4 Summary

In situ forming systems

Implants and microparticles have been developed to avoid daily injections and improve patient compliance. However, in their manufacture process problems could appear like scale-up problems, residual toxic solvents, instability and low encapsulation efficiency. As an alternative, in situ forming implant- (ISI) and in situ forming microparticles- (ISM) systems were developed. The drug is dissolved or dispersed in a concentrated solution of poly(lactide-co-glycolide) (PLGA) in a biocompatible solvent (e.g., N-methyl-2-pyrrolidone - NMP) (ISI) or an emulsion of an internal drug-containing PLGA solution and an external water- (O/W-ISM) or oil- (O/O-ISM) phase. Once the polymer solution/emulsion is injected, the polymer precipitates upon contact with aqueous body fluids and hardens in situ in an implant or in microparticles, which retard the drug release.

Organic PLGA solutions used for the preparation of in situ implant systems are not stable at room temperature and are therefore stored refrigerated within a syringe (e.g., Atrigel®). In addition, the drug is stored separately in dry form in a second syringe and is dissolved/dispersed in the polymer solution just prior to injection. This mixing process requires 100 cycles (the plungers of the two connected syringes are pushed forward and backward 100 times) [99-101]. The idea/question for the present study was: Is it possible to store the PLGA polymer and drug in dry form to be then rapidly dissolved in the polymer solvent just prior to injection? This would eliminate the prior preparation of the PLGA solution and allow storage at room temperature rather than refrigerated (as required for the PLGA solutions).

A rapid dissolution of the polymer in a biocompatible organic solvent during reconstitution is essential for the potential use of PLGA in solid form for the formation of in situ systems.

The time of polymer dissolution decreased with decreasing PLGA particle size (increasing surface area). Lyophilization of PLGA solutions in acetic acid or dioxane resulted in highly porous sponges. These PLGA sponges dissolved more rapidly than the PLGA particles because of a high internal surface area

and rapid penetration of the solvent into the pores. A key factor for the polymer dissolution process was the selection of the organic solvent. The time for dissolution correlated well with the viscosity of pure solvents/resulting polymer solutions and the solubility parameter of the solvent and was in the order of ethyl acetate < NMP < benzyl alcohol < triacetin < benzyl benzoate < 2-pyrrolidone < PEG 400. Solvents with a lower viscosity and a solubility parameter close to the polymer dissolved the polymer rapidly. The short reconstitution times of less than one minute are in a time frame acceptable for the clinical end user, who prepares the injectable in situ system. The dissolution time increased with increasing polymer concentration because of an increased solution viscosity; however, the dissolution process was still very rapid, even a solution with a high polymer content of 40% formed after only approx. 40 sec of mixing. The dissolution time of various PLGA polymers in NMP decreased with decreasing molecular weight because of a decreased solution viscosity (RG 502H vs. RG 503H), decreased hydrophilicity of the polymer (end-capped PLGAs RG 502, 503 in comparison to uncapped PLGAs RG 502H, 503H) and increasing lactide content (R 203 vs. RG 752 vs. RG 502). The mixing rate (number of cycles per second) did not affect the required number of cycles to dissolve the polymer indicating a robust reconstitution process. With ISM, the reconstitution process has to result in the dissolution of the polymer and the formation of the emulsion prior to injection. Both the PLGA dissolution and emulsion formation were possible in less than a minute for both O/O- and O/W-ISM, even at a high polymer content of 30%. The reconstituted emulsion, which would normally be injected immediately after preparation, could be used within a 2 h time frame after preparation. Various possibilities exist to prepare the ISM-emulsions. Three different methods to prepare ISM emulsions were compared and resulted in good reconstitution.

Biodegradable implants

Implants are mostly produced by melt extrusion and melt molding in the form of cylindrical polymer rods with embedded drug. Low dose drugs could result in content uniformity problems and high temperatures during the processes could

lead to degradation of the drug. Thus, the aim of this study was to develop and characterize an alternative method to prepare PLGA implants without the above mentioned problems. The method selected was based on the lyophilization of PLGA solutions, which resulted in sponge-like implants. Since PLGA is not water soluble, organic solvents were used for the lyophilization process. Solvents had to be identified, which dissolve PLGA and which can be frozen and be removed during freeze-drying. The solvent should therefore possess a melting point, which allows freezing in the temperature range used (Tm > -70°C) and have a low toxicity. Acetic acid and 1,4-dioxane fulfilled these criteria and were evaluated. For the implant preparation, polymer and drug (lidocaine base or hydrochloride) were dissolved in the organic solvent. This solution was filled in a mold, frozen (slow: freezer –70°C or fast: liquid nitrogen) and then lyophilized at –40°C and 0.040 mbar for 72h (primary drying) and 10°C and 0.040 mbar for 10h (secondary drying). Additionally to the freezing rate, drug state and solvent type, other parameters such as polymer type and concentration were evaluated. Porous, sponge-like implants were obtained (scanning electron microscopy – SEM). 1,4-dioxane resulted in implants with regular-shaped pores and a continuous PLGA network, while acetic acid resulted in a more irregular structure, like leaflet- or platelet-structure. The difference in the pore structure of the sponges prepared with different solvents is due to the geometry of frozen solvent crystals before sublimation and to the polymer phase separation during the freezing process that was particular for each solvent. The morphology was strongly affected by the freezing rate. Implants prepared by rapid freezing of the PLGA solution have a visually denser structure with smaller pores when compared to larger pores obtained with slower freezing rates. This could be explained with the high nucleation rate and low crystal growth when frozen fast and at a low temperature, which leads to a large number of small crystals. More dense matrices were obtained at higher polymer concentrations.

After freeze-drying, the glass transition temperature (Tg) of the sponges (differential scanning calorimetry – DSC) decreased as a consequence of the residual solvent (thermogravimetric analysis – TGA), which acts as a plasticizer

for the polymer. Also the presence of lidocaine base decreases the Tg of the sponges. From the solubility parameters for PLGA (20.05 $MPa^{1/2}$) and lidocaine base (21.89 $MPa^{1/2}$ – Fedor's group contribution method), solubility could be assumed. It was confirmed with DSC and powder x-ray diffraction (XRD) for both physical mixtures and sponges, explaining thus the plasticizing effect.

Sponges with higher compressional strength (texture analyzer) were obtained by using high molecular weight polymers and higher polymer concentrations. Also 1,4-dioxane sponges were stronger, due to their well defined and regular structure. Three week lidocaine release from the sponges was achieved. The initial burst was decreased by an increase in polymer concentration and/or molecular weight. Further curing of the sponges decreased the residual solvent, increased the strength of the sponges and prolonged the drug release. Studies on swelling behavior, mass loss and water uptake of the sponges showed that the degradation rate of the implants was catalyzed by the presence of lidocaine base (ester bonds cleavage) and the decrease in the implant size. Lidocaine base implants showed no drug recrystallization after two and a half years.