Transactions on Additive Manufacturing Meets Medicine
Trans. AMMM, Vol 1, No 1, 2019, Article ID S03P16

Infinite Science | Publishing

PMMA and PVP based polymers for stereolithographic manufacture of tailored drug release

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Abstract: Poly(methyl methacrylate) (PMMA) and polyvinylpyrrolidone (PVP) based polymers were tested for stereolithographic manufacture of tailored drug release systems. We adjusted the drug release by addition of the photopolymers pentaerythritoltriacrylate (PETA) and poly(ethylene glycol) diacrylate (PEGDA). As a model drug, high molecular weight bovine serum albumin labeled with fluorescein (BSA-FITC) was used. Changes in swelling behavior and drug release were observed. Higher concentrations of the crosslinker reduced the release and the swelling of PVP. PEGDA had a retarding effect on PMMAonly, whereas PETA affected both polymers. The stereolithographic designed drug depots could be applied in wound healings and dentistry.

I. Introduction

Additive manufacturing techniques, such as stereolithography (SLA) enable methods of 3D printing, e.g. inkjet printing, fused deposition modeling and powder bed fusion. Due to the possibility of preparation of complex structures, SLA is gaining relevance in the pharmaceutical industry. Currently, the potential of 3D printing for the production of pharmaceuticals and medical combination products is the subject of many scientific studies. This includes both drug release therapeutics for oral applications and drug releasing implants [1, 2]. Possibilities for increasing the safety, efficiency and accessibility of pharmaceuticals through the use of 3D printing technology are described by Norman *et al.* [1]. In 2015, a 3D-printed drug formulation was approved by the US Food and Drug Administration. In this context, numerous polymers for SLA processes and patient-customized medication were explored [3]. Therefore, we focused our study on adjusting the drug release of the established biomaterials poly(methyl methacrylate) [4] and polyvinylpyrrolidone [5]. In this study, we investigated the influence of the added crosslinkers pentaerythritoltriacrylate and polyethylene glycol diacrylate on the drug release. As a model drug we used the high molecular weight substance, bovine serum albumin labeled with fluorescein (BSA-FITC).

II. Material and methods

Material: The polymer poly(methyl methacrylate) (PMMA, M_w = 335.000 g/mol), the photoinitiator 2-hydroxy-4'-(2-hydroxyethoxy)-2-methylpropiophenone (Irgacure 2959), the crosslinkers pentaerythritoltriacrylate (PETA) and polyethylene glycol diacrylate (PEGDA, M_n = 250 g/mol) were purchased from Sigma-Aldrich, as well as BSA-FITC. Polyvinylpyrrolidone (PVP, K 90, M_w = 336.000 g/mol) was provided by Fluka. *Preparation of the samples:* The polymer, PMMA or PVP, was dissolved in chloroform to obtain a 10 wt% solution. BSA-FITC was dissolved in methanol to obtain a 0.5 mg/mL solution. The photoinitiator solution (31.25 wt% in methanol) was added directly before polymerization to obtain 1.25 wt%. The pure crosslinker, PETA or PEGDA, was added to the polymer solution with a final concentration of 1 v/v, 10 v/v and 20 v/v according to the polymer concentration. The BSA-FITC and Irgacure 2959 solutions were added directly before polymerization. The ratios of the reagents (polymer:crosslinker:BSA-FITC:Irgacure 2959) are for 1 v/v crosslinker samples (87:1:8:4), for 10 v/v samples (78:10:8:4) and for the 20 v/v crosslinker samples (68:20:8:4). The resulting solutions were transferred into the wells of a handmade silicone holder for the preparation of discs (r = 6 mm, h = 1 mm). The samples underwent photopolymerisation in the CL-1000L UV chamber (UVP, USA) at λ = 365 nm for 15 minutes, resulting in a total light dose of I = 30.96 J/cm^2. *In vitro BSA-FITC release:* The *in vitro* BSA-FITC studies were carried out under sink conditions. Each polymer sample (Ø = 6 mm) was immersed in 500 µl Dulbecco's Phosphate Buffered Saline (DPBS, Morphisto, Germany) under agitation in an incubator at 37 °C between sampling events. For each sampling event, the elution medium was completely removed and replaced with fresh DPBS. Fluorescence (excitation/emission 485/520 nm) was determined via FLUOstar Optima plate reader (BMG LABTECH, Germany).

III. Results and discussion

The cumulative *in vitro* BSA-FITC release studies of the crosslinked PMMA and PVP samples are presented in Figure 1. PMMA samples crosslinked with PETA or PEGDA revealed similar drug release profiles. Compared to PMMA samples containing 1 v/v PETA, PMMA samples containing 10 v/v and 20 v/v PETA exhibited a much lower slope, releasing only 75 % and 32 %, respectively, at 9 days. The delivery profiles of PMMA with 1 v/v and 10 v/v PEGDA are similar until day 4. Afterwards, the slopes differ and by 9 days, different BSA-FITC release amounts were observed of nearly 100 % and 81 %, respectively.

DOI: 10.18416/AMMM.2019.1909S03P16

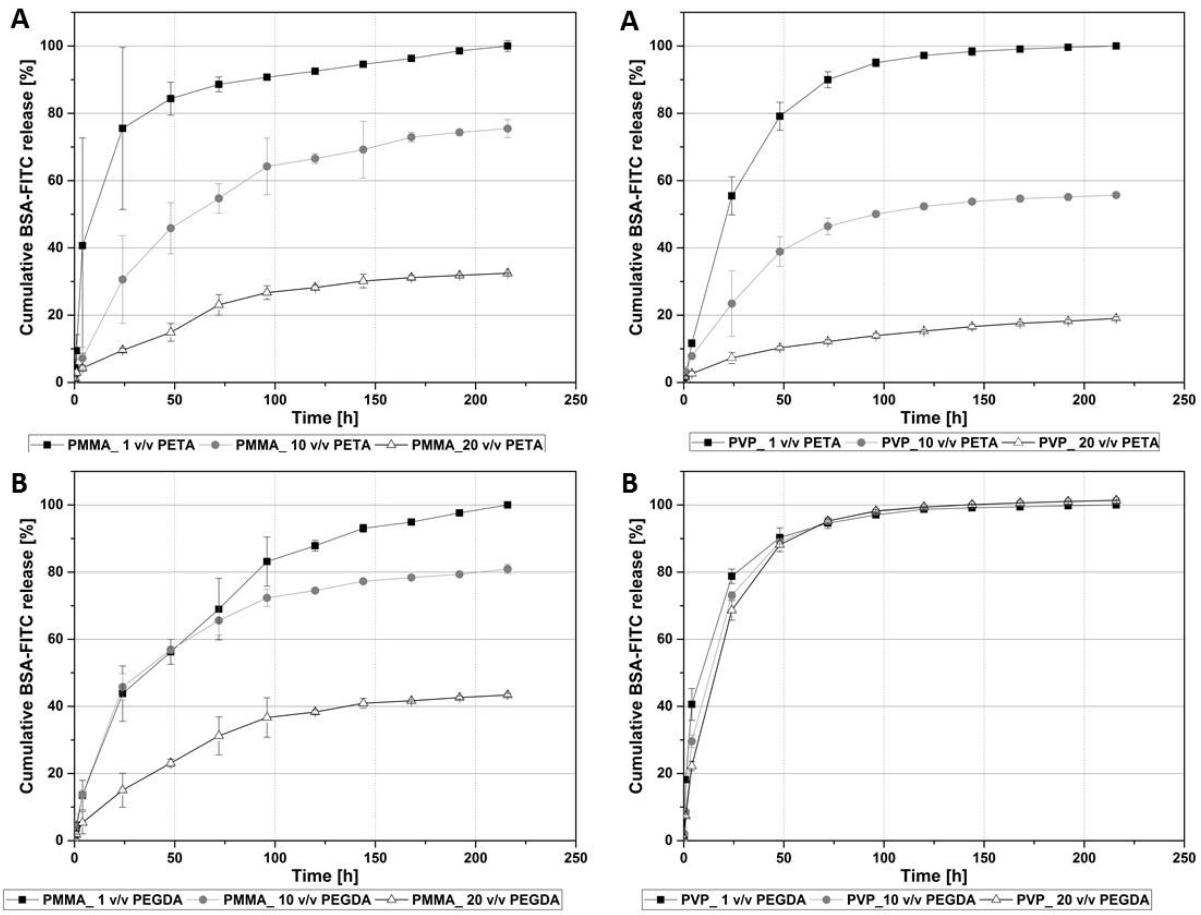

Figure 1: Relative cumulative BSA-FITC release of (left side) PMMA crosslinked with 1 v/v (black), 10 v/v (grey) and 20 v/v (light grey) PETA (A) and PEGDA (B) in PBS and (right side) PVP crosslinked with 1 v/v (black), 10 v/v (grey) and 20 v/v (light grey) PETA (A) and PEGDA (B) in PBS under agitation and at 37 °C (Ø = 6 mm, n = 3).

Samples containing 20 v/v PEGDA caused higher drug retardation with a total release of only 42 %. Therefore, the addition of the crosslinkers decreases the drug release rate. Furthermore, no PMMA samples swelled in the elution medium. All PVP samples with different PETA concentrations showed distinct differences in their release profiles, comparable to PETA-crosslinked PMMA. 10 v/v and 20 v/v PETA crosslinked PVP samples only released 55 % and 19 % BSA-FITC, respectively, within the 9 days observation period. A limited swelling behavior was also observed, depending on the crosslinker concentration. On the contrary, PVP with any PEGDA concentration released almost 80 % of the drug after 24 hours and nearly 100 % after 96 hours, with only marginal differences between the curves. All PEGDA crosslinked PVP samples swelled distinctly. Presumably, PEGDA influenced the swelling behavior crucially, due to its hydrogel properties [6]. The results suggest that BSA-FITC is covalently bound but shows greater integration with the PETA crosslinked systems than the PEGDA crosslinked polymers. Preliminary drug release tests must be repeated and adjusted due to BSA-FITC quenching effects.

IV. Conclusions

The addition of different kinds of crosslinker and changes in crosslinker concentration influence the photopolymerization process. Thus, the resulting drug release profiles and sample material properties, such as swelling, are tunable. Furthermore, the presented drug delivery systems may be promising for improved drug release profiles in various applications in medicine, such as wound healing, tissue engineering and dentistry.

ACKNOWLEDGMENTS

We thank Martina Nerger, Gabriele Karsten, Babette Hummel, Andrea Rohde and Caroline Dudda for their excellent technical assistance.

AUTHOR'S STATEMENT

Research was supported by the German Research Foundation (DFG) within the project "3D printed drug delivery systems with the ability of the time controlled drug release". Authors state no conflict of interest.

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