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It is our great pleasure to present this Supplement Issue on “*Macedonian Pharmaceutical Bulletin*” to the scientific and professional community. This supplement includes the short communications accepted for the *Seventh Congress of Pharmacy in North Macedonia with International participation 2022*, which was held in Ohrid, October 5-9, 2022.

The main theme of the Congress was “Modern trends in Pharmacy: opportunities and challenges” A broad spectrum of topics within the pharmaceutical sciences and practice carefully selected for this special occasion in order to build up a highly interesting and comprehensive program were covered. The contributions submitted to the Congress included 6 plenary lectures, 69 section lectures, and more than 200 posters. This Congress, followed the excellent international tradition, was attended by more than 1000 domestic and foreign participants. We received more than 287 short paper submissions from more than 15 countries. These numbers show that our Congress was aiming for the highest scientific standards, and that it can be considered a well-established venue for researchers in the broad fields of Pharmaceutical sciences and practice.

Sincere thanks to the hosts of the Seventh Congress of Pharmacy in North Macedonia with International participation, Macedonian Pharmaceutical Association and Faculty of Pharmacy, Ss Cyril and Methodius University in Skopje for their vision and commitments.

We would like to thank the companies that showed interest in supporting our efforts during the organization. We acknowledge the sponsoring companies: the platinum sponsor AD ALKALOID, Skopje, the golden sponsors: PLIVA-TEVA, EUROFARM, REPLEK and KRKA, the silver sponsor HEMOFARM and the bronze sponsors: GALENIKA, SEPTIMA and SALVEO,

We would also like to thank our members of the Scientific Committee for their volunteer time and dedication to the critical peer review process. We also wish to thank all the members of the Organizing Committee, whose work and commitment was invaluable.

On behalf of the Advisory and Scientific Committees, we would like to especially thank all internationally prominent researchers, whose work was supposed to be an essential part of the Congress. The interest in publishing their short communications in this issue of the *Macedonian Pharmaceutical Bulletin* is of a crucial importance for reinforcing the overall quality and standards of the bulletin. They give the state of the art of the recent advances in the field of pharmacy research.

The pharmaceutical sciences continue to grow as dynamic scientific interdisciplinary fields. We believe that published short communications will be an excellent source of scientific material in the fast evolving fields in Pharmaceutical sciences and practice.

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This issue of *Macedonian Pharmaceutical Bulletin* contains short papers accepted by the Scientific Committee for the presentation at the 7th Congress of Pharmacy in Macedonia with international participation 2022.

The authors are fully responsible for the contents of their short papers.

All reviewers that were involved in the short papers revision process are sincerely acknowledged.

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Fun-shaped oral dosage forms for the pediatric population fabricated by digital light processing (DLP) 3D printing technique

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Introduction

Three-dimensional (3D) printing as an innovative technology in the field of drug manufacturing has attracted a lot of attention from the scientific and professional public in recent years. Classified into seven main categories, all 3D printing techniques are based on the same layer-by-layer printing mechanism, where the structure of an object is created from a digital 3D file using computer-aided design (CAD) software or imaging techniques (Trenfield et al., 2018).

3D printing techniques have the potential to provide drug dosage forms of precise geometry and variety of shapes, with tendency to revolutionize the way drugs are designed and manufactured (Trenfield et al., 2018). 3D printing also pretends to play an important role in the concept of personalized medicine, allowing dose adjustment according to individual patient needs based on their own characteristics, requirements and conditions of the disease, in order to achieve the most suitable therapeutic outcomes. The approach of "one size fits all" could be changed by using 3D printing techniques in the manufacturing of small batches of patient-tailored medicines (Zema et al., 2017). In this study, digital light processing (DLP), also known as photopolymerization technique which utilizes light irradiation to create solid objects from photoreactive liquid resin, was used to fabricate fun-shaped oral dosage forms with an aim to achieve flexible dose adjustment of atomoxetine hydrochloride (AH), according to the specific needs of pediatric patients.

Materials and methods

Materials

Poly(ethylene glycol)diacrylate (PEGDA, average MW 250) was obtained from Sigma-Aldrich, Japan. Poly(ethylene glycol) (PEG 400, average MW 400) was purchased from Fagron B.V., The Netherlands. Mannitol Parreck[®] M 200 was obtained from Merck, Germany. AH was kindly donated by Hemofarm AD, Vrsac, Serbia. Diphenyl(2,4,6-trimethylbenzoyl)phosphineoxide (DPPO) was purchased from Sigma-Aldrich, Germany.

Preparation of photoreactive suspensions and 3D printing process

Content of AH was 5% (w/w, formulation F1) or 10% (w/w, formulation F2). PEGDA and PEG 400 were used in a constant ratio of 3:1. Both formulations contained 0.50% of mannitol and 0.10% of DPPO. The water content was 5% (w/w, F1) or 10% (w/w, F2), depending on the amount of the active substance.

Fun-shaped 3D models (Mickey Mouse, Ring, Pentagon and Cylinder) were designed in Autodesk fusion software version 2.0.8809 (Autodesk Inc, USA), exported as a stereolithography file (.stl) into the 3D printer software (Chitubox, version 1.7.0) and printed with Wanhao Duplicator 8 printer (Wanhao, China). 3D models of Mickey Mouse and Ring were printed from formulation F1, while 3D models of Pentagon and Cylinder were printed from formulation F2.

Mass, dimensions and drug content determination

3D-printed dosage forms (n = 10) were 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). The drug content was determined UV spectrophotometrically (Evolution 300, Thermo Fisher Scientific, USA) at the wavelength of 270 nm. For standard preparation, 10 mg of AH was dissolved in 10 mL of absolute ethanol, shaken in an ultrasonic bath for 60 min at room temperature, cooled and then filtered through 0.45 µm filters (Millipore, USA). For test preparation one dosage form of each formulation was crushed and all samples underwent the same procedure as described for standard preparation.

In vitro drug release testing

The dissolution test was performed with a USP-I Erweka DT 600 (Erweka, Germany) apparatus, in 500 mL of distilled water at 37 ± 0.5 °C, until a plateau was reached. The basket speed was fixed at 100 rpm, aliquots (5 mL) were withdrawn at time intervals of 15, 30, 45, 60, 120, 180, 240, 300, 360 and 420 min, respectively, filtered through 0.45 µm filters and the amount of AH released was determined at 270 nm. Measurements were performed in triplicate, for each formulation and each dosage form.

Differential Scanning Calorimetry (DSC) and Polarized Light Microscopy

DSC was performed on a DSC 1 instrument (Mettler Toledo, Germany). Samples were subjected to heating at 10 °C/min in the range from 0 to 200 °C under constant nitrogen gas flow of 50 mL/min. The obtained data were analyzed in the STARe software (version 12.10, Mettler, Toledo).

An Olympus BX53-P polarized microscope (Olympus, Japan) was used for visual examination of the internal structure, as well as for crystal detection. Photos were acquired using cellSens Entry Version 1.14 software (Olympus, Japan).

Results and discussion

Fun-shaped 3D models were successfully printed and printing time mainly depended on the geometry of the defined 3D model (on average, 10 minutes for 6 dosage forms), confirming the suitability of DLP technique for obtaining drugs of various shapes and sizes in a short period of time (Stanojević et al., 2021). All of the fabricated dosage forms had a smooth surface and a

uniform shape. The dimensions and mass of the printed dosage forms varied to some extent, which was expected due to the phenomenon of light scattering caused by suspended drug particles (Stanojević et al., 2021). The drug content depended on the amount of AH in the initial formulation and the geometry of the 3D model - 3.19 mg (Cylinder, F2), 4.42 mg (Ring, F1), 8.31 mg (Mickey Mouse, F1) and 26.51 mg (Pentagon, F2), respectively, which indicates the potential of the DLP technique to provide dosage forms with the possibility of "dose tailoring" and individualization of therapy. The results of the dissolution test showed a prolonged release of AH from printed dosage forms. The Ring model exhibited the highest dissolution rate, which was consistent with its high surface area-to-volume ratio, while the Pentagon model exhibited the slowest drug release. DSC analysis showed broad endotherms between 60 and 80 °C, and the absence of sharp melting peak of AH. The drug crystals might have been dissolved during the heating process and therefore, samples were further analyzed by polarized light microscopy. Cross-sections indicated the presence of AH crystals, before and after the dissolution test, due to incomplete drug release from polymeric matrix. The layered structure was also observed confirming the fact that dosage forms were printed in a layer-by-layer manner.

Conclusion

Fun-shaped oral dosage forms with AH were successfully printed with DLP 3D printer. DLP 3D printing technique offers simple and fast way to fabricate innovative drug dosage forms, enabling flexible dose adjustments by varying the amount of incorporated active substance and the geometric shape of the created 3D models, as well.

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