Release of sodium fluoride from poly (L-lactic acid) implants characterized by thermal history

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The method of injection molding of the melt of poly(L-lactic (PLLA), M_w 11 730, containing 7.5% of particles of sodium fluoride smaller than 1 μm was employed to prepare cylinders of a diameter of 2 and 10 mm in length. These matrices with an insoluble active ingredient with an amorphous structure of the carrier obtained by rapid cooling of the melt were annealed at temperatures from 70 to 140 °C in the medium of a hot-air drying plant and liquid paraffin. It has been found that crystallization of PLLA manifested by the rapidity of release of sodium fluoride does not take place at a temperature of 70 °C; at a temperature of 75 °C the effect of annealing of polyester matrices on the decrease in the rapidity of sodium fluoride release was already perceptible. Also in annealing of matrices at temperatures of 120 and 140 °C an identical deceleration of sodium fluoride release as that at 75 °C took place; the rapidity of the development of an effective crystalline phase was higher at higher temperatures. The method of interval cooling with the first stage of slow cooling and the second stage of rapid cooling of the melt of PLLA with 15% sodium fluoride fixed the structure achieved till the moment of the change in the rapidity of cooling. This revealed the temperature range of the development of the effective crystalline phase from the viewpoint of sodium fluoride release lying between 92 and 122 °C.
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1. Introduction

Biodegradable polymers represent a very important group of polymers used in medicine. Due to the fact that they decompose after administration into the organism, they can be employed wherever it is desirable not to have to surgically remove the implanted material again [1]. Therefore, they are used as surgical sewing material, temporary fixing and support systems as well as the systems with prolonged release of active ingredients [2].

An important position in biodegradable polymers is occupied by polyesters of aliphatic α-hydroxy acids, in particular poly(L-lactic acid) (PLLA). They are obtained by either polycondensation or polymerization reaction from the pertinent monomers [3]. PLLA ranks among semicrystalline polymers, it is therefore able to produce a crystalline structure. The crystalline stage of PLLA mostly possesses the character of spherulites with negative birefringence [4]. The character and amount of the crystalline phase depends on the manner of processing of polymer material, for instance in the preparation of systems with prolonged release. Of particular importance is the rate of cooling in the preparation systems from the polymer melt. In the case of very rapid cooling of the melt practically no crystalline phase is formed [5]. The slower the rate of cooling, the larger amount of the crystalline phase is produced [5].

Another method of influencing the amount and character of the crystalline phase of PLLA is annealing – heating the polymer at a certain temperature higher than the glass transition temperature for a certain period of time [6, 7]. The higher the temperature of annealing is and the longer the period of annealing is, the larger the share of the crystalline phase is and the larger the spherulites are [6, 7]. The properties of the crystalline phase are influenced also by the molecular weight of the polymer, distribution of the molecular weight, and the use of a nucleating reagent [8–10]. The amount of the crystalline phase is also changed during degradation in aqueous medium [11, 12]. PLLA and related polyesters of α-hydroxyacids have been employed in many experiments as carriers of active ingredients. Vert *et al*. prepared microspheres from PLLA ($M_n = 35\,000$) and gentamicin sulfate [13]. The microspheres were porous and released the total amount of the drug within 6 h in phosphate buffer. Gupta *et al*. obtained porous microspheres from PLLA and progesteron [14]. Nakamura *et al*. developed implants with prolonged release containing bleomycin [15]. The cylinders (diameter 4.5 mm) were prepared from PDLLA of varying molecular weight (1500–3500). Release *in vitro* (NaCl solution, 37 °C) took place at a rate of about 5% of the original content per day for a period of 3–6 weeks without an initial rapid release of the active ingredient.

The aim of the present paper was to examine the

influence of the rate of cooling, temperature, and the period of annealing on the release of sodium fluoride dispersed in matrices made of the oligoester of L-lactic acid. Also the temperature range was to be found, in which during relatively slow cooling of the melt of the oligoester an effective (from the standpoint of sodium fluoride release) crystalline phase is formed.

2. Materials and method

Sodium fluoride was prepared by precipitation from its aqueous saturated solution with acetone (medium particle size 0.79 μm). The oligoester of L-lactic acid was synthesized in the present authors' laboratory by a previously described polycondensation method [16]. The characteristics of the PLLA were as follows: $M_w = 11\,730$, polydispersity index 2.20, $T_m = 160\,^{\circ}C$, $T_g = 46\,^{\circ}C$. All other chemicals were of analytical or pharmacopoeial grade.

2.1. Preparation of rapidly and slowly cooled implants

The cylindrical bodies were prepared by a previously described method of casting the melt of oligoesters [16]. In the melt, sodium fluoride was dispersed in concentrations of 7.5% or 15.0%. The melt was evacuated using under pressure produced by the piston of a syringe into silicone rubber tubes. The filled tubes were cooled at two different rates, 300 °C per min (rapid cooling in a bath made of water, ice and sodium chloride) and 0.5 °C per min (slow cooling in a slowly cooled oil bath that was previously used for melting). After preparation from the tubes, the rods were cut to form cylinders 1 cm in length. The cylinders were of a diameter of 2.00 ± 0.16 mm.

2.2. Annealing of rapidly cooled samples

Rapidly cooled samples containing 7.5% of sodium fluoride were heated for a certain period of time (5–180 min) at different temperatures in different media (at 70 or 120 °C in a hot-air drying plant, at 75, 120, or 140 °C in liquid paraffin).

2.3. Search for the temperature range for crystallization of the oligoester during slow cooling

Some tubes with the melt containing 15% of sodium fluoride were allowed to cool slowly in an oil bath; at a temperature of 122 °C a portion of the tube with the melt was rapidly separated and inserted into an ice bath. The procedure was similarly repeated at 112, 101 and 92 °C. The obtained rods, after preparation of the tubes, were cut to form cylinders 1 cm in length (diameter 2.00 ± 0.19 mm, weight 40.6 ± 5.3 mg).

2.4. Release of sodium fluoride

The amount of sodium fluoride released from the cylinders into 15.0 ml of TRIS buffer pH 7.4 ($0.05\,mol\,l^{-1}$) isotonized with sodium chloride at 37 °C was determined by means of the fluoride ion-selective electrode. For the testing of release, static conditions were selected. Measurements took place at different time intervals. Buffer was completely replaced at each measurement.

3. Results and discussion

The presented method of the melt injection molding used for preparation of implants is limited for thermostable drugs. Was founded out in our laboratory that chosen ergot alkaloids, biguanides, and organometallic drugs are stable within short time heating until 140 °C (unpublished results).

In previous papers, connections were investigated between the rate of cooling of mixtures of the melt of poly (L-lactic acid) and particles of sodium fluoride on the one hand, and the molecular weight of the carrier [16], concentration of sodium fluoride, and size of its particles [17] on the other hand from the viewpoint of the course of release of sodium fluoride in matrices. Poly(L-lactic acid) can, under suitable conditions, form up to 50% of the crystalline phase [5]. The factor of time plays an important role in crystallization. The crystalline phase develops by two mechanisms – very slow cooling of the melt, or annealing in a water-plasticized state at temperatures higher than the glass transition temperature. On cooling the melt, crystallization lasts for several minutes or several dozens of minutes, on annealing in a plasticized state the period of crystallization takes several days. On the release of sodium fluoride, the crystalline phase functions as a barrier. It is dependent on the continuity of the phase. On crystallization, sodium fluoride particles may act by a nucleating effect that induces the development of the crystalline phase of poly (L-lactic acid) in their close vicinity [17].

Fig. 1 shows a thermogram of a matrix from nearly amorphous poly(L-lactic acid) processed by rapid cooling of its melt. The matrix contains 7.5% of sodium fluoride which does not exert influence on the quantitative expression of the cooling of the melt. The thermogram shows that glass transition takes place at 50 °C, crystallization of the material starts around a temperature of 75 °C, the inflection point of crystallization is at a temperature of 83 °C and the tip of the peak intended for crystallization is at 90 °C.

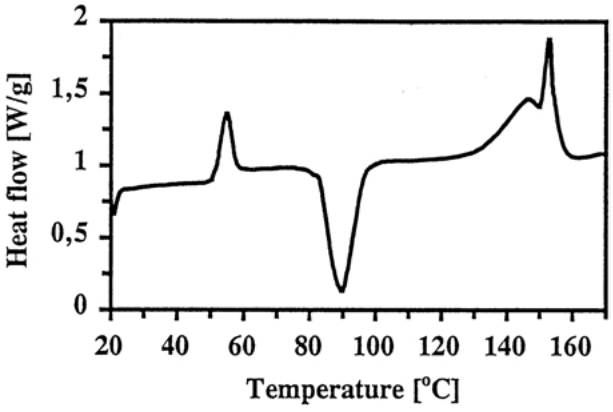

Figure 1 DSC thermogram (10 °C/min) of poly (L-lactic acid) matrices containing 7.5% sodium fluoride prepared by rapid cooling.

3.1. Annealing of rapidly cooled samples

Annealing of polymers is an operation suitable for acceleration of transition of the system to its equilibrium semicrystalline state [18]. Amorphous systems prepared by rapid cooling of the melt from PLLA with an admixture of 7.5% of sodium fluoride were heated in a drier to a temperature of 70 °C, which is a temperature by 20 °C higher than the temperature of the glass transition of the carrier and by several degrees lower than the onset of the endothermic stage of crystallization. Fig. 2 shows the profiles of release of sodium fluoride into TRIS buffer pH 7.4. The crystalline phase developed during slow cooling of the melt produced a barrier with high resistance against diffusion of fluoride ions. The release possesses the kinetics according to zero order. The same picture shows that on annealing of rapidly cooled matrices from nearly amorphous PLLA at 70 °C their release profiles are not changed. For a relatively long period of time from 15 min, via 45 to 180 min no such changes in the structure occur to change the barrier function of PLLA.

The matrices of PLLA with sodium fluoride were heated also in liquid paraffin. The temperature of this liquid medium can be regulated with greater precision than the temperature of the air. At 75 °C a different effect of annealing on the release of sodium fluoride than at 70 °C was demonstrated. Fig. 3 shows that the period of 15-min annealing was too short for the formation of an effective crystalline structure, but the period of heating the matrices for 45 min already manifested itself in deceleration of diffusion. At 120 °C a crystalline structure was formed already within 15 min. This temperature is close to the temperature of the maximal rate of growth of spherulites in high-molecular poly(L-lactic) acid, which was at 127 °C [19]. It has been found that the size of spherulites [6] and the thickness of lamellae [20] increase with increasing temperature. If this restructuralization takes place it is not manifested in the course of sodium fluoride release. The higher rate of release after 45-min heating; at the border of statistical

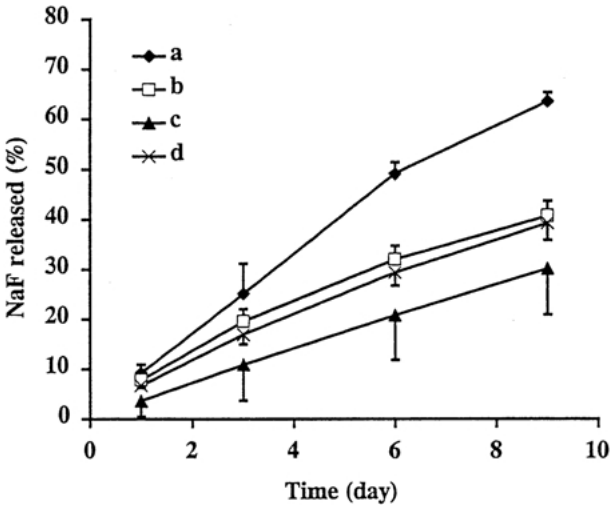

Figure 3 Portion of sodium fluoride (%) released from matrices made of oligoester of L-lactic acid (M_w 11 730); NaF 7.5%; rapidly cooled samples heated in liquid paraffin at 75 °C for a period of 15 (a) and 45 (b) min, or at 120 °C for 15 (c) and 45 (d) min. Average values and the range of values ($n = 3$).

significance; can be due to thermal decomposition of the oligoester carrier by the catalytic action of impurities.

Release of sodium fluoride from matrices annealed in a drier at 120 °C is shown in Fig. 4. The individual curves of release practically merge. The period of annealing longer than 5 min, in an interval up to 127 min, did not exert influence on the release of the fluoride. On long-term heating the matrices are stable in contrast to the situation in Fig. 3. The release took place according to kinetics of zero order. A crystalline phase, barrier-effective for sodium fluoride release, was thus formed in a period of time shorter than 5 min. Nevertheless, the total period of crystallization can be longer. In poly(L-lactic acid) with a value of viscosity-average molecular weight M_v about 400 000 at 140 °C the crystalline phase was being formed for a long time from 2 to 600 min [7]. The average rate of growth of spherical crystalline units was 2 μm/min [6].

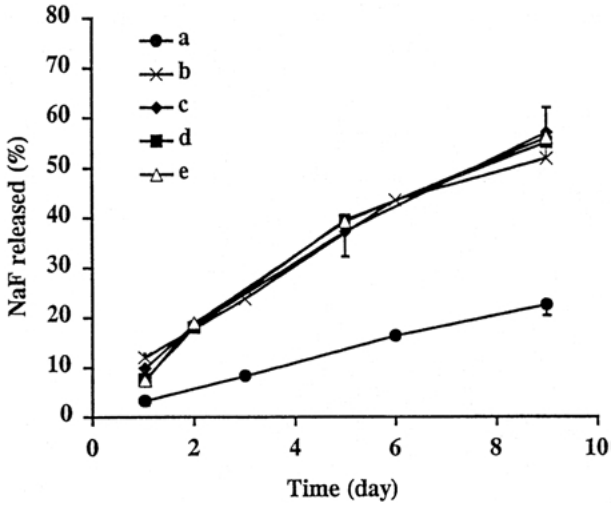

Figure 2 Portion of sodium fluoride (%) released from matrices made of oligoester of L-lactic acid (M_w 11 730); NaF 7.5%; slowly cooled samples (a), rapidly cooled samples (b); rapidly cooled samples heated in a hot-air drying plant at 70 °C for a period of 15 (c), 45 (d) and 180 (e) min. Average values and the range of values ($n = 3$).

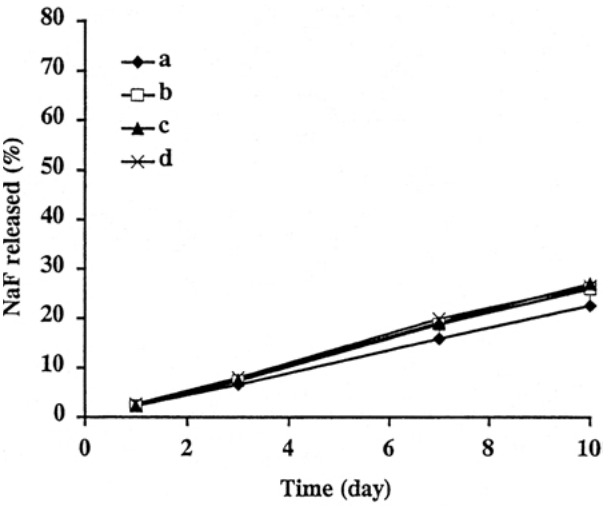

Figure 4 Portion of sodium fluoride (%) released from matrices made of oligoester of L-lactic acid (M_w 11 730); NaF 7.5%; rapidly cooled samples heated in a hot-air drying plant at 120 °C for a period of 5 (a), 15 (b), 45 (c) and 127 (d) minutes. Average values and the range of values ($n = 3$).

Fig. 5 shows the release of sodium fluoride from matrices heated in liquid paraffin to 120 and 140 °C. Identical curves were obtained. At these temperatures identical structuralization of matrices takes place without signs of degradation of the carrier. The systems are structurally stable also for a period of 15 min at 140 °C. There is no difference between the course of release of sodium fluoride from matrices annealed at 120 °C in the medium of air and in the medium of liquid paraffin.

3.2. Temperature interval for crystallization from the melt

Crystallization of PLLA from the melt is limited by two conflicting intermediate phenomena. Nucleation of the crystalline phase takes place at a sufficiently low temperature of the melt and a sufficiently high temperature is needed for subsequent growth. That is why the temperature interval for its crystallization is relatively narrow [21].

A temperature interval has been searched for at which during the cooling of the melt such a crystalline phase is formed which exerts influence on the rate of release of sodium fluoride. The investigation was based on the previously obtained knowledge saying that on cooling the melt of PLLA at a rate of 0.5 °C per min a crystalline phase is formed in the maximal extent, and on cooling at a rate of 300 °C per min virtually no crystalline phase is formed. The temperature of the formation of the crystalline phase effective from the viewpoint of sodium fluoride release was therefore searched for in a descending way by extending the temperature interval of the phase of slow cooling of the melt. This phase was followed by rapid cooling. This fixated the state created before.

Fig. 6 shows the release from PLLA matrices containing 15% of sodium fluoride prepared by slow and rapid cooling in the whole temperature interval from 170 to 20 °C and further the release from matrices prepared by interrupted cooling. The course of the curves

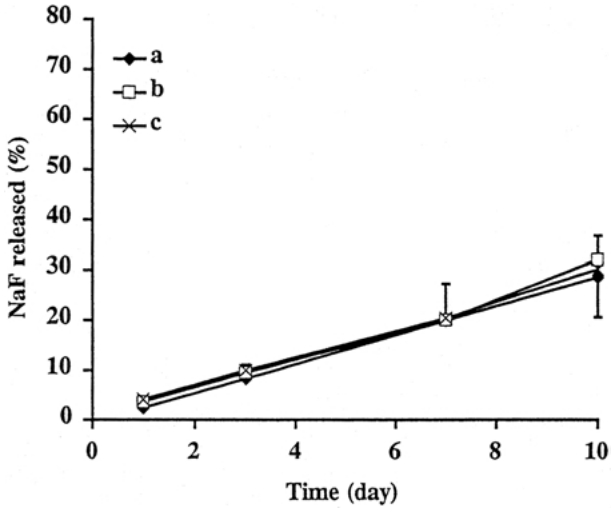

Figure 5 Portion of sodium fluoride (%) released from matrices made of oligoester of L-lactic acid (M_w 11 730); NaF 7.5%; rapidly cooled samples heated in liquid paraffin at 120 °C for a period of 5 (a), or at 140 °C for a period of 5 (b) and 15 (c) min. Average values and the range of values ($n = 3$).

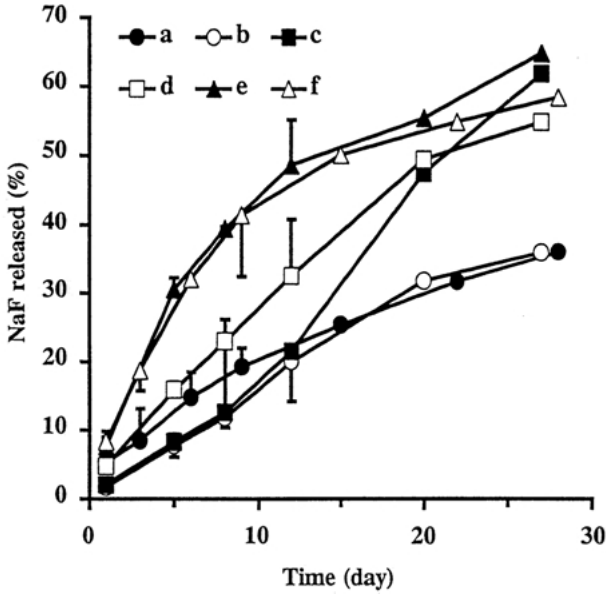

Figure 6 Portion of sodium fluoride (%) released from matrices made of oligoester of L-lactic acid (M_w 11 730); NaF 15.0%; slowly cooled samples from 170 to 20 °C (a), or rapidly cooled samples from 170 to 20 °C (b); samples rapidly cooled after slow cooling to a temperature of 82 °C (c), 92 °C (d), 101 °C (e), 112 °C (f), 122 °C (g). Average values and the range of values ($n = 3$).

clearly shows that structuralization effective from the viewpoint of release of sodium fluoride takes place in a temperature range between 122 and 92 °C. The matrices cooled slowly up to a temperature of 122 °C and then cooled rapidly showed the same release as the matrices cooled rapidly already from a temperature of 170 °C. The matrices cooled slowly up to a temperature of 112 °C and then cooled rapidly showed slower release of the fluoride in the initial eight-day phase, and matrices cooled slowly up to a temperature of 92 °C behaved as to dissolution in the same way as the matrices cooled slowly up to a temperature of 20 °C. From these facts it is possible to deduce that at a temperature lower than 92 °C no further structuralization changes take place in connection with the kinetics of sodium fluoride release. In a temperature range from 92 to 122 °C the thermally induced mobility of the molecules is sufficiently small for nucleation of the crystalline phase and at the same time sufficiently high for the growth of already formed germinal nuclei [19]. In the case of high-molecular poly(L-lactic acid) it has been demonstrated that crystallization takes place at higher temperatures, 140 °C [18] to 163 °C [19].

4. Conclusions

The method of the melt injection molding presented in the paper is a promising tool for the obtaining of biodegradable systems with the controled release of thermostable active compounds. Release of sodium fluoride from matrices of poly(L-lactic acid) is considerably dependent on the thermal history of their preparation using the method of injection molding of the melt represented by the rate of cooling. Matrices in an amorphous carrier produced by rapid cooling of the melt can be subjected to annealing. This accelerates the movement of the system to the thermodynamic equilibrium; a decrease in the rate of sodium fluoride release

can be also achieved. The development of a crystalline phase during annealing is limited by the lower limit of temperature at which the segments of the polyester chain are sufficiently mobile. For the development of this new crystalline phase a sufficient period of time is needed, which is reciprocally dependent on temperature. The technique of interval cooling of molten matrices with an insoluble drug at a low and subsequently a rapid rate was used. A series of decreasing temperatures of the rate change and subsequent measurements of the rate of release revealed a temperature interval of release-effective crystallization of the polymeric or oligomeric carrier, which ranged between 92 °C and 122 °C.

Acknowledgment

Financial support by grant CEZ-MSM 111 600001.

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Received 12 October 1999
and accepted 2 November 2000