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Drug-releasing Biopolymeric Structures Manufactured via Stereolithography

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Abstract

Additive manufacturing (AM) techniques, such as stereolithography (SLA), enable the preparation of designed complex structures. AM has gained interest especially in the tissue engineering field due to the possibility to manufacture patient specific implants. However, AM could be useful also in controlled drug release applications, since the size and shape of the device, pore architecture and surface to volume ratio can be accurately designed. In this study, SLA was used to prepare polycaprolactone scaffold structures containing the model drug lidocaine. The release of lidocaine was studied and the influence of porosity and surface to volume ratio of structures to the drug release was analyzed. Porous samples released lidocaine faster compared to solid ones, whereas the degree of porosity and surface to volume ratio did not have a clear effect on the drug release profile.

Keywords: polycaprolactone, drug release, drug delivery, controlled release, stereolithography, scaffold, additive manufacturing, lidocaine

1. Introduction

There are great opportunities and interest in polymer-based, controlled-release formulations. While sustained release devices slow down the drug release rate and thus show benefits over conventional dose delivery, they are still influenced by environmental conditions resulting in patient to patient variations and require repeated dosages [1]. In contrast, ideal controlled drug delivery devices release drug for a designed time period and at a predetermined rate [2]. Polymer matrix systems are one type of controlled release system, where a drug is dissolved or dispersed in the polymer. The drug is released from the matrix by diffusion, polymer degradation or swelling [1,3]. From the non-degradable matrix system, the drug release is diffusion driven and affected by the concentration gradient, diffusion distance and degree of swelling [3,4].

Pore architecture can affect drug release. Higher surface area to volume ratio has been shown to increase the drug

release rate [5,6] and porous samples release drug faster compared to solid ones [7]. In addition to drug device structure, there are other factors affecting the drug release, such as the properties of drug (size of a drug, water (in)solubility, interaction with polymer matrix), polymer (degradation, swelling and chemical composition) and release medium (pH, temperature, enzymes) [3]. In addition, polymer network density might affect the release. If the drug is in crystalline form in the polymer, the drug release is controlled by the solubility of the drug. Therefore, drug should be dissolved in the polymer matrix to prevent variability in drug release. [7]

There are several traditional methods to prepare porous polymeric materials, such as salt and particle leaching, supercritical CO₂ (scCO₂) foaming and phase separation. These methods can be optimized to create open porosity and the approximate desired pore size range. However, porosity is random and the optimization of porosity, pore size and interconnectivity of pores is a challenge. Therefore, if well-

defined pore architecture is desired, additive manufacturing (AM) techniques are superior [8]. AM allows the preparation of complex predesigned structures via a layer-by-layer manner. With AM, it is possible to control the pore architecture, as well as surface to volume ratio and exact dimensions of structures. Since the structure of the polymer device affects the drug release, controlled drug release rates and profiles can be obtained by predesigning the structure. This would open new possibilities to prepare bioactive implants.

AM techniques, especially inkjet printing, selective laser sintering (SLS), fused deposition modelling (FDM) and stereolithography (SLA), have become increasingly popular within the biomedical field. The focus in combining additive manufacturing and drug release has been on oral drug delivery [9,10] and the first 3D printed tablet is already FDA approved [11,12]. Other application areas, such as transdermal delivery [13] and implants [14], have been researched.

FDM [9,10,15–22], SLA [23] and selective laser sintering (SLS) [24–26] have been used to prepare tablets for oral drug delivery. The research focused on the effects of the external shape and volume/mass ratio [5] and surface area to volume ratio [27] on the drug release. In addition, research has focused on developing pulsatile [28,29], accelerated [24] and/or delayed [30] release of drugs. In oral drug delivery applications, the release times are minutes whereas implants and scaffolds release the drug in days and weeks.

Additive manufacturing with FDM [14,31–35] and inkjet printing [36] has been used to study drug-releasing implants. Continuous liquid interface production (CLIP) [37] and SLA and inkjet printing [13,38] have been used in production of microneedles for transdermal delivery. In addition, topical drug delivery has been proposed [39].

Tissue engineering scaffolds require high porosity and interconnectivity, among other characteristics [40]. Therefore, AM techniques have been extensively used in the tissue engineering field [12]. However, preparing drug releasing scaffolds with AM has not been widely researched. For example, PDMS grid scaffolds with model drug prednisolone were prepared by extrusion-based additive manufacturing and UV-curing [41], CLIP was used to print polycaprolactone- and poly(ethylene glycol)-based scaffolds with rhodamine B-base (RhB) [42] and poly(ethylene glycol) dimethacrylate (PEGDMA) with rhodamine B was prepared via two-photon polymerization [43]. In addition, similar porous structures have been prepared for oral drug delivery with SLS from polyethylene oxide (PEO), Eudragit and ethyl cellulose [26] and with FDM from ethyl cellulose [21]. However, to the best of the authors' knowledge, the incorporation of a drug into a SLA-manufactured implant scaffold has not been previously investigated.

In this study, the drug release from 10 structures with different porosities and surface to volume ratios was

investigated. Photo-crosslinkable polycaprolactone macromer was blended with model drug lidocaine and printed with SLA. The drug release from the scaffold was monitored for 11 weeks. PCL was chosen as the polymer matrix due to its slow degradation time [44,45] and low swelling in water [8], as excluding these factors allows focusing on the effect of the pore architecture on the drug release. PCL has high permeability, which enables diffusion-controlled drug delivery [46]. In addition, low molecular weight methacrylated PCL macromer is printable with SLA without solvents. Lidocaine was used as a model drug due to its low molecular weight and solubility in PCL macromer and water, which enables the diffusion based drug release from polymer matrix. Additionally, low concentrations of lidocaine are readily detectable with UV-spectrophotometry.

2. Materials and Methods

2.1 Materials

For the synthesis of the macromer, monomer ϵ -caprolactone (Sigma-Aldrich, Germany), initiator pentaerythritol (Fluka, Germany), catalyst stannous (II) 2-ethylhexanoate (Sigma-Aldrich, Germany) and methacrylic anhydride (Sigma-Aldrich, Germany) were used. Hexane (technical grade, VWR Chemicals) was used in precipitation on macromer. Chloroform-D (99.8 %, Aldrich, Germany) was used in NMR analysis.

Omnirad TPO-L (IGM Resin Group, the Netherlands) and Orasol orange G (Ciba AG, Switzerland) were used in resin preparation. Lidocaine (Sigma-Aldrich, Germany) was used as a model drug. Lidocaine is a small molecule, with a molecular weight of 234 g/mol and water solubility of 4.1 mg/ml. The melting point of the lidocaine is 66–69 °C. Acetone (technical grade, VWR Chemicals, Finland) and isopropanol (99.6 %, Acros Organics, Belgium) were used in extraction of unreacted resin from printed scaffolds.

Phosphate buffer solution pH 7.4 (USP, FF-Chemicals, Finland) was used as a drug release medium. All chemicals were used as received.

2.2 Preparation and characterization of the poly(ϵ -caprolactone) macromer

Poly(ϵ -caprolactone) (PCL) macromers were synthesized as described previously [8]. Briefly, four-armed, photo-crosslinkable oligomer was synthesized for 5 h at 160°C from ϵ -caprolactone using pentaerythritol (10mol-%) as an initiator and stannous (II) 2-ethylhexanoate as a catalyst (0.02mol-%). The oligomer was functionalized at 60 °C for 24h using excess of methacrylic anhydride to obtain reactive methacrylate groups. Theoretical molecular weight of the macromer was 1590 g/mol. After functionalization, the excess methacrylic anhydride was removed by precipitating in hexane and

macromer was dried under vacuum. ¹H-NMR (Bruker Ultrashield 400MHz) was used to monitor the synthesis to ensure all the monomer (2.66ppm) was reacted to oligomer and all the OH-end groups (3.65ppm and 3.50ppm) were reacted during the functionalization.

2.3 Stereolithography

A resin for preparing 3D designed structured was obtained by mixing 90 wt% PCL macromer with 10 wt% lidocaine at 70 °C. To this mixture TPO-L photoinitiator (5 wt% relative to the macromer) and Orasol Orange dye were added. The amount of dye was determined by the preparation of a working curve. First, a small drop of resin without dye was illuminated for 12s at 700 mW dm⁻² in the SLA apparatus and the curing depth of the resin was determined by measuring the thickness of the obtained network. This was performed in triplicate. Subsequently, dye was stepwise added with the resin containing total amounts of 0.04, 0.08 and 0.11 wt% (relative to the macromer) respectively after the additions. After each step, the curing depths were determined in triplicate. The obtained curve could be extrapolated to determine the total amount of dye needed to obtain an optimal curing depth of 52µm. The resin contained 0.19 wt% (relative to the macromer) Orasol orange dye.

Using the mathematical formulas described by [47,48] cylindrical porous 3D structures with a diamond pore architecture were generated using Mathmod 3.1 (<https://sourceforge.net/projects/mathmod/>). Subsequently these structures were modified to have a diameter of approximately 10mm and a height of 7.5-8 mm and converted into printable .stl files using CAD software (Rhinoceros 3D, Robert McNeel and associates).

The designed scaffolds had porosities in the range of 50 to 90%. Two series of architectures were designed. In the first series (D50, D60, D70, D80 and D90), the pore size range was kept constant and the porosity was changed. In the second series (D520, D565, D70, D800, D960), the porosity was kept constant (70%) and the surface area of the structure was modified by changing the pore size. D70 is used in both series. In addition, solid cylinders (D0) with the same diameter and height was designed and built.

The designed structures were prepared using an Envisiontec Perfactory Mini Multilens. This SLA system is a digital light processing (DLP) system in which the light is projected through a transparent bottom of the resin tank and the build platform moves in a stepwise manner upward out of the resin tank. The projections had a pixel resolution of 32 x 32 µm², the layer thickness was 50 µm with an exposure time of 12 s, a light intensity of 700 mW dm⁻² and a wavelength of 400-550 nm. After building, excess macromer was removed from the structures by extraction from the scaffolds using a mixture of acetone and isopropanol (3:1). Subsequently, the

structures were dried under vacuum conditions. No post-curing was performed.

The density of printed macromer was determined to be 1.12cm³/g by printing a cube and weighing and measuring the dimensions. Porosity of printed scaffolds was determined by measuring the dimensions and weights of samples and calculating the porosity using the density.

2.6 Thermal analysis

Thermogravimetric analysis (TGA Q500, TA Instruments) was used to verify the lidocaine in the scaffolds, and to estimate the drug content in the printed structures. Lidocaine has a lower decomposition temperature than the PCL network. By measuring the change of the mass of the samples between these two temperatures, the lidocaine load could be calculated. Specimens (sample size ~20-30mg) were heated to 600°C at 20 °C/min under nitrogen with a purge rate of 60ml/min.

Differential scanning calorimetry (DSC Q2000, TA Instruments) was used to evaluate the dissolution of the drug into the PCL network. The amount of sample was 6-10mg. The DSC scans were conducted first heating with 10°C/min 40°C to 85°C, cooling to -90°, heating from -90°C to 85°C, and cooling to 40°C. The temperature range was chosen based on the expected glass transition- and melting temperatures of our materials and the temperatures at which the materials were going to be used in this study. The glass transition and melting point were analyzed from the second heating scan. For the analysis of the TGA and DSC results, TA Universal analysis software was used.

2.5 Drug release

For drug release studies, scaffolds were immersed in 20 ml phosphate buffer solution (pH 7.4) and mildly agitated at 90rpm at 37°C. The lidocaine release was monitored using UV/Vis-spectrophotometry (3100PC UV-VIS, VWR). The calibration curve analyzed from absorption peak at 263nm was linear in the range of 0.2-1.5mg/ml. The buffer solution was replaced at different time intervals to keep the drug level in the calibration area and to maintain the sink conditions. The buffer was changed at 1, 7 and 10 weeks for all samples. Buffer for solid samples was changed additionally at weeks 2 and 4. D90 samples were an exception due to a low drug release. Hence, the buffer solution of D90 was changed only at 7 and 10 weeks.

The stability of lidocaine in pH7.4 phosphate buffer was monitored and no change in the absorbance was observed during 11 weeks.

Potential micro-porosity of scaffolds was evaluated using scanning electron microscope (SEM, TM-1000, Hitachi). D70 scaffold was imaged before and after drug release study.

2.5 Mass loss and swelling

The mass loss and swelling of scaffolds were analyzed after 11 weeks in phosphate buffer solution. Scaffolds were quickly dried with pressurized air to remove the buffer solution from the pores and subsequently the swollen mass was weighed (m_s). After 1 week in vacuum, the dry samples were weighed again (m_d). These weights and the initial weight of scaffolds (m_{t0}) were used to calculate the remaining mass (1) and swelling of scaffolds (2) after 11 weeks in buffer solution.

$$\text{Remaining mass} = \frac{m_d}{m_{t0}} * 100\% \quad (1)$$

$$\text{Swelling} = \frac{m_s - m_d}{m_d} * 100\% \quad (2)$$

3. Results and Discussion

3.1 Resin composition

For the preparation of complex-designed 3D structures by stereolithography, the viscosity of the resin [49] and the ability to control the cure depth are essential [47]. A viscosity of around 10 Pa s is most preferable for use in stereolithography [8,50], although resins with higher viscosities have been used successfully [49]. In some cases, the viscosity of the macromer becomes too high and diluents are required to decrease the viscosity [50]. This is especially the case with macromers with a relative high molecular weight [49]. The macromers used in this study were of sufficiently low molecular weight and could thus be used without the addition of any diluents.

The resin used in this study was prepared at 70°C. At this temperature both the PCL and lidocaine are molten and therefore we could obtain a homogeneously mixed resin. TGA measurements showed that lidocaine is stable until approximately 150°C after which it starts to decompose.

Stereolithography is a method in which scaffolds are prepared in a layer-by-layer manner. In stereolithography set-up used in this study, the build platform is moved up out of the resin. This means that each newly formed layer needs to crosslink into the previous layer [49]. If the cure depth is too deep, this will result in structures with smaller pores than designed. Alternatively, if the cure depth is not deep enough layers will not attach and the build will fail after the first layer. It is therefore important to get the cure depth exactly right. The cure depth of the resin can be controlled by the addition of a dye in the resin.

The layer thickness used in this study was 50µm and therefore optimal curing depth is slightly deeper, 52µm. To this end, a working curve was prepared to determine the amount of dye required in the resin. The working curve is shown in Figure 1. After extrapolation it was shown that the resin required 0.19 wt% of dye (relative to the macromer) to reach 52µm curing depth.

Figure 1. Working curve for PCL resin containing 10wt-% of lidocaine. Dashed line is the extrapolation of the working curve and horizontal dotted line demonstrates the required 52µm curing depth.

3.2 Analysis of the scaffolds

Figure 2 shows the CAD model design with a porosity of 79.4% (D80) and its corresponding manufactured scaffold. The obtained porosities are presented in Table 1. The obtained porosities are slightly lower compared to the CAD models, which is due to over cross-linking during the printing process.

Figure 2. a) CAD model and, b) picture of SLA-manufactured PCL structure of D80. c) Diamond structure from the side. d) Pore size (blue (1.2mm) and orange (1.6mm)) and strut thickness (yellow (0.5mm)). Scale bars in a-c represent 1mm.

Table 1. Porosities, pore sizes, strut thicknesses, weights of samples, surface areas and surface area to mass ratios.

	Porosity (%) ^a	Porosity (%) ^b	Pore size range (mm) ^a	Strut thickness (mm) ^a	Weight (mg) ^b	Surface area (mm ²) ^a	Surface area / mass (mm ² /g) ^b
D50	49.7	48.9±0.8	1.3-1.8	1.84	333 ± 2	651	1952±13
D60	59.3	56.1±1.2	1.4-1.9	1.44	283±6	640	2260±48
D70	70.4	67.1±0.7	1.4-1.7	0.92	197±3	671	3411±62
D80	79.4	76.0±0.8	1.3-1.6	0.57	149±2	701	4718±59
D90	89.9	88.0±0.4	1.3-1.7	0.19	70±2	574	8255±220
D520	70.5	69.7±0.6	1.9-2.5	1.25	181±4	517	2866±70
D565	70.9	68.4±0.8	1.7-2.1	1.15	191±3	564	2953±49
D800	70.6	67.8±0.8	1.1-1.4	0.76	200±2	802	4009±49
D960	70.9	66.0±0.6	0.9-1.2	0.62	214±3	959	4481±71
D0	0	N/A	N/A	N/A	678±17	400±3b	592±15

^a designed

^b calculated

The DSC confirmed the dissolution of lidocaine into the PCL matrix. No melting peak of lidocaine was observed in the resin and printed scaffolds.

TGA confirmed that there is lidocaine in the scaffold and gave a rough estimate of the amount. According to TGA, the amount of drug within the scaffold was 9.4wt-%, which is slightly lower than the added 10wt-%. However, the PCL decomposition curve is overlapping with lidocaine decomposition curve and therefore the exact amount of lidocaine is likely to be higher than 9.4 wt-%.

3.3 Drug release studies

Figure 3a shows the different SLA manufactured designs. The initial amounts of drug in the scaffolds (Figure 3b) are calculated from scaffold weights (assuming a drug content of 10wt-%). Figure 3c shows the released drug (mg/ml) from the scaffolds. The drug release follows the initial amounts of drugs in scaffolds: the scaffolds containing the largest amount of drug have the highest release. Figures 3d and 3e show the cumulative drug release from the scaffolds as a percentage of the initial loading. The porous scaffolds exhibited burst release. After one day, the samples (except D90 and D0) had released already at least 25% of the maximum release. After 1 week, all the scaffolds except D90 and D0 reached over 50% release.

Figure 3d shows the cumulative release of scaffolds with different porosities as measured by UV-VIS. The porosity appears to have an effect on the release. First, there is a remarkable difference between porous and solid samples. The drug release from solid D0 is significantly slower. Porosity has been shown to accelerate the drug release compared to solid samples also with FMD printed tablets [7]. Second, while samples D50, D60 and D70 had similar drug release profiles and reached close to 100% release, D80 and D90 reached

lower release of 75 and 50%, respectively. Importantly, between 10 and 11 week time points, no release was observed, except from the solid D0 samples. These results are supported by the measured mass loss of the scaffolds (Table 2). The mass of samples D50, D60, D70, and D0 decreased almost 10%, which corresponds to the 10wt-% of lidocaine in scaffolds prior to the release whereas sample D80 and D90 did not decrease their mass by 10% during the release study. PCL is slowly degrading and therefore the mass loss of scaffold is due to lidocaine release.

Table 2. Swelling, remaining mass and drug release calculated from mass loss and measured with UV-spectrometry after 11w.

	Swelling (%)	Mass (%)	Drug released (%) ^a	Drug released (%) ^b
D50	0.58±0.01	90.3±0.2	97.5±0.2	104.3±1.2
D60	0.54±0.02	90.3±0.0	97.5±0.1	103.8±1.2
D70	0.29±0.02	91.3±0.1	86.3±0.1	100.9±1.3
D80	0.14±0.04	93.2±0.1	68.4±0.1	74.6±1.1
D90	0.03±0.02	96.3±0.2	37.5±0.2	50.2±1.8
D520	0.44±0.02	91.1±0.1	89.5±0.1	93.9±1.3
D565	0.46±0.02	90.9±0.2	91.4±0.2	99.9±1.2
D800	0.30±0.05	92.0±0.1	80.0±0.1	89.8±0.6
D960	0.34±0.01	93.1±1.0	69.1±1.0	76.8±1.9
D0	3.16±0.12	90.1±0.1	99.3±0.1	90.4±1.6

^a calculated from mass loss

^b release measured with UV-spectrophotometry

Figure 3. a) Pictures of dried scaffolds (diameter 10mm, height 7.5-8mm) after drug release with order D50, D60, D70, D80, D90, D520, D565, D800 and D960, b) amounts of lidocaine in scaffolds after building and c) cumulative release of lidocaine. d-e) Released drug as a percentage of initial loading with d) changing porosity and e) changing surface area. The structures have same colours of symbols in all of the figures. (n=6)

The difference in the release may however, not be the result of a difference in porosity. D80 and D90 have the thinnest struts (0.19-0.57mm, Table 1) of the scaffolds in this series. We hypothesize that part of the lidocaine is released during the 10 min post-processing phase with acetone and isopropanol after printing the scaffolds. Acetone swells cross-linked PCL matrix slightly, which may promote the lidocaine release from PCL. In addition, lidocaine is readily dissolving to acetone [51] with higher amounts (around 2000mg/ml at 22°C) compared to water (4.1mg/ml). The extraction of resin is an important step in SLA printing process. To prevent the

drug from dissolving in the extraction solvent, the post-processing procedure can be changed. The solvent composition can be adjusted. However, the solvent must dissolve the uncured resin easily. In addition, as the solvent almost readily dissolves resin remaining in the pores if the structures, the extraction time can be drastically shortened. Subsequently, any remaining resin can be post-cured. An additional benefit of the post-curing would be the depletion of the active (non-reacted) double bonds in the scaffold.

Figure 3e shows the cumulative release of scaffolds with the same porosity, but different surface area to mass ratios.

Figure 4. a) SEM images of scaffold D70 before (a, c and e) and after (b, d and f) drug release study. Salt particles from phosphate buffer solution used in the drug release study can be seen in images b), d) and f). Scale bars represent 2mm (a and b), 1mm (c and d) 200µm (e and f).

Even though there are remarkable differences in surface area to mass ratio between the scaffolds (Table 1), only samples D800 and D960 appear to have significantly different lidocaine release. However, as the strut thickness of the D800 and D960 samples is very low (Table 1), this is most likely not the result of the different surface areas, but due to the previously described extraction process.

Previous studies have shown that higher surface area to volume ratio increased the drug release rate [5,6]. In addition, a study showed that a larger surface area and shorter diffusion distance has been shown to accelerate the drug release rate [42]. This is clearly not the case for the samples used in our study. However, in a study of non-degradable PDMS grid structures, much like in our study, porous samples experienced initial burst release and the degree of porosity and surface area to volume ratio did not have a remarkable effect on the release of the drug [41].

Further structural and material properties that may affect the drug release of the lidocaine have to be discussed. The structures used in this study are macroporous structures. As can be seen in Figure 4, the structures do not exhibit microporosity, neither before nor after the drug release studies. Furthermore, it is critical to note that the drugs can only be released after diffusion of the drug through the polymer network to the surface of the network as the PCL does not degrade in the timespan of this study. In addition, the drugs are not chemically attached to the network. The drugs are first dissolved into the macromer resin and are subsequently physically trapped in the polymer network after crosslinking.

The drug release profiles of such systems are influenced by the crosslink density and hydrophilicity of the polymer networks [52]. More hydrophobic networks results in slower drug release [53]. The PCL used in this study is very hydrophobic. As is shown in Table 2, the porous scaffolds showed minimal swelling (<0.6%). Therefore, the mesh size of the PCL network may be very close to the hydrodynamic diameter of the lidocaine. If this is indeed the case, this will restrict the diffusion of the lidocaine to the surface of the implant [54]. In the networks of this study, that may be the decisive factor determining the released rate, limiting the effect of pore size and surface area.

The lidocaine is a relatively small molecule (243 g/mol). We expect other drugs and pharmaceuticals with similar or larger sizes to have the same issues with diffusion as lidocaine when used in combination with the polymer from this study. The diffusion of lidocaine in the PCL could be increased by changing the molecular weight of the PCL macromer to obtain a lower crosslink density or make the polymer more hydrophilic by preparing a copolymer of PCL with an hydrophilic counterpart such as poly(ethylene glycol).

4. Conclusions

Porous, drug-containing PCL scaffolds with a designed architecture were successfully manufactured by SLA. The model drug lidocaine was dissolved in the polymer matrix and was released by diffusion. Porosity clearly affected the drug release: porous samples released lidocaine with a burst whereas drug release from solid samples was significantly

slower. However, the degree of porosity and surface to mass ratio did not have an effect to the release; instead, the polymer network may be the restricting factor in the diffusion of the drug.

Post-processing of SLA manufactured scaffolds includes uncured resin removal with solvent dissolving the resin. This step may affect the drug loading in the scaffold. Therefore, especially thin structures (<1mm) may release drug partly already in the post-processing. Post-processing could be modified by shortening the immersion time and applying post curing.

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