Temporal Control of Drug Release From Biodegradable Polymer: Multicomponent Diclofenac Sodium Releasing PLGA 80/20 Rod

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Received 20 February 2007; revised 13 June 2008; accepted 15 July 2008
Published online 20 October 2008 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jbm.b.31243

Abstract: In our previous studies we have reported on the development of diclofenac sodium (DS) releasing rods. However, their drug release profiles were unsatisfactory. To enhance the drug release properties of the implant, we have developed a system whereby various elements can be combined into one implant. Melt extruded, self-reinforced (SR), and sterilized (S) DS-containing SR-PLGA 80/20 billets were combined to produce multicomponent implants with various compositions. These components were basically heat pressed together to form multicomponent rods. Drug release from single component and multicomponent rods was defined using a UV-Vis spectrophotometer. DS was released from individual components within 82–111 days and from multicomponent rods within 50–70 days. Thermal properties were analyzed using differential scanning calorimetry (DSC). The melting temperature (T_m) of multicomponent implants was about 157°C, change in heat fusion (ΔH) was 13.3 J/g, and the glass transition temperature (T_g) was 55.4°C. Mechanical strength was measured for 2 weeks and it decreased from 55 to 15 MPa. In conclusion, by compression molding three components with different release rates it is possible to control the temporal release from multicomponent rods. Released DS concentrations were within range for 49–74 days depending on the fractions of individual components used. © 2008 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 89B: 518–526, 2009

Keywords: drug delivery/release; biodegradation; NSAIDs; sustained release; bone

INTRODUCTION

Extensive research has already been undertaken with biodegradable polymers to develop implants for bone fixation and drug release applications. In addition to normal tissue reactions that follow their implantation, biodegradable polymeric implants can cause an inflammatory response at later stages when the release of polymeric particles and irritating biodegradation products begins, leading to recruitment of macrophages, giant cells, and osteolysis of bone.[1–3] These adverse effects have provoked the idea of the development of implants which release agents with properties that can address such inflammatory reactions.

Nonsteroidal anti-inflammatory agents (NSAIDs) are a widely used group of drugs for the treatment of inflammatory reactions. Promising results have already been obtained from experiments in which diclofenac sodium (DS) and bioabsorbable polymers were combined.[4,5]

One of the first ester-based drug releasing materials was cement, made of nonbioresorbable polymethyl methacrylate loaded with gentamicin.[6] However, due to the poor control of drug release from the cement, leading to subtherapeutic doses, we are currently facing a problem of increasing bacterial resistance to gentamicin.[7] Adequate release rates and concentrations are essential to achieve the necessary therapeutic effects from a drug releasing device. Recently, our group has successfully combined polymers, ceramics, and drugs resulting in multifunctional, antibiotic releasing, osteoconductive, load-bearing implants for bone management.[8,9] The control of drug release from these materials has been based mostly on matrix hydrolysis, followed by a change in textural and rheological behavior, matrix erosion, and/or drug dissolution and diffusion, with significant dependence on drug solubility and concentration.[10–12]

The aim of this study was to prove the point and develop an active agent or multiple agents releasing implant materials, with controllable and constant drug release properties, using compression molding technique and to characterize its drug release and mechanical properties. The main hypothesis was that by combining components with different release profiles, the resulting profile is a combination of those of the components in proportion to their volume fractions. The selected drug was DS, which is one of the most

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Contract grant sponsor: "EXPERTISSUES;"; contract grant number: NMP3-CT-2004-500283
Contract grant sponsor: The Technology Development Center in Finland; contract grant number: TEKES 90220
Contract grant sponsor: The Academy of Finland; contract grant number: Project 37726

widely used NSAID and clinically one of the most effective NSAID for treatment of both inflammation and pain.[13,14] The high melting point (T_m) of DS allows processing at the high temperatures as used in melt extrusion and compression molding. Two different types of implants were manufactured. The effect of sterilization to drug release rate was studied by sterilization of the second multicomponent implant.

MATERIALS AND METHODS

Materials

Commercially available poly(D,L lactide and glycolide) 80/20 (PLGA 80/20) (Purasorb®, Purac Biochem Bv, Gorinchem, The Netherlands) was used as the matrix (carrier) material for DS (Sigma-Aldrich, Espoo, Finland).

Methods

Compounding. The polymer and the drug were first dried separately in a vacuum oven (Binder VD 115, WTB Binder, Germany) for 2 days. Then the polymer (PLGA 80/20) and the drug (DS) were mechanically mixed using an electric blender (Retsch Grindomix GM200, Retsch GmbH and Co. KG, Haan, Germany). The materials were mixed at a speed of 2000 rpm for 20 sec repeating the procedure four times. After mixing, the drug and polymer were again put into the vacuum oven to dry. In the final stage of drying, the mixture was heated at 80°C for 8 h to remove all remaining moisture.

Preparation of Component A by Extrusion. The polymer granules and DS (powder) were formed into billets containing 8% by weight of the drug using a small scale laboratory extruder. Mixed drug and polymer were fed via hopper, into the extruder barrel at a rate of 11.4 g/min. The diameter of the die was 3 mm. The extruded billet was channeled through a cooling system (pressurized air and water-cooled plate) to a manually controlled drawing belt to optimize the diameter of the rod and the surface properties. Extrusion parameters were adjusted during the extrusion process.

Preparation Component B by Self-Reinforcement. Some of the rods were self-reinforced (SR) using a solid stage deformation technique. The rods were drawn vertically through a die, 1.4 mm in diameter. The drawing speed was 16 mm/min and the temperatures in the cylinder and the die were both 87°C. The SR billets were 1.16–1.27 mm in diameter resulting in a draw ratio of about 4.

Preparation of Component C by Sterilization. Some of the SR billets were sterilized with 25 kGy γ-irradiation by Willy Rüsch Ltd. (Kernen-Rommelshausen, Germany).

Preparation of Multicomponent Implants. Multicomponent implant type-1 (MC-1). The implant was made from three components comprising one compounded billet (component A), one SR billet (component B), and one sterilized SR billet (component C). Billets had a diameter of 1.0–1.27 mm and the length of 25 mm. The three components were placed into a two piece stainless steel mold with a slit diameter of 1.5 mm. The mold had three holes for heating elements in the ends; one in its upper part and two in its lower part. The components were compression molded using charge compressor (NIKE Hydraulics Ab, Eskilstuna, Sweden) to form one uniform rod. The temperature during compression molding was 120°C and the applied pressure was 20 MPa. Heat was turned off immediately after reaching the target temperature and the mold was cooled down to a room temperature with a circulating cold water cooling system. The resulting multicomponent rods had a diameter of 1.5 mm and length of about 30 mm.

Multicomponent implant type-2 (MC-2). The implant was made from six components comprising of one compounded billet (component A), three SR billets (component B), and two sterilized SR billets (component C). The diameter of component A was 2.3 mm and for B and C it was 1.2 mm. Component A was placed in the mold first and then components B and C were added randomly. The mold was similar to the one used for preparation of MC-1, except the slit diameter was 3 mm. In addition, the mold had caps in the ends of the slit to provide better control of pressure. Components were heat pressed to form a uniform rod using similar parameters to those used for preparation of MC-1.

Multicomponent implant type-3 (MC-3). The implants were manufactured using a similar mold and parameters as for MC-2. The MC-3 implants were sterilized with 25 kGy γ-irradiation by Willy Rüsch Ltd. (Kernen-Rommelshausen, Germany).

Determination of Drug Release. Drug release measurements were performed using a UV-spectrophotometer (UNICAM UV 540 UV-VIS spectrophotometer, Thermo Spectronic, Cambridge, UK). Samples were precisely weighed and then placed in vials filled with 10 mL of phosphate buffer solution (KH_2PO_4 + NaOH, pH 7.4 $\pm$ 0.02, 0.13 mol/L). The ratio of sample weight and buffer was about 10 mg/mL. During hydrolysis the amount of buffer was doubled because of the decrease of pH caused by acidic degradation products of the polymer matrix. Bottles were kept in a rotating (100 rpm) incubator (Multitron AJ 118 g, Infors, Bottmingen, Switzerland) at 37°C. There were three parallel samples of MC-1 and five of MC-2 and MC-3 for every measurement.

Drug release profiles for samples were determined by measuring the concentration of released DS in the phosphate buffer at suitable intervals. Samples were kept in the bottles and the buffer was poured into test tubes and concentrations measured with UV at a wave length of 276 nm.

Bottles were always refilled with fresh buffer solution. After the UV measurement, the pH was also measured with a pH meter (Mettler Toledo MP 225 pH Mettler-Toledo GmbH, Schwerzebbach, Switzerland). During the first week, measurements were made more frequently (6 h, 1 day, 2 days, 3 days, etc.) to define how often they were needed. Based on the initial results, less frequent measurement points were defined. These were usually between thrice a week and once a week. Daily release rates were calculated by dividing the amount of drug released by the time since the last measurement. From these results drug release profiles were developed for individual multicomponent implants. The actual drug content inside the rods was measured by dissolving the rod specimens in a mixture of chloroform and ethanol (1:4). Chloroform was used to dissolve the polymer matrix and ethanol to dissolve the drug. The amount of DS in the ethanol solution was measured using a UV-Vis spectrophotometer.

Pearson product–moment correlation coefficient analysis was applied for statistical analysis of correlation between drug release from single- and multicomponent implants. The correlation between components and MC-1 was calculated using values of average daily concentration, because components and MC-1 had different number of parallel samples. The correlation of drug releases between components and MC-2 and MC-3 were analyzed from all parallel samples.

Determination of Mechanical Properties. The shear strength of MC-1 was tested with an Instron 4411 material tester (Instron Ltd., High Wycombe, England). Shear tests were carried out using the modified method based on standard ASTM B 769-94. The shear strength (τ) is then given by:

$$\tau = F/2A \quad (1)$$

where F is the force at fracture and A is the area of the cross section of the sample. In the three-point method that was utilized, the sample is sheared at two points and that is why the cross-sectional area is multiplied by two. The crosshead speed was 10 mm/min, initial clamp distance of 5 cm and load cell 0.5 kN.

In addition to tests on initial rods, rods were also tested for *in vitro* properties after 3, 7, and 14 days immersion at 37°C in KH_2PO_4+NaOH buffer. Five parallel samples were used for every measurement.

Characterization of Microstructure. Scanning electron microscopy (SEM) was used to analyze the microstructure of MC-1 implants. SEM imaging was carried out using a JEOL T100 (JEOL Ltd., Tokyo, Japan) SEM using 5-kV acceleration voltage. The rods were cut and mounted, with carbon glue, onto a copper base. Before SEM imaging, the samples were sheared and coated with gold using an Edwards S150 sputter coater.

Thermal Properties. Thermal properties were studied using TA instruments Q1000 differential scanning calorimeter (DSC) equipment. The heating cycle was from 10 to 200°C and back again to 10°C at a rate of 20°C/min with indium as a calibration standard. The heating program was run twice. Melting point (T_m) and heat of fusion (ΔH) were determined from the first program cycle. The glass transition temperature (T_g) was determined from the second program cycle. All components (A, B, and C) were tested in addition to MC-1 (after 0, 3, 7, and 14 days *in vitro*).

RESULTS

Drug Release

Component A: There was a huge peak during the first day *in vitro* [Figure 1(a)]. After that the release rate increased slowly from zero to 2 μg/mL/day over a period of 40 days *in vitro*. After 54 days *in vitro*, the drug release rate increased to a level of 15 μg/mL per day followed by a decline to 5 μg/mL per day. The release rate increased again to a level of 15 μg/mL per day after 96 days *in vitro*. The total release period was 111 days [Figure 1(b)]. The mean standard deviation of measurements was 0.70 μg/mL.

Component B: After the initial burst, the release increased during the first 8 days *in vitro* to a level of 5 μg/mL per day and remained there for 20 days [Figure 1(a)].

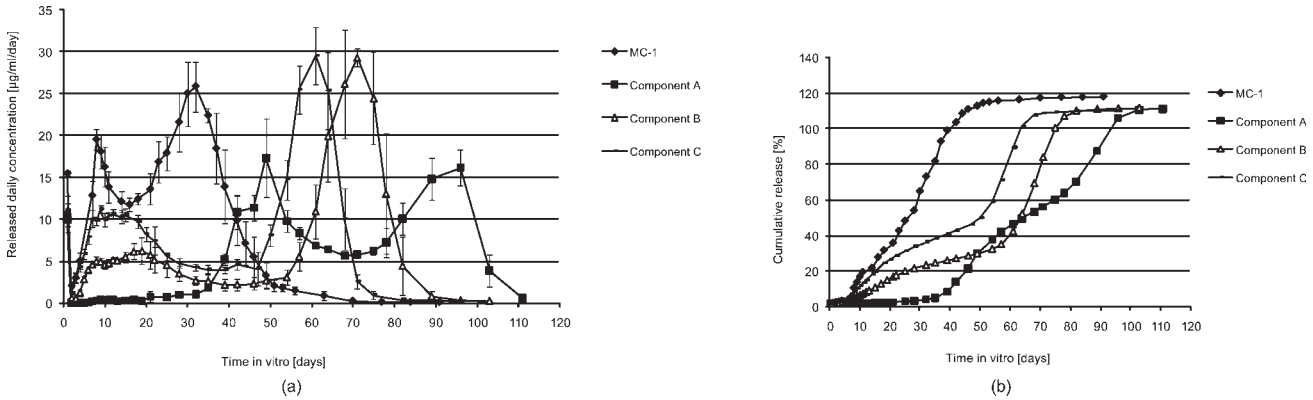

Figure 1. (a) Daily released drug concentrations of multicomponent implant-1 and components A, B, and C. (b) Cumulative release curve of multicomponent implant-1 and components A, B, and C.

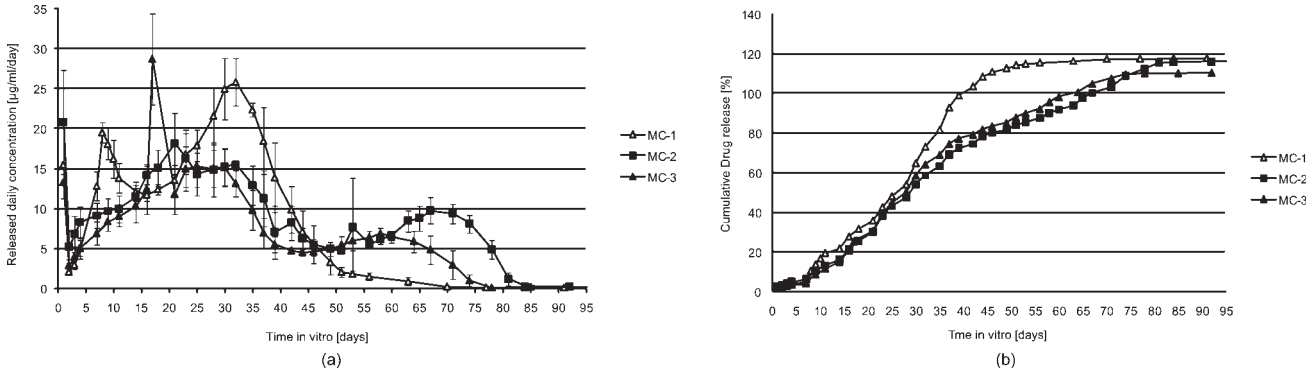

Figure 2. (a) Daily diclofenac sodium concentrations released from multicomponent implants MC-1 (three parallel samples), MC-2 (five parallel samples), and MC-3 (five parallel samples). The total drug release period lasts for 63, 84, and 77 days, respectively. (b) Cumulative drug release from multicomponents: multicomponent implant-1, MC-2, and MC-3.

After that, the release decreased to 2.5 μg/mL/day and remained at that level for 20 days. The release jumped up to 30 μg/mL/day after 71 days and decreased to zero at day 89. The release lasted for 95 days. Most of the drug was released in the first 55 days *in vitro* [Figure 1(b)]. The mean standard deviation of measurements was 1.47 μg/mL.

Component C: After the initial burst, the drug release rate increased to 10 μg/mL/day for about 18 days [Figure 1(a)]. Then the rate decreased to 5 μg/mL/day for 25 days followed by huge release of up to 30 μg/mL/day. The drug release lasted for 82 days. Most of the drug was released during the first 50 days *in vitro* [Figure 1(b)]. The mean standard deviation of measurements was 1.07 μg/mL.

MC-1: After the initial burst, the drug release rate increased to 20 μg/mL/day during the next 5 days and then decreased to almost zero in a further 10 days. During the next 14 days, it increased again to a level of 25 μg/mL/day [Figure 2(a)]. After that the release rate decreased gradually to zero with a drug release period of 63 days [Figure 2(b)]. The mean standard deviation of measurements was 1.57 μg/mL.

MC-2: After the initial burst, the release rate increased gradually to around 15 μg/mL/day during the next 17 days and stayed at that level for a further 16 days [Figure 2(a)]. The release rate then decreased to a level of 5 μg/mL/day during the next 16 days followed by a peak between 5 μg/mL/day and 10 μg/mL/day during next 18 days. The drug release ended on day 84 [Figure 2(b)]. The mean standard deviation of measurements was 1.84 μg/mL.

MC-3: After the initial burst, the release rate increased up to 28 μg/mL/day during the first 16 days *in vitro* [Figure 2(b)]. During the next 5 days, the release rate decreased to 15 μg/mL/day and remained at this level for 12 days. After that it gradually decreased to 5 μg/mL/day during the next 8 days remaining at that level for 10 days. The total release period was 77 days [Figure 2(b)]. The mean standard deviation of measurements was 1.45 μg/mL. The initial amount of drug in the components and multicomponents was found to be 5.8 wt %.

Correlations between MC-1 and components A, B, and C were -0.56, -0.37, and -0.15, respectively. Correlations between MC-2 and components A, B, and C were -0.41, 0.18, and 0.16, respectively. Correlations between MC-3 and components A, B, and C were -0.41, -0.26, and 0.32, respectively. Correlation of drug release rates between MC-1 and MC-2 and MC-3 were 0.39 and 0.48, respectively. Correlation of drug release rate between MC-2 and MC-3 was 0.65.

Mechanical Properties

The initial shear strength of MC-1 was 55 MPa, which was same as the shear strength of initial component A. After 2 weeks in hydrolysis, shear strength decreased to 15 MPa. At the same time the components of the multicomponent implant started to disintegrate and handling as an integrated implant became difficult. The initial shear strengths of components B and C were 88 and 93 MPa, respectively.

Microstructure

The microstructure of MC-1 was studied by SEM for only 2 weeks, because the components started to disintegrate and preparation of a representative sample became impossible. Before hydrolysis, integration of components seemed to be continuous (Figure 3) and no clear boundaries between different components could be observed. However, on the surface of MC-1, little cuts and flakes were observed in the boundaries of different components (Figure 4). SEM analysis of cut rods revealed good integration of components even after 1 week of hydrolysis (Fig 5). Some drug particles were seen on the cut surface and some arrow tip-like crystals were also observed.

Thermal Properties

Heat fusion (ΔH) of component A, B, and C were 4.3, 24.6, and 25.2 J/g, respectively. The melting point of component

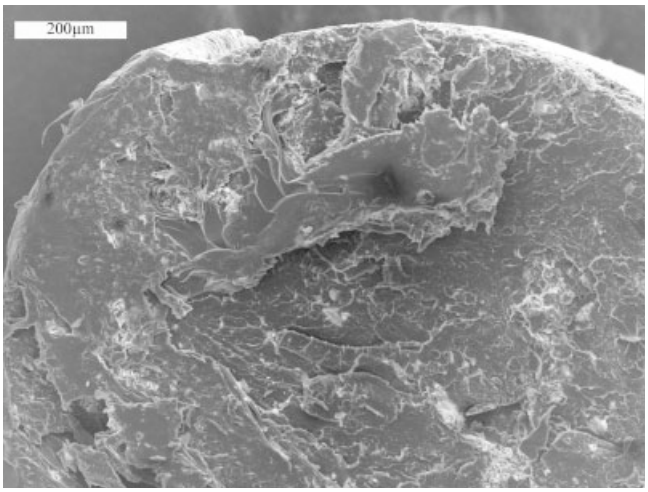

Figure 3. SEM picture of cross-sectional area of initial multicomponent implant-1. No clear boundaries between different components can be seen.

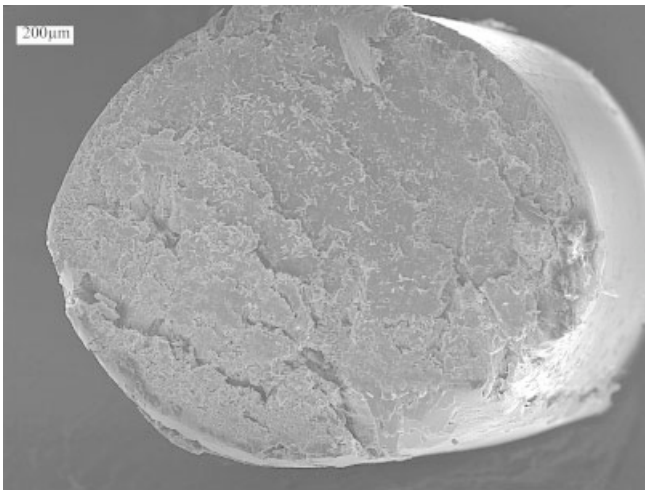

Figure 5. SEM picture of multicomponent implant-1 after 1 week in hydrolysis. No clear boundaries between components can be observed.

A was about 159°C, component B was about 155°C, and component C was about 156°C. All the components showed relaxation of orientation below 70°C as negative heat flow. In component B (SR-rod), some cold crystallization was observed between 80 and 110°C [Figure 6(a)].

Glass transition temperatures (T_g) were analyzed from the second heating cycle. The glass transition temperatures of components A, B, and C were 55.5, 48, and 54.1°C, respectively [Figure 6(b)]. Component B also showed crystallization between 110 and 150°C, which melted at 154°C. All the components showed some relaxation around 160°C.

The initial heat of fusion of MC-1 was 13.3 J/g and the melting point was 157°C [Figure 7(a)]. During 2 weeks of hydrolysis the melting temperature did not change. In all samples (0, 3, 7, and 14 days) some relaxation occurred between 42 and 59°C.

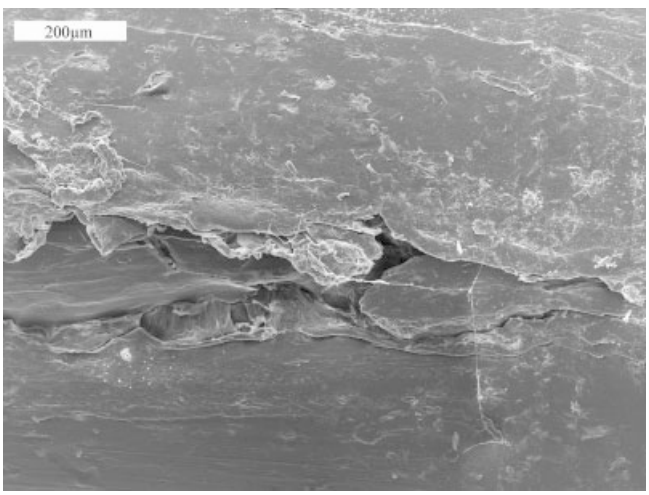

Figure 4. SEM picture of the surface of the multicomponent implant-1 with a flap and with cracks.

The second heating cycle of MC-1 showed that the initial glass transition temperature was 53°C [Figure 7(b)]. Some relaxation can be observed at 158°C. Some cold crystallization and melting can be observed between 100 and 160°C. During 2 weeks of hydrolysis the melting temperature increased and the longer the implants were immersed the more cold crystallization was observed.

DISCUSSION

The early bioabsorbable bone fixation devices made of SR PGA/poly(L-lactic acid) (PLLA) were introduced in the fixation of ankle fractures.[15] Other implants were developed from polymers that retain their strength properties for prolonged period of time, such as PLLA.[16–18] However, it was later noticed that PLLA may not reabsorb completely,[19] which might cause unwanted chronic inflammation and other complications.[2] Eventually, some of these PLLA devices had to be treated surgically 3–5 years after implantation.[20,21] As a fast bioresorbable copolymer, PLGA later gained acceptance in applications in nonweight-bearing bone, such as in craniomaxillofacial (CMF) surgery. In fact, there are various clinical reports on bioabsorbable devices used successfully as screws, plates, and tacks[22–29] in the CMF area.

Bioabsorbable polymers play a role in various drug delivery devices that have been developed over several decades.[5,8,9,30,31] Most of these studies show that the drug release rate is mostly determined by the diffusion of drug from the matrix and the degradation properties of the polymer in addition to the processing history. However, some approaches to temporal control of drug release have been made. Babazadeh[10] achieved temporal control by hydrolytically linking an ibuprofen-based drug with a labile ester bond to a hydrophilic monomer and copolymerizing it with a hydrophobic polymer. The drug was released selectively

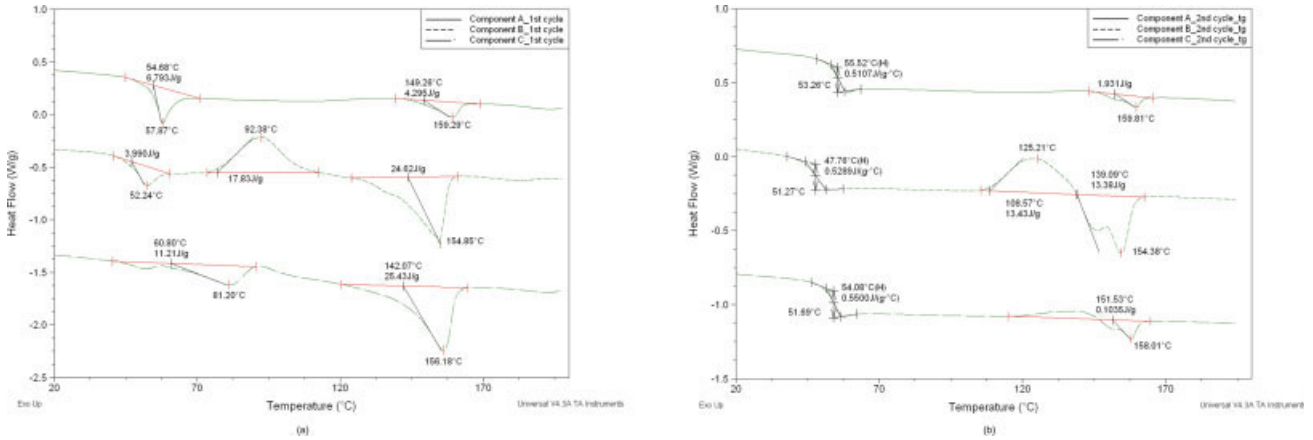

Figure 6. (a) The first heating cycle of DSC of components A, B, and C. The cold crystallization of component B can be seen between 80 and 110°C before the melting phase between 120 and 160°C. (b) The second heating cycle of DSC of components A, B, C. The glass transition temperature was estimated from this cycle. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

by hydrolysis of the ester bond. Another approach was made by Cheah et al.,[32] who studied the effect of a laser sintering technique in producing drug releasing devices. The release changed as the microstructure of device was changed. In this study, one of the aims was to develop a method of manufacturing a biodegradable device, where the release of a drug or multiple drugs can be adjusted by combining together components with different release properties.

Based on the properties of PLGA, compression molding was a suitable processing method for manufacturing multicomponent implants from rod-shape components.[33] Compression molding is a known method for processing of ceramics, metal powders, and for manufacturing simple polymer pieces.[34,35] The advantages include relatively easy production, reproducible results, reasonable costs, etc. However, it suffers from limitations including slow production rates, the possible size and shape of products, and the need for an accurate mold design.

Self-reinforcing by solid state techniques produces holes around the drug particles and most probably increases the surface area availably for hydrolysis.[36] When heat is applied to SR material, the orientation of the polymer chains disappears. The first phase of release of components B and C is most probably caused by buffer penetration into the slightly porous matrix and between components eluting the drug. The second, strong phase is most probably due to bulk degradation of the polymer matrix with simultaneous release of the drug. Thus, any inflammatory reaction that degradation products of the polymer might cause can then be controlled by simultaneous release of the drug. These assumptions can explain the observation that when the release of MC-1 is compared with the release curves of the initial components [Figure 1(a,b)], compression molding

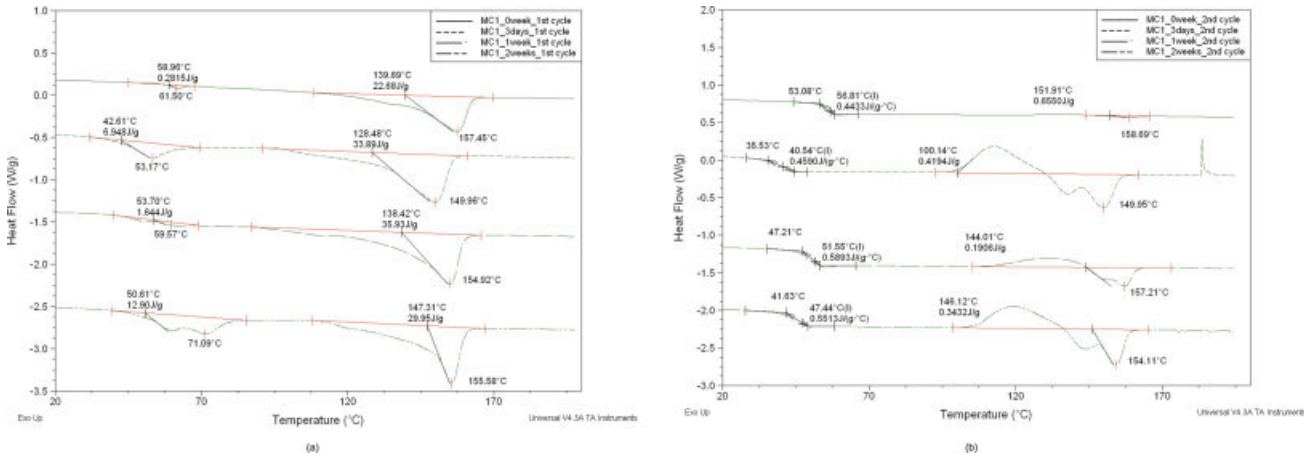

Figure 7. (a) The first heating cycle DSC of the multicomponent implant-1 in hydrolysis (0, 3, 7, and 14 days). (b) The second heating cycle of DSC of the multicomponent implant-1 in hydrolysis (0, 3, 7, and 14 days). The glass transition temperature was estimated from this cycle. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

seemed to speed up the drug release. The shape of the MC-1 curve follows the trend of the curve for the non-SR component A, which has not gone through major changes because of its short processing history. In addition, loss of mechanical strength supports this assumption because the shear strength of MC-1 was similar to that of non-SR component A. The reinforcing effect of self-reinforcing was lost during compression molding.

In this study, the molds were filled with components in a random order. Consequently, the implants were not identical to each other. The release of drug from different sides of multicomponent implants varied according to the type of component from which it was released. Despite possible differences, it can be seen that the release from parallel samples were quite similar indicating that there is no large effect on total drug release from these structural variations. Comparison of drug release curves of different MCs revealed that the shapes of the drug release curves of implant types MC-2 and MC-3 are quite similar [Figure 2(a,b)]. However, release curves of MC-2 and MC-3 were different from those of implant type MC-1. Statistical analysis revealed that drug release component A had a large correlation with MC-1 drug release rates. However, component B had only a medium correlation and component C a small correlation. In MC-1, the portions of all components were equal (each 1/3) and the general assumption might be that the correlation of components would be quite similar. However, the results can be explained by the degree of processing history of the original components as described earlier. Correlation of component A with MC-2 and MC-3 was medium and for components B and C, it was small. These results were not straightforward as it was expected. The differences of correlations could also be explained by different processing histories, different proportions of components in MC-2 and MC-3 (A, 56%; B, 27%; and C, 18%), and the different size of MC-1 and MC-2/MC-3. The interdependence between these parameters has to be studied further.

The effect of sterilization by irradiation is closely related to polymer structure.[37] Gamma irradiation can reduce material strength by breaking polymer chains and consequently affecting the drug release.[38] The accelerating effect of sterilization[36] on drug release was observed between the release curves of nonsterilized and gamma-sterilized SR components and also between nonsterilized and sterilized MC implants (MC-2 and MC-3, Figures 1 and 2). In our earlier preliminary studies with the component rods that were used in this study, the bioactivity of the drug was maintained after melt extrusion and gamma sterilization.

Thermal analysis of the initial components A, B, C, and the implant MC-1 revealed that heat treatment did not have a great effect on melting temperatures. Thermal analysis (first cycle) of components and MC-1 revealed abnormal endothermal reactions nearby 60°C; this can be due to relaxation of the orientation of the polymer chains [Figures 6(a) and 7(a)]. Component B had cold crystallization phenomena at about 90°C, most probably due to self-reinforcement. The second heat cycle curve [Figure 6(b)] also showed a large cold crystallization phenomenon in component B and its melting temperature, thus indicating that self-reinforcement releases more space for polymer chains to move and to release energy. The second heat treatment revealed similar cold crystallization phenomena in hydrolyzed MC-1 samples. This might be caused by component B and also by crystallization of oligomers that can be produced during hydrolysis. The DSC curve of component C showed a similar cold crystallization reaction to component B, but it was much smaller. Changes in thermal properties are quite complex and have to be studied more carefully in the future.

When considering the potential application of local drug release in relation to large bone fixation, multicomponent implants developed here do not seem to have sufficient strength in its present form. For bone fixation, it is important that the strength of the device is great enough initially (cortical bone 65.3 MPa)[39] and remains so until the healing and new bone formation have finished and there is no longer a need for fixation. Manninen et al.[40] studied SR sintered PLLA screws for olecranon osteotomies fixation of sheep. The sintered SR PLLA screws (diameter 4.5 mm) have an initial strength of ~76 MPa. After 6-week-incubation in phosphate buffer +37°C, the shear strength was approx. 62 MPa. *In vivo* studies with sheep indicate that these implants maintain a strength of 8.8 MPa for 6 weeks. Usually, fixation needs to provide support over a healing period of 4–6 weeks.[16,41] It can be deduced from previous information that an implant should have a strength of 9 MPa 6 weeks after an operation to ensure its effectiveness in large bone fixation. In this study, the strengthening effect of the self-reinforcement of components was lost during compression molding of MC-1. When compared with initial the SR-rod and sterilized SR-rod, the strength of MC-1 was lower by a factor of two. Thus, a shear strength for MC-1 of 55 MPa decreasing to 15 MPa in 2 weeks, is not adequate for load-bearing applications. Within 2 weeks, most fractures will have formed some callus, provided that the fixation is not rigid. The shear strength of human cranial bone (cancellous bone) is 21.4 MPa[42] so that, when considering the CMF area, it can be assumed that the strength indicated earlier should be sufficient for cranial fracture fixation. It should also be remembered that the healing period is influenced by the anatomical area,[2,43–45] the age of the patient,[46] micromotion,[47] and weight-bearing.[48–50] In general, 21.4 MPa can be regarded as the minimum limit of strength that an implant should have. In an MC-1 implant, even though SEM analysis showed good integration between components, the detachment occurred too early. Reasons for early disintegration of components might be related to design of the mold, inadequate compression molding parameters, roughness of the surface of the implant, increased water penetration, and weakening of the adhesion between components. It is obvious also that

increased water penetration also has an effect on drug release profiles.

In some studies, early administration of nonsteroidal NSAIDs has shown some inhibitory effect in bone healing.[51–53] On the other hand, other reports have shown no apparent effect on bone healing in treatment with cyclooxygenase (COX) inhibiting NSAIDs.[54,55] In addition, NSAIDs have been shown to inhibit osteoclast-like cell formation, which might help to reduce osteolysis.[56,57] In the light of these contradictory reports, the clinical situations in which NSAIDs can be used remains to be defined. In the literature, there is no data available about local therapeutic diclofenac levels in bone. Since all the data that was found from the literature were based on oral or intravenous administration of drugs only blood concentrations are reported. The minimum reported therapeutic concentration in synovial fluid was 0.12 μg/mL, which can be regarded as the lower limit of therapeutic concentration. The usual oral therapeutic dosage of DS is 150–200 μg/day, however the mean measured concentration in plasma is 6.1 μM (1.8 μg/mL).[58] There are only few cases about overdosing of DS in the literature. The highest reported plasma concentration was 60 μg/mL, which can be considered as the maximum limit of therapeutic concentration.[14]

CONCLUSIONS

This study shows that by compression molding components having different drug release profiles, the resulting combined release is a combination of those of the original components. The processing history of original components also has an effect on the combined release rates. Compression molding of extruded material decreases the initial strength of components and seems to cancel out the effect of self-reinforcement. The bonding of components to each other did not last long enough and the shear strength did not fulfill the requirements for fixation devices for bone, hence they need to be enhanced.

The authors thank Ms. Hanna Jukola for her technical support.

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