercial DLP 3D printer has been used to manufacture small batches of combined two-layered polypills, tablets containing different drugs physically separated into a single dosage form, disclosing the potential of the DLP 3D printing technique to be exploited in the field of personalized medicine. The obtained results confirm the amenability of this innovative technology in the fabrication of combined medicines in a simple and fast way, which implies that it could also be a suitable promising tool for decentralized pharmaceutical manufacturing. Although the drug formulations were printable, further research and optimization of the formulation factors are needed in light of achieving complete release of HHT and WS drugs from the polymeric matrix and precise geometry according to the developed 3D model.

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3D tehnika digitalne obrade svetlosti (DLP) primenjena u izradi dvoslojnih tableta: koncept kombinovane polipilule

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Kratak sadržaj

Uvođenje tehnologije 3D štampe u oblasti farmacije uslovilo je razvoj fundamentalnih promena, pri čemu serijska proizvodnja velikih šarži pretenduje da bude zamenjena malim serijama lekova prilagođenih prema specifičnim potrebama pacijenata. Cilj istraživanja bio je da se formulišu i izrade dvoslojne tablete primenom tehnike digitalne obrade svetlosti (DLP). Hidrohlortiazid (HHT, 5%, m/m) i varfarin-natrijum (WS, 5%, m/m) odabrani su kao model lekovite supstance. Proces štampanja sproveden je u prisustvu 0,1% fotoinicijatora, pri konstantnom masenom odnosu poli(etilen glikol)diakrilata i poli(etilen glikola) 400, 1:1, uz dodatak 10% vode. Jednoslojne 3D tablete prečnika 8,00 mm i debljine 1,50 mm, koje sadrže HHT, odnosno WS, kao i kombinovane dvoslojne 3D tablete, sa svakom od aktivnih supstanci u posebnom sloju, uspešno su odštampane. Prilikom ispitivanja brzine rastvaranja lekovite supstance iz jednoslojnih tableta, došlo je do trenutnog (81,47±1,47%, nakon 45 min), ali nepotpunog oslobađanja WS, i produženog i potpunog oslobađanja HHT (98,17±3,11%, nakon 8 h), dok je iz kombinovanih tableta zapaženo znatno sporije i nepotpuno oslobađanje obe lekovite supstance. Potvrđeno je odsustvo interakcija i prisustvo slojevite strukture. DLP tehnika pruža mogućnost jednostavne i brze izrade kombinovanih tableta, pri čemu je dalja optimizacija formulacionih faktora neophodna u cilju postizanja potpunog oslobađanja lekovite supstance.

Ključne reči: DLP tehnika, hidrohlortiazid, varfarin-natrijum, kombinovane 3D tablete, personalizovana medicina