Lidocaine Release from Polycaprolactone Threads

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ABSTRACT: In the field of resorbable devices, drug eluting sutures represent an applied research field on which the reliability of both production processes and mathematical prediction modeling were tested. Indeed, poly-ε-caprolactone pellets were compounded with lidocaine and then extruded to obtain highly loaded threads. The complete and rapid release demonstrated that the extrusion process does not alter the drug, which is confirmed to be embedded in an open porous matrix, being free to be solvated by uptaken water and to diffuse. Release profile and polymer degradation were simulated through a mathematical model based on conservation laws that allowed to assess release kinetic and to confirm the understanding of involved phenomena, as it fit experimental data. Reliability and robustness of chosen model allow to monitor the overall quality of manufacturing because any discrepancy between experimental and simulated data can be adopted to assess drug distribution uniformity within the device. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 117: 3610–3614, 2010

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INTRODUCTION

In recent years, bioresorbable systems became a quite established reality in the field of controlled drug release. Such devices, indeed, are suitable for delivery not only of drugs, but also factors, proteins, and genes: while device degradation takes place, loaded substances diffuse out the matrix with controlled kinetic.[1–6] Among all possible devices, drug loaded sutures represent an interesting research field, with some systems previously investigated and described in Refs. 7 and 8. The phenomena involved are widely studied and can be generally understood: degradation is governed by "diffusion and reaction" laws and occurs because of polymer hydrolytic degradation, where diffusion process for water, monomer, olygomers, and drugs follow the ordinary diffusion mechanism (i.e., the Fick's laws).[9,10] Nowadays, a better reliability of drug delivery profiles emerged and models are gradually replacing the "trial and error" approaches to design these devices.[10–12] Among most complete and recently developed models, being based on fundamental laws and taking into account the full ensemble of all involved phenomena, those developed by Arosio et al.[11] and Perale et al.[12] can be mentioned here. Both models addressed the drug release from bioresorbable suture threads through the same physics but with a different mathematical complexity. Those models were extensively validated against several experimental data for different polymer/drug systems.[11,12] Thus, once the release mechanism is properly assessed, the matching of experimental release data with predictions from a previously validated model can be adopted to verify reliability of device manufacturing. Indeed, if the manufactured device behavior is able to follow the trends predicted by a reliable model for a uniformly drug loaded system, positive conclusions about homogeneity and whole production procedure can be safely drawn. Moreover, assessing uniformity of drug distribution is not always analytically simple and economically valuable, while often a concentration gradient driven release test is not only easier but also cheaper and more reliable.

For all these reasons, in this experiment, poly-ε-caprolactone pellets were loaded with lidocaine chloride (an anesthetic drug commonly used in surgery and better known as Xylocaine®), and such obtained pellets were then processed by micro-extrusion to obtain suture threads. *In vitro* lidocaine release from

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such threads was examined. Materials, processes, and methods were taken from those suggested in literature, to provide a solid rationale to the experimental work. Specifically, the two-step process that was implemented here allowed higher drug loads with respect to those obtainable by means of impregnation techniques.[7,8] Moreover, devices manufactured with that technique exhibit a satisfying uniformity of drug distribution over device cross section as well as along their extension.[12] It is important to notice that drug release reliability (i.e., the ability to predict pharmacologic effects during time) is particularly important when developing painkilling suture threads, which are able to provide at least some analgesic effect during wound healing. The final aim of our work were, indeed, to assess feasibility of implemented production process and to prove reliability of chosen model for monitoring overall quality of manufacturing.

MATERIALS AND METHODS

Raw materials

Experimental data were obtained through the *ad hoc* production of drug filled resorbable devices. Raw materials and device preparation and analysis are the same as presented in Perale et al.[12] except for the use of lidocaine chloride. Lidocaine chloride ($C_{14}H_{22}N_2O \cdot HCl$) is an anesthetic compound commonly used in surgery and widely studied in Ref. 13. It has a 3.58 mg/mL solubility in water. As regards, polymer, poly-ε-caprolactone (PCL) was used. PCL is a well-known bioresorbable aliphatic polyester that can be easily processed by extrusion.[14–16] Raw material was supplied in small pellets by Sigma Aldrich (Germany), with a mean molecular weight of about 80 kDa. As in Perale et al.,[12] this choice derives from the necessity of a high molecular weight and thus stable polymer, whose characteristic degradation time at room temperature is much longer than drug release characteristic time.[17]

Sample preparation

Homogeneous compounding of PCL pellets and lidocaine salt was achieved by mixing within a cyclonic mill in moist atmosphere. Exsiccation was then performed to obtained pellets (vacuum oven at 37 ± 2°C for 24 h) to avoid water uptake that can affect degradation and release profiles.[12] Lidocaine load applied was 10% in weight. Loaded and dried pellets were directly extruded. Extrusion was performed vertically with a 3-zone microextruder, using a special screw and die and a 2.5 mm pin.[12] Obtained filaments were cooled with air while being pulled; this operation leads to a diameter shrinking to a value of 1.5 mm.[12] Vacuum sealing was then applied and samples were kept at −80°C to preserve them. Filaments were cut into smaller fragments, to avoid data scattering due to a no, strictly, perfect diameter uniformity within long tracts. Two series of samples were prepared to allow parallel testing and thus evaluate mean values.

Drug distribution evaluation

Drug distribution was grossly evaluated on thread cross section by means of Environmental Scanning Electron Microscopy imaging (alias ESEM, Evo 50 EP Instrumentation, Zeiss, Germany) together with Energy Dispersion Spectroscopy (alias EDS, Cambridge Instruments, UK). EDS was used to detect the presence of chlorine, with respect to other elements, as indicator for the presence of lidocaine salt in thread section.[12]

Drug delivery assessment

Aforementioned prepared samples were cut into pieces weighting each 0.040 g (±0.001 g) and thus containing about 4 mg of lidocaine each. Each sample was placed in 3 mL of distilled de-ionized water sealed batch, and they were all kept at constant temperature (37°C, ± 2°C) and totally shaded from direct light. Solution was replaced with clean de-ionized water to maintain as high as possible, and the driving force as to best and most realistically simulate *in vivo* condition, where degradation products and drug are metabolized and eliminated quickly by the organism. Water was thus changed every two hours during the first day of release test, then daily in the days that followed. Samples were analyzed with an UV spectrophotometer to determine the presence of released lidocaine. Instruments and procedure were set accordingly to Lambert-Beer law (calibration equation used was $y = 0.0384x + 0.0121$ and wavelength 216.5 nm). Before spectroscopy solutions were neutralized with 10 m*M* of NaOH to allow better spectral resolution, as the used drug is a hydrochlorine salt. The same experimental setting was applied but this time phosphate buffer saline solution (PBS) was used instead of water. Measurements were taken at same time points.

Modeling aspects

Suture thread degradation and drug release were simulated through the mechanistic model developed by Perale et al.[12] This model involves the diffusion of water, monomer and drug through the polymeric matrix. Water interacts with polymer to produce its oligomers by degradation reactions. Moreover, water interacts with the drug solubilizing it, in agreement

TABLE I
Summary of the Main Model Equations (Polymer Degradation and Drug Diffusion through the Device) as in Ref. 12

$$R_n = k_P\left\{\sum_{j=1}^{n-1}[P_j][P_{n-j}] - 2[P_n]\sum_{j=1}^{\infty}[P_j]\right\} + \frac{k_P}{K_{EQ}}\left\{2[W]\sum_{j=n+1}^{\infty}[P_j] - [W](n-1)[P_n]\right\} \quad (1)$$

$$\frac{\partial([P_n])}{\partial t} = R_n + D_n\nabla^2[P_n] \quad n = 1,\infty, \quad (D_n = 0 \text{ for } n \geq 2) \quad (2)$$

$$\frac{\partial[W]}{\partial t} = -\sum_{j=1}^{\infty} R_j + D_W\nabla^2[W] \quad (3)$$

$$\frac{\partial d_p}{\partial t} = -2k_C([i]^* - [i])/\rho_i \quad (4)$$

$$\varepsilon\frac{\partial[i]}{\partial t} = D_i\nabla^2[i] + N\rho_i k_C([i]^* - [i])\pi d_p^2 \quad (5)$$

Equations (1)–(5) are the polymerization rate, the mass balances for: the n-length polymer chain P_n, water W, the dissolution of the solid drug particles embedded in the polymeric matrix i, the drug dissolved in the water contained in the device porosity.
$[P_n]$, $[W]$, $[i]$ = concentration of polymer chain, water, and dissolved drug;
D_n, D_W, D_i = diffusivity for polymer chain, water and drug;
k_C = mass transport coefficient for drug dissolution;
$[i]^*$= lidocaine water solubility;
ε = polymer porosity;
N= number of lidocaine particles per unit polymer volume;
d_p = lidocaine dispersed particle diameter.

with the thermodynamics of its solubility. Then, the solubilized drug diffuses through the polymeric matrix towards the solution surrounding the device, driven by the concentration gradient. The polymer degradation is described by an autocatalytic process, where the role of the catalyst is played by the carboxylic moiety of the monomer itself. Because the model development was already addressed in detail in Ref. 12, the main equations are summarized in Table I for the sake of completeness. The population balance equation was solved with the moment methods,[18] and finally the whole model was numerically integrated in Fortran language.

RESULTS AND DISCUSSION

Threads were continuously produced by the extrusion plant, which was fed with the drug compounded polymeric pellets. For the sake of experimental needs, once cooled down to air temperature, the threads were cut into homogeneous pieces and kept as described.

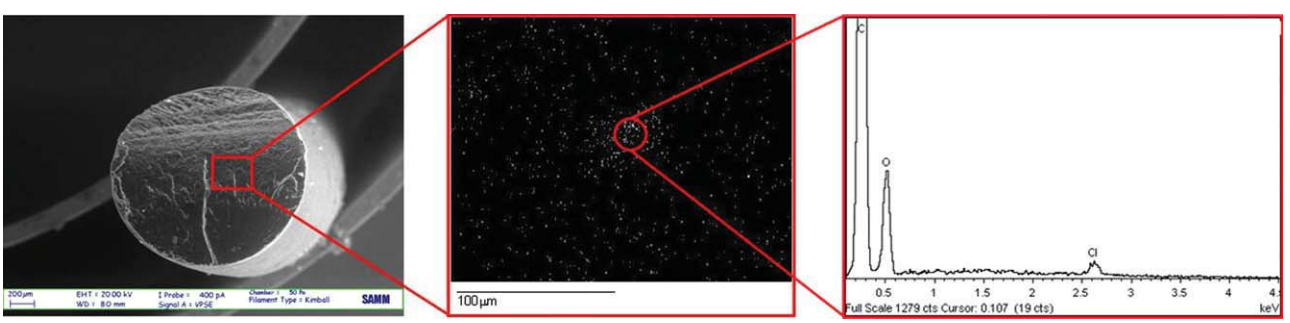

Figure 1 ESEM image of thread cross section, evidencing lidocaine grossly uniform distribution by means of EDS plots showing (white dots) the presence of Chlorine (2.6–2.7 keV peak on spectrum). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE II
Main Numerical Parameters Adopted for the Simulations, all Taken at 37°C

Device radius	$R = 0.15$ cm
Device length	$L = 4.5$ cm
Polymer molecular weight	MW = 80000 g/mol
Polymer polydispersity	PD = 1.2
Monomer molecular weight	$M_i = 114.1$ g/mol
Polymer density	$\rho = 1.2$ g/cm^3
Polymerization rate constant	$k_p = 1.10^{-12}$ cm^3/mol/s
Polymerization equilibrium constant	$K_{EQ} = 1.10^{-3}$
Effective monomer diffusivity	ε, $D_1 = 1.10^{-10}$ cm^2/s
Effective water diffusivity	ε, $D_W = 1.10^{-6}$ cm^2/s
Effective drug diffusivity	ε, $D_i = 1.10^{-7}$ cm^2/s
Lidocaine density	$\rho_i = 1.1$ g/cm^3
Lidocaine dispersed particle diameter	$d_p = 1.10^{-6}$ cm

Drug distribution along the thread was grossly assessed via ESEM and EDS, which was confirmed an acceptable homogeneity: an example of drug distribution within thread cross section is illustrated by images of Figure 1, showing a low magnitude cross section (ESEM image) and a zoomed portion, where the presence of chlorine is assessed by EDS.

The solution surrounding thread samples was changed frequently during release experiments and maximum lidocaine concentration reached in the solution was never higher than 0.33 mg/mL, which is less than 1/10 of solubility (i.e., 3.58 mg/mL), having thus neglectable effects on effective driving forces given by concentration gradient between thread and outer solution.

Thanks to this result, the modeling hypothesis of having almost zero concentration of lidocaine outside the thread, and thus maximum and constant concentration gradient between thread and solution, can be reasonably and safely considered as valid. Release profile and manufacturing data regarding suture threads were then simulated using model of Ref. 12 and introducing parameters are summarized in Table II. Poly-ε-caprolactone and lidocaine data were calculated according to literature and data fitting was performed.[11,12] The comparison between experimental drug release data and simulated profile is plotted in Figure 2, where releases are expressed as cumulative percentages, i.e., as progressive fractions of 100%, which represents the full load in each sample. More precisely, dots represent the experimental data achieved in deionized water, which are expressed as mean values of two samples with the experimental error, where model prediction is represented by a continuous line. Release performed in PBS gave comparable results to those in water being in the same range of deviation with respect to experimental tolerance. These data are not plotted for sake of clarity of Figure 2.

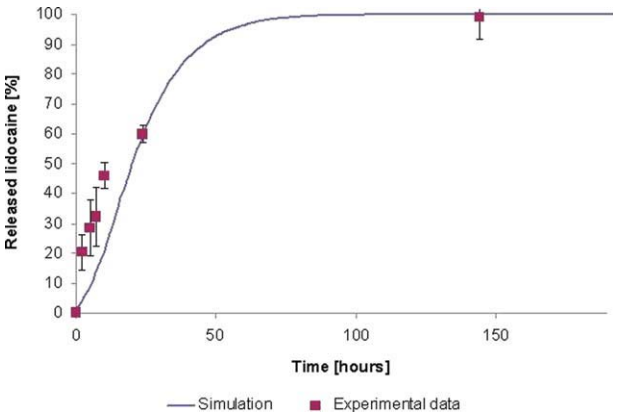

Figure 2 Release of lidocaine in water from poly-ε-caprolactone suture threads; comparison between experimental data in water (dots) and model prediction (continuous line).

A strong agreement between the two sets of data can be noted. Experimental and simulated profiles are absolutely comparable, witnessing that the model properly assessed release mechanism and meaning that system kinetic was correctly understood. Furthermore, initial drug release, i.e., in the first 24 h, appears to be slightly faster than expected by model predictions. This can be justified with a not perfectly uniform drug distribution in the thread and thus with a greater concentration of lidocaine in the thread outer volume. Moreover, a further confirmation came by the fact that already after 24 h model predictions and experimental data fit perfectly. At present, these discrepancies can be adopted as an index for the reliability of the manufacturing process in obtaining a uniformly loaded system.

Lastly, polymer degradation was also calculated in a changing water environment, simulating *in vivo* conditions as previously described. The degradation is expressed through reduction of average molecular weight and its trend is illustrated in Figure 3. It can be immediately noted that the drug release time

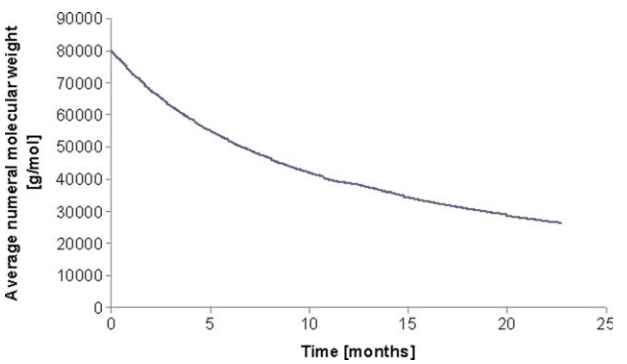

Figure 3 Polymer degradation (variation of the average molecular weight) for the poly-ε-caprolactone suture threads left in water being regularly changed.

scale is completely different from the degradation process one.

The full drug release is completed within about three days, while significant polymer degradation appears after almost one year, in agreement with the two characteristic times: $\tau_D \approx R^2/D_i \approx 63$ h ≈ 2.7 days and $\tau_R \approx K_{EQ}/k_p\,[W] \approx 5 \times 10^7$ s ≈ 1.5 years. Thus, for practical use, polymer degradation model can be totally omitted in describing these systems, being erosion phenomena negligible in the time scale important for drug release. Moreover, because the very high water solubility of lidocaine chloride (i.e., 3.58 mg/mL) the dissolution process described by eq. (4) is faster than the diffusion described by eq. (5). The two characteristic times are $\tau_d \approx d_p/k_c \approx {d_p}^2/4D_i \approx 10^{-5}$ s and $\tau_D \approx R^2/D_i \approx 63$ h ≈ 2.7 days, respectively. Thus, in a very oversimplified approach, lidocaine release from PCL threads can be simulated only through eq. (5) assuming the lidocaine to be fully solubilized in water in correspondence with the initial time.

CONCLUSIONS

Lidocaine release from poly-ε-caprolactone suture threads produced by micro-extrusion was investigated to assess the reliability of the manufacturing process. The full and rapid release of the loaded drug demonstrates that the extrusion process does not alter the drug and that the loaded amount is embedded in an open structure porosity that let it to be available for the release. The ESEM and EDS images demonstrated that the drug is almost uniformly distributed within the thread cross-section. The experimental data about the release and the polymer degradation were simulated through a conservation laws based model that allowed the determination of the relevant constant describing the phenomena involved. In particular, in these systems, the polymer does not degrade in the time frame of interest for the release process and the dissolution of the drug particle embedded in the polymeric matrix is among the fastest process (together with water uptake). Accordingly, in the examined system, the release process can be addressed very simply by describing the transient diffusion of the solubilised drug through the polymer porosity. Last, but not least, the discrepancy between the experimental and the calculated data can be adopted to quantify the nonuniformity of the drug distribution within the suture cross-section. In particular, the accelerated release in correspondence of the initial times can be related to a tendency to concentrate the drug near the thread rim by the examined manufacturing process.

In conclusion, going into detail regarding the choice for lidocaine eluting threads, it is important to notice that drug release reliability is particularly important when developing painkilling sutures, and the results here achieved confirm both manufacturing process suitability and model predictions reliability, thus suggesting their potential application for quality assuring purposes.

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