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Short communication

Digital light processing 3D printing of Hydrochlorothiazide with modified release

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Introduction

Additive manufacturing also known as 3D printing gains more attention in scientific research due to its great advantages in simple and fast producing custom-designed products. 3D models created with computer-aided design (CAD) are presented to the printers and with different techniques, printing layer-by-layer desired products are made. Most used techniques in additive manufacturing are fused deposition modeling (FDM), material and ink jetting, sintering and vat polymerization techniques. Stereolithography (SLA) and digital light processing (DLP) are the most frequently used techniques in vat polymerization due to their advantages. In DLP technique, a digital micromirror is used for gradually exposing and solidifying a layer of liquid photopolymer solution following a layer-by-layer mechanism (Adamov et al., 2022; Zhu et al., 2020).

Nowadays additive manufacturing finds its place in medicine by producing medical devices, implants, prostheses and medical equipment. 3D printing has enormous potential in personalized medicine as a result of different possibilities in production of dosage forms with desired shapes that contain one or more active compounds that can have different release profiles. 3D printing helps in overcoming the problem with permeability and solubility of some drugs and enables using drugs from different BCS classes.

On that hand the aim of this study was to manufacture 3D printed tablets (printlets) with hydrochlorothiazide (HHT) as active pharmaceutical ingredient. HHT is commonly used in the treatment of high blood pressure and has low solubility, low permeability, exhibiting poor oral absorption (BCS Class IV) which makes it suitable as a model drug for 3D printlets.

Materials and methods

Digital light processing 3D technique was used for manufacturing the printlets with HHT as model drug.

Photopolymer solution was prepared with mixing equal parts of poly (ethylene glycol) diacrylate (PEGDA, average MW 700) and poly (ethylene glycol) (PEG 400, average MW 400) and then distilled water, HHT as an active compound and diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide (DPPO) as photo initiator were added. The composition of photopolymer solution (grams of each compound in 100 g solution) is given in Table 1.

Table 1. Composition of photopolymer solution

Compound	Mass (g) in 100g solution
HHT	10
DPPO	0.1
PEGDA	39.95
PEG400	39.95
Water	10

Afterwards using Wanhao Duplicator 8 printer (Wanhao, Zhejiang, China) equipped with a 405 nm UV

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lamp, cylindrical-shaped tablets with a diameter of 8.00 mm and thickness of 3.00 mm were printed. The HHT printlets were manufactured with the following conditions: layer high - 0.1 mm, exposure time - 40 s, bottom exposure time - 50 s, lifting distance - 5 mm, bottom lift speed – 60 mm/min, lifting speed – 60 mm/min and retract speed – 150 mm/min.

Printlets were characterized by polarization light microscopy, FTIR microscopy, uniformity of mass, uniformity of content and *in vitro* drug release test.

The internal structure of the 3D tablets was visually examined using Olympus BX53-P polarized microscope (Olympus, Tokyo, Japan) with UPLFLN4XP and UPLFLN10XP objectives.

The infrared spectra were obtained by ATR module of a Furrier transform infrared spectrometer (FTIR) (Carry 600 diamond ATR, USA). Each spectrum was recorded in the 4000–650 cm^{-1} range, with a resolution of 4 cm^{-1} and averaged from 32 scans.

Variation in the mass was established with the method for uniformity of mass of single-dose preparations from the European Pharmacopeia (method 2.9.5). Before the test was caried out, tablets were washed with 2-propanol and wiped with a tissue to eliminate the uncured liquid from their surface.

Uniformity of content was determined with the test for uniformity of single-dose preparations form European Pharmacopeia (method 2.9.6). Drug content was detected with UV/VIS spectrophotometry at a wavelength of 273 nm, using UV/VIS spectrophotometer (Evolution 300, Thermo Fisher Scientific, Waltham, MA, USA). For implementation of the test, tablets were crushed and mass equivalent to an average mass of the tablet was weighted and dissolved in 10 ml absolute ethanol in volumetric flask and shaken in ultrasonic bath for 20 minutes. Afterwards they were cooled at room temperature and then filtered through 0.45 µm filters (Millipore, Bedford, MA, USA).

In vitro drug release test was performed according to dissolution test for solid dosage forms by European Pharmacopeia (method 2.9.3). The test was done (n=3) in 500 mL of distilled water for 9 h, using a mini-paddle USP-II Erweka DT 600 (Erweka, Langen, Germany) apparatus with the rotation speed of 50 rpm, at 37±0.5 °C.

Results and discussion

Ten cylindrical tablets were printed at once within 20 minutes, using the DLP 3D technique which shows the advantages of this technique for fast and simple production of small batches of tablets at a room temperature.

Images from polarization light microscopy showed parallel layers, that can be seen on Fig. 1a., which confirms that tablets were printed layer-by-layer.

a)   b)

Figure 1. Cross-section of 3D printed tablet a) before and b) after dissolution

The presence of all characteristic peaks of the compounds in the photopolymeric solution and the modification of bonds due to the photopolymeric reaction can be seen on the FTIR spectra of the tablets. The spectra also confirms that interactions between drug and polymers have not occurred during the printing of tablets.

HHT printlets had smooth surface but lacked clearly defined border, which resulted with variation of their mass (220.69±13.91 mg) and the percentage of drug content of 68.75±0.21%.

In vitro drug release studies pointed that HHT printlets released ~ 20% of the drug after 30 minutes, ~ 50% within the 3rd and 4th hour and more than 80% after 9th hour, thus meeting the criteria for prolonged-release dosage forms according to the Recommendation on dissolution testing (5.17.1) in European Pharmacopoeia. After the dissolution test printlets had remained intact, showing no signs of erosion or disintegration which can be seen in the images of the polarized light microscopy (Fig. 1b).

Conclusion

The obtained results confirmed the advantages of using the DLP technique for printing small batches of tablets. Although the HHT printlets have shown promising properties, further research and optimization of the conditions is required in order to obtain 3D printed tablets with appropriate uniformity of mass and increased drug content.

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