

Robert Mau*, Thomas Reske, Thomas Eickner, Niels Grabow and Hermann Seitz

DLP 3D printing of Dexamethasone-incorporated PEGDA-based photopolymers: compressive properties and drug release.

Abstract: Photopolymerizing, high-resolution 3D printing methods such as Stereolithography (SLA) or Digital Light Processing (DLP) are very promising for the manufacturing of drug-incorporated, patient specific implants. However, a drug-load may be limited by adequately solubility of the active pharmaceutical ingredient (API) in the photopolymer. Furthermore, a drug-load may affect the mechanical properties of the material negatively.

Here, we investigate the DLP 3D printing of drug-incorporated photopolymers. Polyethylene glycol diacrylate (PEGDA, $M_n = 700$ g/mol) is used as matrix polymer and Dexamethasone (DEX) is used for drug-loading (10 g/L and 20 g/L). Compressive properties, drug release and drug stability of 3D printed test samples were analyzed. DEX was found to be sparingly soluble in the PEGDA-based photopolymer. Not all drug particles can be dissolved at a concentration of 20 g/L and a slurry-like suspension is formed. Drug-incorporated photopolymers of 10 g/L (solution) and 20 g/L (suspension) were processed successfully via DLP. The higher the drug-load, the lower the compressive strength. Mechanical properties can be improved via a post-curing in a UV light curing box. Drug-incorporated 3D printed test samples show burst-release of DEX. The post-curing process does not affect drug release. DEX degrades in 3D-printed test samples significantly (~ 30 %) over a several days time period.

Keywords: Digital Light Processing (DLP), Polyethylene glycol diacrylate (PEGDA), Dexamethasone (DEX), drug delivery, drug release, compressive strength

<https://doi.org/10.1515/cdbme-2020-3105>

*Corresponding author: **Robert Mau:** Microfluidics, University of Rostock, Justus-von-Liebig-Weg 6, 18059 Rostock, Germany, robert.mau@uni-rostock.de

Thomas Reske: Institute for Implant Technology and Biomaterials e. V., Rostock-Warnemünde, Germany, thomas.reske@iib-ev.de

Thomas Eickner, Niels Grabow: Institute for Biomedical Engineering, University Medical Center Rostock, Germany, thomas.eickner@uni-rostock.de, niels.grabow@uni-rostock.de

Hermann Seitz: Microfluidics, University of Rostock, Germany, hermann.seitz@uni-rostock.de

1 Introduction

3D printing technology has gained much attention in life science and medical fields such as tissue engineering and bioprinting, organ and disease modeling as well as the manufacturing of patient specific implants and drug-delivery-systems (DDS). The utilization of photopolymerizing 3D printing methods such as Stereolithography (SLA) or Digital Light Processing (DLP) is promising due to a high degree of flexibility on the adjustment of the polymerization parameters [1][2]. However, 3D printing is still at an early stage in the pharmaceutical field. In the case of photopolymerizing 3D printing methods, DDS manufacturing may be limited by adequate solubility of the active pharmaceutical ingredient (API) in the photopolymer. Furthermore, a drug-load may affect the mechanical strength of the material negatively.

This study deals with the DLP 3D printing of a Dexamethasone (DEX)-incorporated Polyethylene glycol diacrylate (PEGDA)-based photopolymer. PEGDA is a biocompatible, photopolymerizable material and known to be relevant for DDS [3][4]. DEX is a corticosteroid used as an anti-inflammatory agent [5].

2 Materials and methods

2.1 Preparation of (drug-incorporated) photopolymers

PEGDA-based photopolymer compositions with and without a drug-load were prepared as shown in Table 1. PEGDA of molecular weight of $M_n = 700$ g/mol (PEGDA₇₀₀) was used as a matrix polymer and Lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP) was used as the photoinitiator. Orange G dye was added for light absorbing to improve printing performance, see [6]. Deionized (DI) water was added for optimal solubility of LAP and Orange G in the composition. The API Dexamethasone (DEX, Pharmaceutical Secondary Standard, Certified Reference Material) was used

for drug-loading investigations. DEX was solved in the liquid photopolymer composition at ambient atmosphere ($T = 21\text{ }^{\circ}\text{C}$), using a magnetic stirring device over a time of 12 hours. All substances were purchased from Sigma Aldrich Chemie GmbH, Munich, Germany.

Table 1: Prepared (drug-incorporated) photopolymer compositions. The weight percentage of LAP and Orange G is based on the mass of PEGDA in the compositions.

Composition	LAP % w/w	Orange G % w/w	DI water % w/w	DEX g/L
C1	0,1	0,1	30	-
C2	0,1	0,1	30	10
C3	0,1	0,1	30	20

2.2 DLP 3D printing process

DLP 3D printing was performed using a VIDA 3D printer (envisionTEC GmbH, Gladbeck, Germany). 3D printing parameters for the photopolymer compositions were investigated previously [6]. The photopolymer compositions were processed using a light exposure time per layer of 40 s and a layer height of $100\text{ }\mu\text{m}$ (Z-resolution). The voxel size in XY-direction of the VIDA device is $73\text{ }\mu\text{m}$. The wavelength of the DLP projector is 405 nm, which is in accordance with the absorption spectra of the photoinitiator LAP and the light absorber Orange G.

Directly after finishing the DLP 3D printing process, all samples were washed for a few seconds with isopropanol (>99%, Sigma Aldrich Chemie GmbH, Munich, Germany) to remove unpolymerized liquid photopolymer. To investigate the effect of a post-curing process C1 and C2 test samples were post-cured for $t = 5\text{ min}$. For this step a UV light curing box (envisionTEC GmbH, Gladbeck, Germany) was used.

2.3 Compressive properties

Determination of compressive properties (compressive strength σ_M and compressive strain ε_M) according to EN ISO 604 were undertaken. Compression test cylinders with a nominal height of $h = 10\text{ mm}$ and a diameter of $d = 10\text{ mm}$ were manufactured by using the described DLP 3D printing process. The test cylinders were built in an upright position on the build platform of the VIDA device. For the determination of the compressive properties the uniaxial testing system zwickiLine Z5.0 (Zwick GmbH & Co.KG, Ulm, Germany) was used. The pre-load was set to 0,5 N and the testing

velocity was set to 1 mm/min. DLP 3D printed test cylinders of with and without drug-load (C1 – C3) were tested. The effect of a post-curing process on compressive properties was investigated for C1.

2.4 Drug release and drug stability investigations

Cumulative drug release was investigated for 3D printed test samples of the PEGDA-based photopolymer composition C2. For the investigations disc-shaped test samples with a diameter of $d = 6\text{ mm}$ and a height of $h = 0,5\text{ mm}$ were used. The test samples were manufactured via the described DLP 3D printing process with and without utilizing the post-curing process.

To investigate drug release, the time course of DEX release from test samples was determined at $T = 37\text{ }^{\circ}\text{C}$ in NaCl solution (0,9 %). Individual samples were immersed in 2 mL elution medium at 100 rpm for a total duration of $t = 57\text{ h}$. The elution medium was renewed after specified time periods. The concentration of DEX in the elution medium was measured utilizing HPLC (Wiss. Gerätebau Dr.-Ing. H. Knauer GmbH, Germany). Afterwards the residual amount of DEX was extracted using methanol. Stability of DEX in 3D printed test samples was investigated by determination of the residual DEX amount after 0, 3 and 8 days via extraction using methanol. Test samples therefore were stored in a membrane box at ambient atmosphere ($T = 21\text{ }^{\circ}\text{C}$) in the absence of light.

3 Results and discussion

3.1 Preparation of photopolymers

DEX was found to be sparingly soluble in the PEGDA-based photopolymer composition. The result was, not all drug particles dissolved at a concentration of 20 g/L (C3) and an opaque, slurry-like suspension was formed. In case of a concentration of 10 g/L (C2) the solubility of DEX in the composition was high enough to form a clear solution. A limited drug-concentration in the photopolymer, which is typically in the low percentage range (< 6%), is a known limitation of photopolymerizing 3D-printing methods [3].

3.2 DLP 3D printing process

All photopolymer compositions C1 – C3 were processed successfully via the described DLP 3D printing method. Figure 1 shows examples of 3D printed compression test

cylinders. The test cylinders of the drug-incorporated clear solution (C2) look the same as the samples of C1. They appear translucent and display an adequate printing accuracy ($\varnothing h = 9,9$ mm, $\varnothing d = 9,6$ mm). In the case of composition C3 the test cylinders appear opaque and the drug particles appear to be distributed homogeneously. Following these results, no significant effects of drug particle sedimentation during the 3D printing process were found. However, C3 test cylinders show irregularities of form. These may have been provoked by the opacity of the liquid photopolymer composition, thus leading to inhomogenous activation of LAP.

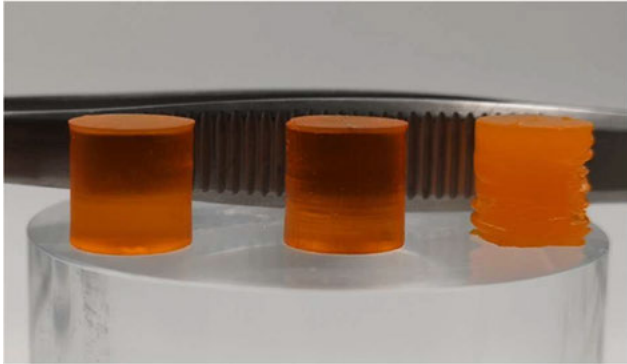


Figure 1: DLP 3D printed test cylinders of C1 (left), C2 (middle) and C3 (right).

3.3 Compressive properties

All test cylinders, irrespective of whether they were drug-incorporated or not, showed a brittle failure characterized by burst-like fracturing, as exemplarily shown in Figure 2. For all test cylinders there was a significant compression strain ε_M before fracturing. The mechanical properties, especially σ_M , are improved significantly when utilizing a post-curing process, as shown for C1 test cylinders (Figure 3). This accords with [3]. Compression strain ε_M is less affected by a post-curing process (Figure 4). The mechanical properties are comparable with findings in literature about stereolithographic



Figure 2: A burst-like fractured test cylinder of C1.

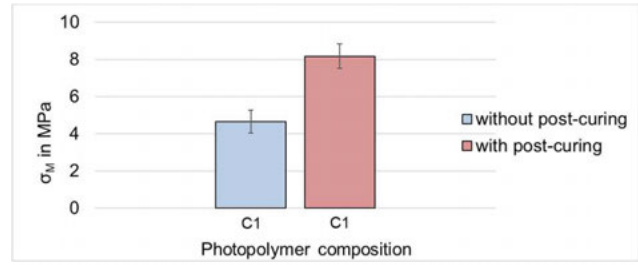


Figure 3: Effect of post-curing on compressive strength σ_M of C1 test cylinders (n=5).

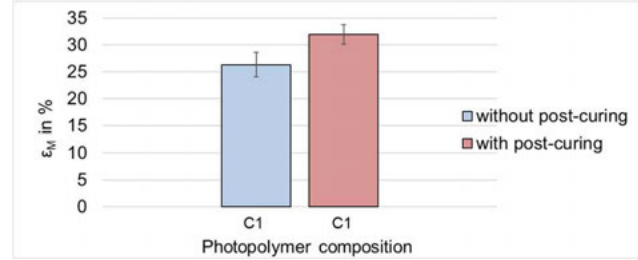


Figure 4: Effect of post-curing on compression strain ε_M of C1 test cylinders (n=5).

3D printed PEGDA₇₀₀-based materials, see [7]. However, it has to be considered that the photopolymer composition differs (e.g. used photoinitiator, content of water).

It was found that the higher the drug-load, the lower the compressive strength σ_M (Figure 5). In contrast, there is not such a significant decrease of compression strain ε_M (Figure 6). It should be noted that C3 test cylinders had irregularities of their shape (see Figure 1), which may affect the compressive properties. But the trend of decreasing mechanical strength with increasing drug-load accords with findings in literature,

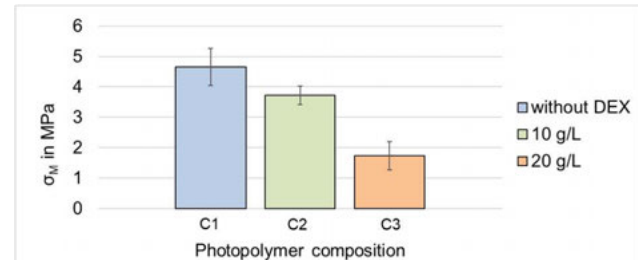


Figure 5: Effect of drug-loading on compressive strength σ_M of C1 test cylinders (n=5).

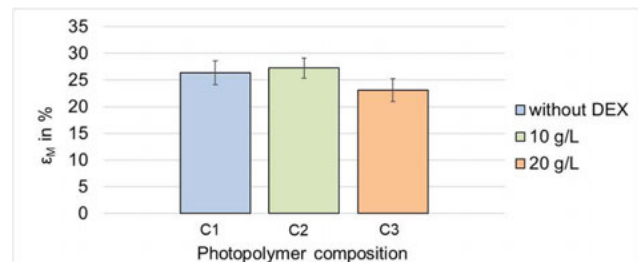


Figure 6: Effect of drug-loading on compression strain ε_M of C1 test cylinders (n=5).

as demonstrated before for PEGDA₇₀₀ drug-incorporated with acetylsalicylic acid (ASA) [7].

3.4 Drug release and drug stability

Figure 7 shows the drug release from C2 test samples, which were processed with and without a post-curing. The curves show an initial burst release of DEX from the test samples. About 95 % of the DEX is released in the period of the first six hours, comparable to findings in literature using ASA [7]. The post-curing process does not affect the rapid drug release significantly. Values higher than 100 % were determined due to an estimated DEX amount based on the composition in the printing process. Reduction of the water content after drying results in a falsely higher DEX mass.

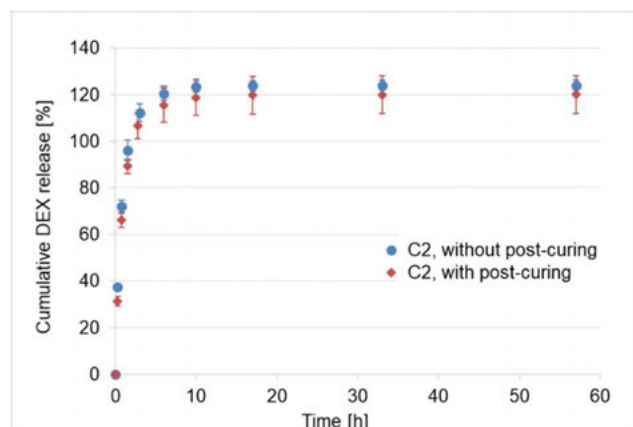


Figure 7: Cumulative DEX release of DLP 3D printed samples of C2 photopolymer composition (n=5).

DEX was found to degrade significantly in the DLP 3D printed test samples (see Table 2). The amount of DEX seems to drop about 30 % in a week. Regarding the high amount of DEX found in drug release studies, it seems DEX does not degrade during the 3D printing process but during storage afterwards. DEX is known to be unstable in aqueous media and to form multiple oxidative degradation products, which can be initiated by factors such as UV-light [5]. Here, it is likely that the relatively high content of water in the photopolymer composition initiates drug degradation, which needs to be investigated in further studies.

Table 2: Analyses of stability of DEX in DLP 3D printed test samples.

Storage time in days	0	3	8
Amount of DEX in µg	122	108	82,5

4 Conclusion

DLP 3D printing of DEX-incorporated PEGDA₇₀₀-based photopolymers has been demonstrated (clear drug-solution as well as drug-suspension). The utilized DLP 3D printing process enables the processing of slurry-like photopolymers with suspended drug particles. The 3D printed parts seem to include homogenously distributed DEX particles. However, the printing performance, as well as the mechanical strength, is reduced by a drug-load, especially in case of 3D printing a slurry-like drug-suspension. Nevertheless, the 3D printing of drug-suspensions holds high potentials for relatively high drug-concentrations in a DDS. Furthermore, it was demonstrated that a post-curing process can increase the mechanical strength of DLP 3D printed parts. However, a post-curing doesn't appear to affect drug release.

In further studies, the 3D printing of photopolymers with suspended drug particles will be focused on.

Author Statement

Research funding: The authors would like to thank the Federal Ministry of Education and Research of Germany (BMBF) for financial support for RESPONSE – Partnership for Innovation in Implant Technology in the program Zwanzig20 – Partnership for Innovation.

Conflict of interest: Authors state no conflict of interest.

References

- [1] Aimar A et al. (2019) The Role of 3D Printing in Medical Applications: A State of the Art. *J Healthc Eng* 2019: 5340616. doi: 10.1155/2019/5340616
- [2] Konasch J et al. (2019) A Novel Hybrid Additive Manufacturing Process for Drug Delivery Systems with Locally Incorporated Drug Depots. *Pharmaceutics* 11(12): 661. doi: 10.3390/pharmaceutics11120661
- [3] Palo M et al. (2017) 3D printed drug delivery devices: Perspectives and technical challenges. *Expert Rev Med Devices* 14(9): 685–696. doi: 10.1080/17434440.2017.1363647
- [4] Rekowska N et al. (2019) Thermomechanical properties of PEGDA in combination with different photo-curable comonomers. *Current Directions in Biomedical Engineering* 5(1): 319–321. doi: 10.1515/cdbme-2019-0080
- [5] Matter B et al. (2019) Dexamethasone Degradation in Aqueous Medium and Implications for Correction of In Vitro Release from Sustained Release Delivery Systems. *AAPS PHARMSCITECH* 20(8): 320. doi: 10.1208/s12249-019-1508-7
- [6] Mau R et al. (2019) Preliminary Study on 3D printing of PEGDA Hydrogels for Frontal Sinus Implants using Digital Light Processing (DLP). *Current Directions in Biomedical Engineering* 5(1): 249–252. doi: 10.1515/cdbme-2019-0063
- [7] Vehse M et al. (2014) Drug Delivery From Poly(ethylene glycol) Diacrylate Scaffolds Produced by DLC Based Micro-Stereolithography. *Macromol. Symp.* 346(1): 43–47. doi: 10.1002/masy.201400060