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PEGDA drug delivery scaffolds manufactured with a novel hybrid AM process

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Abstract: Drug delivery systems (DDS) are the most promising tools for the development of effective and safe treatments tailored to the special needs of each patient. Additive manufacturing (AM) as an approach in the manufacturing of DDS should ensure an exact formation of a requested individual scaffold, but also a precise incorporation of needed drug combinations and concentrations. The technique used for the preparation of the samples investigated in this paper is a novel hybrid AM process, which combines stereolithography and inkjet printing, for printing the basic DDS body and placing drug depots respectively. Therefore, it should be possible to adjust the release of the drug by positioning drug depots according to the diffusion of the drug through the scaffold. In this study, the drug release rates from the first 3D printed samples containing acetylsalicylic acid (ASA) as a model drug are shown.

I. Introduction

Patients undergoing a conventional pharmacotherapy often suffer from various side effects. These occur frequently due to the traditional dosing selection, which does not take into consideration coexisting metabolic diseases or the age of the patients. Thus, new solutions offering individually tailored medication are required and are intensively developed [1].

One of the most interesting approaches is the creation of drug delivery systems (DDS). An excellent DDS device should ensure effective and safe treatment for systemic and local ailments. The predominant and promising DDS preparation technique is additive manufacturing (AM), which can easily form scaffolds according to the individual anatomical and application needs [2].

Some novel manufacturing methods, such as the process described by Konasch et al. create a great chance for the development of systems, which apart from the personal design can offer also accurate dosing and the release of active substances [3]. This hybrid printing technique employs both stereolithography for the creation of the base body of the system and the inkjet printing for a precise dosage and positioning of the drug depots. Therefore, the release of the drug should be controlled by the drug diffusion through the polymerized base polymer.

In our previous studies we have investigated the properties of conventionally polymerized samples to broaden the knowledge concerning the basic material – poly(ethylene glycol) diacrylate (PEGDA) and the influence of different factors, such as washing process and the addition of comonomers on the material's physical and biological behavior [4]. In this study, release studies of the low molecular weight drug, acetylsalicylic acid (ASA) from the first 3D printed samples are presented.

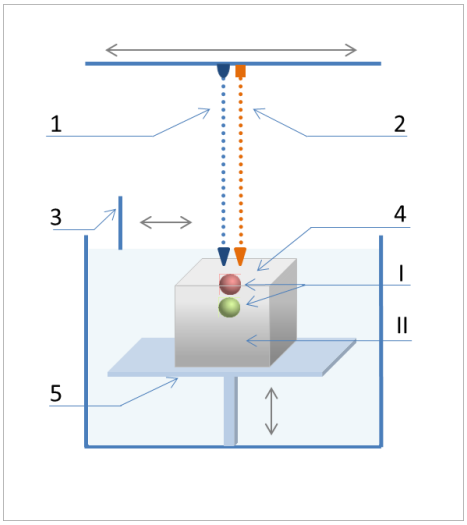

Figure 2: Graphical presentation of the novel additive manufacturing technique for a drug delivery system. Movable elements:1- inkjet module, 2- diode laser, 3- sweeper, 5- vertical platform. DDS with local different drug depots (4) is formed from the base polymer, in this case PEGDA and cured, line by line. The inkjet print head applies specified amounts of the drug solution in the desired areas, which is shown as red and green drug depots (I). The applied drops are cured to fix the drug in the matrix of the basic body of a system (II).

II. Material and methods

II.I. Chemicals

Poly(ethyleneglycol) diacrylate Mn=700 g/mol (PEGDA), photoinitiator: Lithium phenyl-2,4,6-trimethyl¬benzoyl¬phosphinate (LAP), methanol, acetylsalicylic acid and its solvent dimethyl sulfoxide were purchased from Merck KGaA (Darmstadt, Germany).

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II.II. Sample manufacturing

The sample preparation was performed as described in [3]. The basic parameters of the process are presented in table 1.

Table 1: The basic settings of the sample printing

Property/ Device settings	**Amount/ Unit**
Design: cube	4x4x4 mm
Basic material	PEGDA + 50% H_2O
Wavelength of the laser	405 nm
Number of the depots	4, each 0.5 mm from the surface in the middle of the cube on one plane
PI concentration	0.07% LAP (w/w)
Active substance solution	250 mg ASA/ mL DMSO
Theoretical amount of ASA in a sample	10 µg, 2.5 µg/ depot

II.III. Drug release study

The drug release study was conducted for each sample separately in 4 mL of isotonic sodium chloride solution elution at 37°C, 100 rpm and in protection from light. The release was continued for 48 h, with the medium exchange at particular time points. The residual release of ASA was performed afterwards in methanol. Standard solutions were prepared in methanol.

II.IV. ASA determination

ASA concentrations were measured with a HPLC device (Wiss. Gerätebau Dr.-Ing. H. Knauer GmbH, Germany). A C18 TL76 5 µm, 24x4 mm column was used. Isocratic elution occurred with water/ACN/H3PO4 (600:400:2) as solvent [5].

III. Results and discussion

Figure 1 presents the relative cumulative release of 10 µg of ASA from PEGDA+50% H2O 3D printed samples. To cover the burst release at the beginning of experiment, the medium was exchanged every 15 minutes during the first hour. After this time averagely 45% of the incorporated ASA is released, after six hours 95% are already released. The release rate is rather quick, according to the structure of ASA – here, no double bonds, that could be activated by the PI to form covalent bonds with the main polymer PEGDA. Therefore, the elution shows up to be controlled by the diffusion only. To investigate this process, further studies should be performed with different locations of drug depots. Other variations that can be applied with this new manufacturing method include the influence of such factors as concentration of the incorporated drug solution, the depot size or the base polymer – water ration in the scaffold resin.

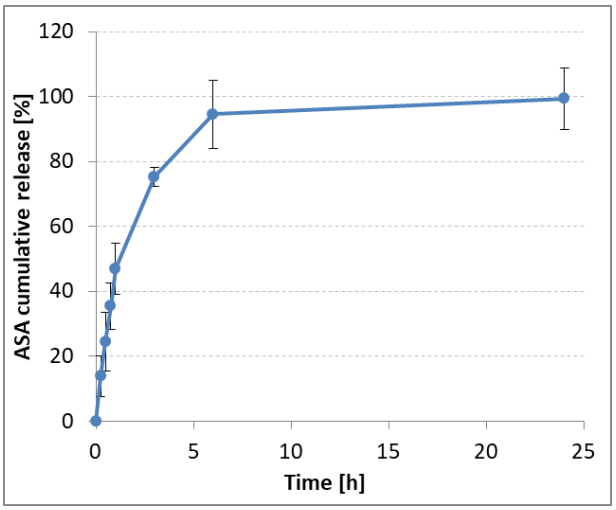

Figure 1: The cumulative release of ASA in [%] within 24 hours from PEGDA+50% H2O 3D printed samples containing a total of 10 µg of ASA in 4 depots, each 0.5 mm from the surface in the middle of the cube on one plane. Release in 4 mL of 0.9% NaCl at 37°C at 100 rpm (n=3).

IV. Conclusions

It was possible to utilize a novel hybrid additive manufacturing process to produce PEGDA + 50% H2O samples with the incorporated ASA as a model drug and to perform the drug release studies. Therefore, the presented method is adequate and should be considered as an interesting approach concerning the development of patient-tailored drug delivery systems. The presented result are promising and investigations should be continued to improve the recurrence of sample preparation and broaden the knowledge concerning the influence of the material composition and the printing settings on the drug release rates of different model drugs.

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Author's statement

Conflict of interest: Authors state no conflict of interest. Ethical approval: The conducted research is not related to either human or animal use.

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