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Formation of Poly(ε–Caprolactone) Scaffolds loaded with Small Molecules by Integrated Processes

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1. Introduction

The design of biomaterials went through many changes in the last decades. In the 1960s and 1970s the aim was to match the physical properties of the tissue to be replaced. It was considered favorable if the body showed only minimal immune response to an implant[1,2]. The next generation of biomaterials was supposed to induce a controlled and favorable response of cells and tissues to the implant. A specific aim was to enhance cell adhesion and proliferation. At the same time, resorbable biomaterials were developed which degraded as the tissue regenerated. The third-generation of biomaterials[2-4] combines these ideas leading to biomaterials for tissue engineering which are both bioactive and bioresorbable. They stimulate cell response and guide tissue growth while being resorbed the natural extracellular matrix is formed and tissue develops. Insofar they act as temporary substitute for the extracellular matrix. The goal is a regenerated tissue which is finally indistinguishable from the original body tissue. Tissue engineering can either take place *in situ* within the body by stimulating the endogeneous regeneration or in a bioreactor followed by implantation of the engineered tissue construct. Designing a scaffold[5-7] requires considerations regarding the material, its processing, and cell stimulation.

Especially cell stimulation by the addition of bioactive molecules such as growth factors, cytokines, DNA, and/or small molecule drugs is considered an important instrument in biomedical applications and tissue engineering[8-10]. The most common approach for the loading of scaffolds with drugs is a two-step process. Scaffold formation followed by surface coating of bioactive molecules. A disadvantage of surface loading is the high release rate at the beginning of the placement in the body or release medium, which is disadvantageous for many applications[11], and thus drug concentration decreases rapidly (“burst effect”)[11]. Once the surface coating has been dissolved, no drug is available anymore although the tissue regeneration is only at its beginning and the scaffold is nearly completely retained.

A strategy to control drug release at a specific rate over a longer time is bulk loading of a biodegradable polymer in which the drug release is either controlled by delaying the drug dissolution, which is realized by a polymer matrix that dissolves slower than the drug, or by diffusion, where the drug diffuses through voids[12] or in case of small molecules also through the bulk. The mechanism of biodegradation of the polymer, either surface erosion or bulk degradation, influences the mechanism of drug release. Surface erosion occurs when the water permeation is slower than the hydrolysis of the polymer chains and is typical for polyanhydrides and poly(ortho esters). Bulk degradation is common among aliphatic polyesters and is characterized by water diffusion rate that is higher than the polymer chain scission rate. Bulk integration of bioactive molecules can be realized by two different methods. The drug loading can be realized by a two-step process, in which the scaffold is fabricated first followed by drug loading. Alternatively, an integrated or single-step process can be employed, in which scaffold formation and drug loading is carried out simultaneously. In the two-step process drug-loading is typically performed by equilibrium partitioning in highly concentrated drug solutions which has several disadvantages (e.g. uneven distribution within the bulk, loading rate is limited by the maximal solubility of the drug in the solvent)[11]. The integrated process, the second method, has the advantages that drug contents can be achieved. Among the reasons is the possibility of forming polymer drug aggregates[12]. Furthermore the drug can be distributed homogenously within the bulk. As the presence of the drug during the scaffold formation process may have a strong effect on the scaffold morphology, the drug loading needs to be compatible with the scaffold formation process.

In this paper, we developed two integrated processes for the formation of scaffolds loaded with small molecules and investigated the influence of a small molecule on the morphology of the obtained scaffold. Our strategy was to select two established processes for scaffold formation, which fulfill the requirements needed for an integrated process such as enabling the homogeneous mixing of the small molecule and the matrix. This homogeneous mixing can be achieved either by a homogeneous dispersion or by dissolving the compounds either in a solvent or in the melt. Furthermore, the matrix material should be established in the area of medical devices, ideally already established for drug delivery applications, and should be a biodegradable polymer which has been investigated for scaffolding. A small molecule was selected as a model compound for small molecule drugs such as antibiotics or anti-inflammatory drugs or analgetica. Criteria for selecting this model substance was its ease of detection both within the matrix and within future drug release studies and furthermore its suitability for the selected formation processes.

In order to fulfill the above mentioned criteria, a freeze-drying process (FD)[13-16] and a pressure quench foaming process (PQ)[17,18,19] were selected among the numerous available processes for formation of porous structures. For the freeze-drying process, a homogeneous solution of the polymer in a solvent is frozen which is then removed by freeze-drying. By varying the polymer concentration and the cooling procedure, the pore size can be influenced. The PQ process, investigated as a second method, uses supercritical carbon dioxide[19] as a foaming agent, although also the foaming with carbon dioxide

at elevated temperatures is known[20,21]. A homogeneous solution of the polymer and the supercritical carbon dioxide is prepared at high pressure. The sudden depressurization leads to microporous open foams. The variable parameters which determine the pore size are the foaming temperature, depressurization rate, and gas saturation time[22]. The advantage of comparing these two methods of formation is that they are based on two different principles, which are the basis for several other scaffolding methods: In case of FD a polymer solution system is used and in case of PQ a polymer melt system.

Poly(ε-caprolactone) (**1**) was chosen as the polymeric scaffold material for this study because it has been extensively investigated as a scaffold material[23-30] and for controlled drug release applications[31]. Poly(ε-caprolactone) is well suited for long-term delivery systems such as contraceptives like Capronor™, which has a one-year delivery[31]. Furthermore it is compatible with the selected formation processes due to its solubility in organic solvents such as dioxane, which is needed for the FD process, and its melting point is suitable for the PQ process. Sudan Red G (**2**) was selected as a model substance for a lipophilic, small molecule drug because of its facile optical detection and release control, e.g. by UV spectroscopy, and its good solubility in organic solvents, which is a prerequisite for the FD foaming process. Thus this paper describes the influence of the variable parameters of the two foaming processes on the foam morphology, which is characterized by its porosity, pore accessibility by nitrogen gas, and pore size. Furthermore, the influence of the Sudan Red G concentration on the foam morphology and its distribution within the foam, which is necessary in order to anticipate the release kinetics, is evaluated.

2. Methods

2.1 Scaffold preparation

Materials: Poly (ε-caprolactone) (PCL) (CAPA 6806, Solvay Caprolactones, UK) having M_n = 80 000 according to provider information, 1,4-dioxane (SeccoSolv, Merck, Germany), carbon dioxide (CO_2) (99.99%; Linde, Germany), Sudan Red G (SRG) (Fluka, Germany).

Preparation of blends from PCL and SRG for PQ: All blends from PCL and SRG (1, 5, 11, and 43 wt % SRG) were prepared by premixing the powder and co-processing them in a laboratory small scale co-rotating twin screw extruder (Minilab CTW-5, Thermo Electron, Germany). The preset screw speed was always 150 rpm at a temperature of 90 °C. Afterwards the blend was pulverized in liquid nitrogen in a cryomill.

Freeze-drying process: PCL was dissolved overnight in p-dioxane at 80 °C, typically 100 g of solution was prepared. In case of the SRG foams, a 10 wt % PCL solution was prepared to which the desired amount of SRG was added, i.e. in case of a 10 wt % load 1 g SRG was added to 100 g of the PCL-dioxane solution. The polymer solution was poured into plastic vials having a diameter of 3.1 cm (25 g or 10 g solution per vial, depending on the desired foam size) or 2.0 cm (10 g solution per vial). The polymer solution was cooled

stepwise to 0 °C (16 h at 12 °C, 90 min at 6 °C, 150 min at 3 °C, 120 min at 0 °C). The vials were then placed into a freeze dryer (ALPHA 2-4 LSC, Martin Christ Gefriertrocknungsanlagen GmbH, Germany) to remove the solvent (48 h at 5 °C, p = 1.03 mbar). After the freeze drying, residual solvent was removed by drying the foams at RT at 0.1 mbar for 48 h.

Determination of the amount of soluble CO_2 in PCL: The solubility of CO_2 in PCL was determined by saturating PCL chips, which have a diameter of 25 mm and height of 1.5 mm (chips were produced by injection moulding in a Minijet, Thermo Haake, Germany), with supercritical carbon dioxide. The amount of desorbed CO_2 was determined by the weight loss of the chip after removal from the vessel in dependence of the time. The results were evaluated according to the Berens method[22].

Pressure quench process: The experimental setup (Fig. 1) consists of a 600 ml inox T316 high pressure vessel (Parr Instrument, Germany) (01), aluminium spacer to reduce CO_2 consumption (to 276 ml) and filling time, a PU 1586 HPLC syringe pump (Jasco, Germany) with liquid cooled pump head (06) and a coil precooler (05). Valves, tubes and fittings were supplied by Swagelog,Germany, pressure sensor type M22-6-M-B35D-1-4-D-00 by Gefran, Germany. Pressures and temperatures were monitored by a 8-channel analog/digital converter with 8-bit resolution and a sample rate of 1 Hz.

6 g of PCL or blended polymer powder was filled in 20 ml sample beakers having a diameter of 29 mm and a height of 50 mm. For each run, three beakers were placed in the pressure vessel. After positioning the beakers into the pressure vessel, the vessel was filled with CO_2 by a syringe pump. To determine the foaming parameters, temperature and pressure the vessel is preheated to the desired foaming temperatures with constant pressure or with constant temperature filled to desired pressures. After reaching the desired parameters the three-way valve was set in closed position and a constant saturation time of 60 minutes starts to reach the equilibrium. After saturation the three-way valve was set in quench position that the CO_2 escapes through the valve which is limited by the needle valve behind to adjust the depressurization rate. The experiments to define the depressurization rate was carried out under constant pressures and temperatures. To ascertain the influence of different contents of SRG in the PCL blend constant foaming parameters were used: 50°C, 10 MPa, 60 Minutes saturation time and two turns at the needle valve, which results in a middle depressurization rate of 0.55 $MPa \cdot s^{-1}$. After pressure relief, the samples were removed and stored under room conditions (23 °C, 50% relative humidity) for 24 h before testing. The blends containing SRG were tested twice under the same foaming conditions. Pure PCL was processed at each run too.

2.2 Scaffold characterization

Scanning Electron Microscopy (SEM): The foams were cut in liquid nitrogen, fixed on holders with a conductive adhesive, and sputtered with magnetron (EMI Tec XY, Great Britain). The prepared samples were investigated using a

LEO 1550 VP electron microscope with a Schottky emitter (LEO, Germany) at an acceleration voltage of 3 kV.

Solvent residue: The solvent residue content of the FD- foams was checked by dissolving 0.5 g of a foam sample in 1.5 g N-Methyl-2-pyrrolidone (NMP, Merck, Germany) at 50 °C. The sample is injected into the headspace (Hewlett Packard, Headspace Sampler HP7694, USA) and is equilibrated for 30 min at 90 °C and is finally transferred into the GC (Gaschromatograph 5890 Series II, Hewlett Packard, USA) where it is heated from 100 °C to 200 °C. For the detection a column (DB 624, J&W Scientific, USA) having a flame ionization detector is used.

Determination of the porosity, accessibility of the pores by nitrogen and foam density: The relative content of pores, which are accessible to nitrogen gas ("open pores"), was determined by pycnometer measurements. The measurements were carried out according to the instructions of the manufacturer in a 60 cm^3 test cell at 20 °C in a Ultrafoam Pycnometer 1000 (Quantachrome Instruments, USA) using nitrogen as a displacement fluid (6 psi) and 10-fold repetition of each measurement. The foam density was calculated from the geometric volume and the mass of the foam sample. The total porosity corresponds to the ratio of the foam volume and the volume of the corresponding compact, non-foamed PCL or PCL mixed with SRG. The density of PCL (1.168 g/cm^3) and SRG (1.226 $g \cdot cm^{-3}$) was determined by pycnometry.
In case of the FD foams, the surface of the foams was equalized by cutting of parts of the top layer to determine the geometric volume prior to the measurements. The measurement was carried out with at least four foams of each kind. The PQ foams were prepared for the measurements by cutting off the top and the bottom of the cylinders before the measurement. The measurements were carried out with two foams of each kind.

Determination of the pore size frequency: The pore size distribution was determined by mercury porosimetry measurements using a Mercury porosimeter Pascal 140 and Mercury porosimeter Pascal 440 (Fisons Instruments, Italy).

Differential Scanning Calorimetry Measurements (*DSC*) were carried out in a temperature interval between -100 and +200 °C in pierced AL-lids under nitrogen atmosphere with Phönix DSC 204 F1, Netzsch, Germany. Three heating and cooling runs were measured. The melting enthalpy of the foams was determined from the first heating run, other thermal effects in the second heating run.

The Melt Volume Rate (MVR) was measured with a melt indexer (Meltflixer MT, Thermo Elektron, Germany) according to DIN EN ISO 1133 (160 °C and 2.16 kg).

3. Results

PCL Scaffolds

Highly porous PCL scaffolds were obtained either by FD and PQ foaming process. Process parameters, which were varied, are the polymer concentration in case of the FD method as well as the foaming temperature and depressurization rate in case of the PQ process. The influence of these parameters on pore size and structure, accessibility of the pores by nitrogen, and porosity was evaluated.

In case of the FD process, solutions of PCL in p-dioxane with different PCL concentrations (3, 5, 6, 7.5, 10, 15 wt %) were cooled down stepwise below the freezing point of the solution. Neither during this cooling process nor when cooling down slowly from room temperature (1 °C per 10 min) a cloud point could be observed. Instead the p-dioxane crystallized spontaneously at temperatures below 10 °C. FD-PCL foams showed a strong tendency to form funnels which amplified when cooling the solutions quickly by immersing them in liquid nitrogen. The porosity of the foams depended on the polymer concentration (Fig. 3) and decreased linearly from 96% (3 wt % solution) to 81% (15 wt % solution) with increasing concentration of the polymer solution, which is in accordance with results reported[23]. The pores of the foams were completely accessible by nitrogen gas according to measurements in the pycnometer. The 3 wt % foam was very brittle and instable. In case of the 3 and 6 wt % foams, one specimen was fabricated and evaluated. The other foams were fabricated in larger quantities and were evaluated between three (15 wt %) and 13 times (5 wt %). In all cases, the reproducibility was very high and showed deviations of less than 0.5% concerning the total porosity and the amount of open pores. Mercury porosimetry measurements were performed to evaluate the pore sizes up to 140 µm. However larger pores are neglected by this method. The average pore size decreased from 58 µm to 16 µm with increasing polymer concentration. At the same time also the pore size distribution became narrower.
The SEM of the cross-section (Fig. 4) of the FD-foams, which were fabricated from differently concentrated PCL solutions, revealed no major differences in the morphology concerning the pore structure and size, which varied between 10 µm and 200 µm. The SEM figures of the PCL FD-foams showed a completely different morphology on the outer surfaces of the foam than in the cross-cuts (Fig. 4). The surfaces, which were in contact with the vial during the formation procedure, i.e. the bottom and the side, show a denser layer of approximately 200 µm thickness, which is characterized by smaller pores with sizes of up to 70 µm. The top surface shows a completely different morphology with larger pores of up to 210 µm and a scale-like structure.

Foaming of PCL starts at 30 °C at an equilibration pressure >14.5 MPa which is reached in a solid PCL chip after a gas saturation time of 100 minutes. The equilibration time to saturate a PCL power was hence fixed at 60 minutes concerning to the shorter way of diffusion in the powder. The influence of pressure and temperature was investigated to ascertain the amount of CO2 dissolved in PCL at equilibrium. The amount of dissolved CO2 increases with higher pressures (Tab. 1), at the same time the CO2 concentration in the polymer decreases with rising temperatures. The linear extrapolation of the curves revealed that 9 wt % CO_2 was dissolved at a pressure of 10 MPa and 50 °C.

The preparation of PCL scaffolds by PQ foaming was carried out with supercritical CO_2 at temperatures between 10°C to 60 °C. The influence of the foaming temperature under constant pressure on the average pore size is shown in Fig. 5. Depending on the applied foaming temperature, pores of 20 µm to 800 µm in diameter can be reached with pure PCL. The pore size increases up to a foaming temperature of 55 °C and decreases with higher foaming temperatures because the temperature in the reactor is also responsible for the viscosity of the polymer when the oversaturated PCL starts foaming during quenching.
Besides the temperature and the pressure, the foam formation is also influenced by the depressurization rate. Rates were varied from 0.1 up to 2 $MPa \cdot s^{-1}$ by adjusting the needle valve. When using depressurization rates of 1.5 $MPa \cdot s^{-1}$ and higher, the CO_2 in the vessel tends to freeze because of the high energy consumption of the phase transition from liquid to gas. Small depressurization rates cause larger pores because the nucleated pores have sufficient time to grow. In every experiment with varying temperatures or pressures in this paper, the needle valve (Fig. 2), which controls the depressurization rate, was consistently opened for two turns allowing a middle depressurization rate of 0.55 $MPa \cdot s^{-1}$.
As described above, all foams were fabricated in cylindrical beakers which were barred by a pierced polyethylene lid to allow venting of CO_2. Therefore the foams have an orientation of the inner structure in direction of the lid (z-axis), while in the other directions (x-, y-axis) the foams are rotation-symmetric. Thus an anisotropic structure is generated (Fig. 5).

SRG loaded PCL scaffolds

Polymeric scaffolds prepared from PCL were loaded with the model substance SRG in integrated processes, either based on the FD or on the PQ process. In order to be able to compare the influence of the SRG on the foaming process and the morphology, only the SRG concentration was varied while the other parameters were kept constant. The influence of this parameter on the SRG inclusion in the matrix, pore size and structure, accessibility of the pores by nitrogen, and porosity was evaluated.
In case of the FD method, the p-dioxane solutions containing 10 wt % PCL were selected to be loaded with SRG. A solution of PCL and SRG in dioxane was prepared at elevated temperatures and was then cooled down stepwise in analogy to the foaming process of the unloaded PCL foams. Again no cloud point was observed during the cooling process. Instead the solutions with a high SRG content (20 and 30 wt % SRG) crystallized spontaneously at room temperature, while the remaining solution froze at lower temperatures. No funnel formation was observed for these scaffolds (except for the foam with a 1 wt % SRG content) presumably due to the SRG crystal formation. After freeze-drying, SRG crystals (for foams with 5 wt % SRG and higher) could be seen on the surface of the foam. Only the scaffold with 1 wt % SRG showed similar properties to the pure PCL-foams and showed a tendency to funnel formation and no prior crystallization of the SRG. The porosity (Fig. 7) of the loaded foams remained basically unchanged and corresponds to the values of the unloaded 10 wt % PCL foam. The foams, both loaded and unloaded, were

tested for their solvent residue in a headspace GC with a detection limit of 5 ppm. In all cases (loaded and unloaded foams), no residue was detected.
The SEM pictures (Fig. 8) of the FD foams loaded with 20 wt % and 30 wt % clearly show crystal needles. Foams with a high SRG concentration tend to become brittle and the typical scaffold morphology was replaced by a haystack-like morphology due to the crystallization of the SRG. The pore sizes in the cross-section were up to 160 µm. Mercury porosimetry measurements showed an average pore size of about 30 µm for nearly all foams, while the pore size distribution increased strongly (Fig. 9) with an increase of SRG load.

SRG loaded PCL scaffolds which were prepared by PQ foaming were prepared from powder at a foaming temperature of 50 °C, a pressure of 10 MPa having a CO_2 saturation time of 60 minutes and an average depressurization rate of 0.55 $MPa \cdot s^{-1}$. The amount of SRG was varied between 1, 5, 11, and 43 wt %. The SRG seemed to colour the foam homogeneously, no phase separation, e.g. surface crystallization, between PCL and SRG was detectable with the eye. However, all foams showed SRG needles or trapezoid like crystals (Fig. 11) distributed in the PCL matrix. The crystals are in the range of 0.6 – 3 µm. The presence of SRG, which is well soluble in the polymer melt, reduces the melt viscosity (Fig. 10) of the blend which was indicated by the increasing melt volume rate (MVR). The MVR increased from 1.42 ± 0.03 $g \cdot min^{-1}$ (pure PCL) to 3.2 ± 0.03 $g \cdot min^{-1}$ (43 wt % SRG) because of the influence of SRG (160 °C, 2.16 kg) compared to the SEM pictures (Fig. 8) with a magnification of 100 showed the effect of different loadings with SRG. A SRG content of 1 wt % does not influence the foam structure compared to pure PCL. Pores are present in the range between 50 and 300 µm diameter. Higher loadings with 5 to 43 wt % SRG reduced the maximum pore size to 150 µm diameter and also smaller pores of 20 µm were detected.
Pycnometry measurements confirmed the influence of SRG on the pore size and distribution because the porosities measured by geometric data decreased with higher loading from 82% (1 wt % SRG) to 66% (43 wt % SRG). Similar to the FD foams, all foams showed to be completely accessible by nitrogen gas according to measurements in the pycnometer.

DSC measurements (Fig. 12) of the loaded FD and PQ foams revealed a melting point of 61 to 64 °C during the first heating, the melting enthalpy decreased proportionally to the SRG loading from 71 $J \cdot g^{-1}$ (1 wt % SRG, PQ foam) to 44 $J \cdot g^{-1}$ (43 wt % SRG, PQ foam). Pure PCL shows a melting point of 56 °C and a melting enthalpy of 68 $J \cdot g^{-1}$. A SRG loading of 20 wt % and higher showed a second melting peak at 155 °C and thus revealed that the SRG is not completely dissolved in the (molten) PCL in case of a SRG fraction of 20 wt % and more. The SRG crystals of the foams, which were observed in the SEM of the foams already at a much lower concentration, are obviously dissolved in the molten PCL due to the much lower melting point of PCL compared to SRG, which showed a melting point of 183 °C in the DSC. Since only the first heating of the DSC gives the relevant information on the foam, only this heating segment is pictured even though a second heating and cooling was carried out.

4. Discussion

This paper verifies that PCL foams can be processed by both methods by a FD as well as by a PQ process and it evaluates the influence of the parameters, which can be varied within each process, on the pore size and overall scaffold morphology. The main parameter which can be varied for the FD foams is the polymer concentration of the solution leading to foams with porosities of 96% to 81% and pore sizes of 10 to 200 µm. The higher the concentration, the lower is the foam porosity and the lower is the average pore size. The pores of all FD foams are accessible by nitrogen gas.

The PQ foams on the other hand have three main parameters which can be varied: the foaming temperature, which influences the viscosity of the polymer, the gas saturation pressure, and the depressurization rate. The increase of the foaming temperature results in larger pore sizes up to a limit. The gas saturation pressure is responsible for the total amount of desorbt CO_2. High pressures results in smaller pores because of the faster supercolling of the melt. The gas saturation time defines the time to reach the equilibrium between desorbtion and resorbtion of gas molecules in the polymer sample. Powders were saturated after 60 minutes, when gas consumption is zero. The depressurization rate controls the time for pore growth to pore stabilisation. High depressurization rates result in smaller pore sizes. By variation of these defined parameters, PCL scaffolds with a porosity of 80% and pore sizes between 50 and 350 µm were fabricated. The PQ foams show a slightly lower accessibility of nitrogen gas to the pores (94%) than the FD foams, have a broader pore size range, and also the skin formation is much stronger than for the FD foams. The most obvious difference between both foams is the anisotropy of the PQ foams characterized by a much larger pore diameter in the direction of expansion.

Both methods are well suited for the foam formation and incorporation of the model substance SRG in a single step process. SRG-PCL foams fabricated by the FD process were generated with a dye content of 1 to 30 wt %. The foams with the highest SRG content of 20 wt % and 30 wt % show SRG crystallization prior to the freezing of the whole solution which also dominates the scaffold morphology as the SEM pictures reveal. SRG crystal needles were detected on all foams with a SRG content of 5 wt % or higher showing that a phase separation took place between the PCL and the SRG during the freezing. Thus the foams would show an initial high release rate when being placed into a release medium. Only the foam with a 1 wt % SRG load showed no separate SRG crystallization, therefore a constant release rate can be anticipated. The pores of all SRG loaded foams were completely accessible to nitrogen. The foam porosity remained basically unchanged for all concentrations. The pore size distribution became broader, while the average pore size remained unchanged. While the incorporation of 1 wt % SRG showed no impact on the morphology of the FD foams, higher rates of SRG showed a drastic impact on the scaffold morphology and lead to a phase separation.

In the PQ process SRG was incorporated in concentrations of 1 to 43 wt %. Only in case of the 1 wt % SRG loading the morphology is not influenced by the small molecule. The higher SRG loadings influenced the foaming conditions by reducing the viscosity of the blend during the foaming process. This reduction in viscosity caused smaller cell sizes, which were in the range of 70 to 180 µm, and a reduction of the porosity. Since the viscosity of a polymer melt is a function of several parameters, among them the temperature, it would be possible to adapt the viscosity to the amount of SRG by reducing the foaming temperature. In this paper, however, all parameters were kept constant in order to examine the influence of SRG content on the foaming process and the morphology. The SEM pictures show that in contrast to the FD foams the SRG is mainly incorporated in the PCL matrix material where it is nearly homogenously distributed. Only tiny crystal needles were detected on the surface. The release rate of the SRG will therefore be controlled by the diffusion of the dye through the matrix or the degradation of the matrix. Thus a burst effect is not anticipated for the PQ foams with a high SRG loading.

Substituting SRG by lipophilic, small molecule drugs and using PCL as a matrix material, is expected to result in similar foam morphology characteristics. In case of the FD process the solubility of the small molecule in the selected solvent, is a very important parameter to consider. If its solubility in p-dioxane is higher than the solubility of SRG, then also higher loading rates can be achieved. When aiming at very high loading rates, the PQ process is the method of choice. Integrated processes for the preparation of drug loaded scaffolds are versatile and efficient methods which have a high application potential in different tissues engineering applications.

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